We dedicate this book to all people living with diabetes and the healthcare professionals who look after them. We would also like to dedicate this book to our families without whose support and encouragement the book would never have been finished.

Textbook of Diabetes

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Preface to the Fifth Edition

It is seven years since the last edition of the *Textbook of Diabetes* was published and despite many advances in the understanding of diabetes and its treatment over that time, the management of diabetes still remains a major global burden for people with diabetes, their families, and the wider society in which they live. Whereas the global prevalence of diabetes according to the International Diabetes Federation affected 246 million people in 2010, the current estimate is 415 million and is projected to rise further. One in 10 of the world's population has diabetes and one person dies because of diabetes every 6 seconds. Twelve percent of global health expenditure is spent on diabetes. The challenge to people with diabetes and their healthcare professionals has never been greater.

Despite the ever-increasing numbers, better management is starting to pay dividends. The outlook for those with diabetes appears to be improving, at least in high income countries where an individual's risk of developing complications and losing years to diabetes is falling. If the variation between the best and worst care could be obliterated, much morbidity and mortality would be prevented.

Ironically, as the volume of information and the vast numbers of resources available in this digital age have increased, many are finding it overwhelming to keep abreast of the new advances. It is particularly challenging to determine the validity of many source materials. In this textbook, we aim to bring together a series of *up-to-date* chapters from an international group of leading diabetes specialists who provide accurate and clinically relevant information to both academic and practicing diabetes healthcare professionals. Having the key information in one volume still has its merits, and this is further enhanced by *online* access and searchability.

The editors have retained the structure from the previous edition, with a similar length and number of chapters. We begin with a history of diabetes that provides many valuable insights from the past. The book then takes us through the epidemiology of diabetes, the physiology and pathogenesis of diabetes before moving onto management. We have taken a broad view in these sections recognizing that diabetes management encompasses so much more than drug therapy alone. A discussion of the microvascular and macrovascular complications then follows before a new section on the psychosocial aspects of diabetes. Different models of care as well as the management of diabetes in special groups are included before the final section looks into the future. There are new chapters on the biology of glucagon, the microbiome and diabetes, cancer, non-alcoholic fatty liver disease, and end-of-life care. These additions reflect the advances in our understanding of diabetes, its management, and have implications for a variety of related disorders.

As editors, we are only too aware of the hard work that goes into the production of a comprehensive and up-to-date book such as this. Our thanks go to each and every chapter author, who, despite busy academic and professional lives, were prepared to devote the time, energy, and expertise to provide their essential contributions to the text. Thank you for your forbearance of our nagging e-mails!

We are also grateful for the immense help we have received from our publisher, Wiley-Blackwell. Our commissioning editor, Priyanka Gibbons, who took over from Oliver Walter, during the book's development, has provided guidance, encouragement, and support. Our thanks also go to Gill Whitley who kept the momentum going when Rob Blundell left, and to the rest of the production team. The book looks even better than the last edition!

We hope you enjoy reading the book, whether it be dipping in or reading from cover to cover, as much as we did editing it. We have all taken away useful novel information that will aid our daily professional lives and we hope that this book will help you to support those with diabetes in the widest sense of this meaning.

Richard Holt
Clive Cockram
Allan Flyvbjerg
Barry Goldstein
February 2016

List of Abbreviations

AACE	American Association of Clinical Endocrinologists
AAV	adeno-associated vectors
ABP	ankle blood pressure
ACCORD	Action to Control Cardiovascular Risk in Diabetes
ACE	angiotensin-converting enzyme
ACHOIS	Australian Carbohydrate Intolerance Study in Pregnant Women
ACR	albumin : creatinine ratio
ADA	American Diabetes Association
ADP	adenosine diphosphate
AICAR	5-aminoimidazole-4-carboxamide-1β-D-ribofuranoside
AMDCC	Animal Models for Diabetes Complications Consortium
AMP	adenosine monophosphate
Apo	apolipoprotein
aPWV	aortic pulse wave velocity
Arx	aristaless-related homeobox
ATP	adenosine triphosphate
AUC	area under the curve
BCAA	branched-chain amino acid
BMD	bone mineral density
BMI	body mass index
BM-MNC	mononuclear bone marrow-derived stem cell
BPH	benign prostatic hyperplasia
bpm	beats per minute
BTX-A	botulinum toxin type A
CABG	coronary artery bypass grafting
CA-MRSA	community-associated methicillin-resistant *Staphylococcus aureus*
CAPD	continuous ambulatory peritoneal dialysis
CBG	capillary blood glucose
CBT	cognitive–behavioral therapy
CCM	corneal confocal microscopy
CDA	Canadian Diabetes Association
CDC	cardiosphere-derived stem cell
CDC	Centers for Disease Control and Prevention
CDE	Certified Diabetes Educator
CEMACH	Confidential Enquiry into Maternal and Child Health
CETP	cholesteryl ester transfer protein
CGM	continuous glucose monitoring
CI	confidence interval
CKD	chronic kidney disease
CML	carboxymethyllysine
CNS	central nervous system
COC	combination oral contraceptive
COX	cyclooxygenase
CPC	cardiac progenitor cell
CRP	C-reactive protein
CSII	continuous subcutaneous insulin infusion
CT	computed tomography
CV	coefficient of variation
CVD	cardiovascular disease
DAWN	Diabetes Attitudes, Wishes, and Needs study
DCCT	Diabetes Control and Complications Trial
DKA	diabetic ketoacidosis
DPP	dipeptidyl peptidase
DSN	diabetes specialist nurse
DVLA	Driver and Vehicle Licensing Agency
EASD	European Association for the Study of Diabetes
ECG	electrocardiography/electrocardiogram
eGFR	estimated glomerular filtration rate
EMA	European Medicines Agency
ER	endoplasmic reticulum
ERCP	endoscopic retrograde cholangiopancreatography
ERK	extracellular signal-regulated kinase
ERM	ezrin–radixin–moesin
ESC	embryonic stem cell
ESRD	end-stage renal disease
ESRF	end-stage renal failure

FDA	Food and Drug Administration (USA)
FDC	fixed-dose combination
FDKP	fumaryldiketopiperazine
FFA	free fatty acid
FGF	fibroblast growth factor
FHWA	Federal Highways Administration
FMD	flow-mediated endothelium-dependent arterial dilation
FOXO	forkhead box O
FXR	farnesoid-X receptor
G6P	glucose-6-phosphatase
G-6-P	glucose-6-phosphate
G6PD	glucose-6-phosphate dehydrogenase
GAD	glutamine acid decarboxylase
GCGR	glucagon receptor
GCK	glucokinase
G-CSF	granulocyte colony-stimulating factor
GDF	growth differentiation factor
GDM	gestational diabetes mellitus
CF	cystic fibrosis
GI	gastrointestinal
GLO	glyoxalase
GLP-1RA	GLP-1 receptor agonist
GLUT	glucose transporter
GPR	G-protein-coupled receptor
GRPP	glicentin-related pancreatic polypeptide
GWA	genome-wide association
GWAS	genome-wide association studies
HAPO	Hyperglycemia and Adverse Pregnancy Outcomes
HbA_{1c}	hemoglobin A_{1c}
HBV	hepatitis B virus
HCV	hepatitis C virus
HDL	high-density lipoprotein
HGF	hepatocyte growth factor
hGH	human recombinant growth hormone
HHS	hyperosmolar non-ketotic hyperglycemic state
HR	hazard ratio
HRT	hormone replacement therapy
HRV	heart rate variability
HSC	hematopoietic stem cell
hsCRP	high-sensitivity C-reactive protein
IADPSG	International Association of Diabetes Pregnancy Study Groups
IAsp	insulin aspart
IAUC	incremental area under the blood glucose curve
ICA	islet cell antibody
ICU	intensive care unit
i.d.	intradermal
IDDM	insulin-dependent diabetes mellitus
IDeg	insulin degludec
IDF	International Diabetes Federation
IDL	intermediate-density lipoprotein
IDRS	Indian Diabetes Risk Score
IgG	immunoglobulin G
IGR	impaired glucose regulation
IGT	impaired glucose tolerance
IKKβ	inhibitor κB kinase-β
IL	interleukin
IMT	intima-media thickness
InsR	insulin receptor
IRMA	intraretinal microvascular abnormality
ISPAD	International Society for Pediatric and Adolescent Diabetes
IT	information technology
IVUS	intravascular ultrasound
IWGDF	International Working Group on the Diabetic Foot
JBDS	Joint British Diabetes Societies
KDIGO	Kidney Disease: Improving Global Outcomes
K_M	Michaelis constant
LADA	latent autoimmune diabetes in adults
LDL	low-density lipoprotein
LDL-C	low-density lipoprotein cholesterol
LDLR	low-density lipoprotein receptor
LGA	large-for-gestational age
LIRKO	liver-specific InsR knockout
LPS	lipopolysaccharide
Lst	limostatin
LV	left ventricular
LVEF	left ventricular ejection fraction
MAOI	monoamine oxidase inhibitor
MDI	multiple daily injection
MDRD	Modification of Diet in Renal Disease
MG53	mitsugumin 53
mGDP	mitochondrial glycerolphosphate dehydrogenase
MGO	methylglyoxal
MI	myocardial infarction
MIBG	*m*-iodobenzylguanidine
MIRKO	muscle-specific InsR knockout
MODY	maturity-onset diabetes of the young
MPGF	major proglucagon fragment
MPO	myeloperoxidase
MRI	magnetic resonance imaging
MSC	mesenchymal stem cell
MS	mass spectrometry
mTOR	mammalian or mechanistic target of rapamycin
mTORC1	mechanistic target of rapamycin complex 1
MTPI	microsomal transfer protein inhibitor
NAD	nicotinamide adenine dinucleotide
NaDIA	National Diabetes Inpatient Audit
NAFLD	non-alcoholic fatty liver disease
NANC	non-adrenergic, non-cholinergic
NCV	nerve conduction velocity
NEFA	non-esterified fatty acid

MFMU	Maternal–Fetal Medicine Units Network
NEP	neutral endopeptidase
NFκB	nuclear factor κB
Ngn3	neurogenin 3
NHANES	National Health and Nutrition Examination Survey
NHS	National Health Service
NICE	National Institute for Health and Care Excellence
NIDDM	non-insulin-dependent diabetes mellitus
NIH	National Institutes of Health
NMU	neuromedin U
Nox	NAD(P)H oxidase
NOD	non-obese diabetic
NPH	neutral protamine Hagedorn
NRTI	nucleoside reverse-transcriptase inhibitor
NSAID	non-steroidal anti-inflammatory drug
NT-3	neurotrophin-3
NT-proBNP	N-terminal pro-brain-type natriuretic peptide
OCP	oral contraceptive pill
OGIS	oral glucose insulin sensitivity
OGTT	oral glucose tolerance test(ing)
OR	odds ratio
oxLDL	oxidation of low-density lipoprotein
PAS	periodic acid–Schiff
PBA	phenylboronic acid
PC	prohormone convertase
PCB	polychlorinated biphenyl
PCI	percutaneous coronary intervention
PCR	polymerase chain reaction
PCSK-9	proprotein convertase subtilisin kexin type 9
PDH	pyruvate dehydrogenase
Pdx1	pancreatic duodenal homeobox 1
PGF	placental growth factor
PI	protease inhibitor
PI3K	phosphatidylinositol 3-kinase
PID	proportional integral derivative
P/KX	combined pancreas/kidney transplantation
PNDM	permanent neonatal diabetes mellitus
PPAR	peroxisome proliferator-activated receptor
PROactive	Prospective Pioglitazone Clinical Trial in Macrovascular Events
PTDM	post-transplantation diabetes mellitus
PTP1B	protein tyrosine phosphatase 1B
PYY	polypeptide YY
QoL	quality of life
RA	receptor agonist
RAMP	receptor activity-modifying protein
RCT	randomized controlled trial
RDN	renal denervation
RECORD	Rosiglitazone Evaluated for Cardiac Outcomes and Regulation of Glycemia in Diabetes
REMS	Risk Evaluation and Mitigation Strategy
rHuPH20	recombinant human hyaluronidase
RMR	resting metabolic rate
ROS	reactive oxygen species
RR	relative risk
RR	risk ratio
RT-PCR	reverse transcriptase polymerase chain reaction
SCFA	short-chain fatty acid
s.c.	subcutaneous
sdHDL	small, dense high-density lipoprotein
sdLDL	small, dense low-density lipoprotein
SDS-PAGE	sodium dodecyl sulfate polyacrylamide gel electrophoresis
SGA	second-generation antipsychotics
SHP	short heterodimer protein
SMBG	self-monitoring of blood glucose
SMI	severe mental illness
SNP	sub-basal nerve plexus
SSRI	selective serotonin reuptake inhibitor
T1DM	type 1 diabetes mellitus
T2DM	type 2 diabetes mellitus
TAG	triacylglyceride
TB	tuberculosis
TCF7L2	transcription factor 7 like 2
TE	transient elastography
TIND	treatment-induced neuropathy in diabetes
TLR	toll-like receptor
TNDM	transient neonatal diabetes mellitus
TNFα	tumor necrosis factor alpha
Treg	regulatory T cell
TSH	thyroid-stimulating hormone
TZD	thiazolidinedione
UKPDS	UK Prospective Diabetes Study
US	ultrasound
UT	University of Texas
VEGF	vascular endothelial growth factor
VLCD	very low calorie diet
VLDL	very low-density lipoprotein
VRIII	variable-rate intravenous insulin infusion
WGS	whole-genome sequencing
WHO	World Health Organization
XO	xanthine oxidase
YY1	Yin Yang 1

About the Companion Website and Companion Digital Edition

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1 Diabetes in its Historical and Social Context

1 The History of Diabetes Mellitus

Robert B. Tattersall[1]
University of Nottingham, Nottingham, UK

Key points

- Polyuric diseases have been described for over 3500 years. The name "diabetes" comes from the Greek word for a syphon; the sweet taste of diabetic urine was recognized at the beginning of the first millennium, but the adjective "mellitus" (honeyed) was only added by Rollo in the late 18th century.
- The sugar in diabetic urine was identified as glucose by Chevreul in 1815. In the 1840s, Bernard showed that glucose was normally present in blood, and showed that it was stored in the liver (as glycogen) for secretion into the bloodstream during fasting.
- In 1889, Minkowski and von Mering reported that pancreatectomy caused severe diabetes in the dog. In 1893, Laguesse suggested that the pancreatic "islets" described by Langerhans in 1869 produced an internal secretion that regulated glucose metabolism.
- Insulin was discovered in 1921 by Banting, Best, Macleod, and Collip in acid-ethanol extracts of pancreas. It was first used for treatment in January 1922.
- Diabetes was subdivided on clinical grounds into *diabète maigre* (lean subjects) and *diabète gras* (obese) by Lancereaux in 1880, and during the 1930s by Falta and Himsworth into insulin-sensitive and insulin-insensitive types. These classifications were the forerunners of the etiological classification into type 1 (insulin-dependent) and type 2 (non-insulin-dependent) diabetes.
- Insulin resistance and β-cell failure, the fundamental defects of type 2 diabetes, have been investigated by many researchers. The "insulin clamp" method devised by Andres and DeFronzo was the first accurate technique for measuring insulin action. Maturity-onset diabetes of the young was described as a distinct variant of type 2 diabetes by Tattersall in 1974.
- Lymphocytic infiltration of the islets (insulitis) was described as early as 1901 and highlighted in 1965 by Gepts who suggested that it might be a marker of autoimmunity. Islet cell antibodies were discovered by Doniach and Bottazzo in 1979.
- The primary sequence of insulin was reported in 1955 by Sanger and the three-dimensional structure by Hodgkin in 1969. Proinsulin was discovered by Steiner in 1967, and the sequence of the human insulin gene by Bell in 1980. Yalow and Berson invented the radioimmunoassay for insulin in 1956. The presence of insulin receptors was deduced in 1971 by Freychet, and the receptor protein was isolated in 1972 by Cuatrecasas.
- The various types of diabetic retinopathy were described in the second half of the 19th century as were the symptoms of neuropathy. Albuminuria was noted as a common abnormality in people with diabetes in the 19th century and a unique type of kidney disease was described in 1936 by Kimmelstiel and Wilson. The concept of a specific diabetic angiopathy was developed by Lundbæk in the early 1950s.
- Milestones in insulin pharmacology have included the invention of delayed-action preparations in the 1930s and 1940s; synthetic human insulin in 1979; and in the 1990s novel insulin analogs by recombinant DNA technology.
- The first sulfonylurea carbutamide was introduced in 1955, followed by tolbutamide in 1957 and chlorpropamide in 1960. The biguanide phenformin became available in 1959 and metformin in 1960.
- That improved glucose control in both type 1 and type 2 diabetes was beneficial was proved by the Diabetes Control and Complications Trial (1993) and the UK Prospective Diabetes Study (1998).
- Landmarks in the treatment of complications include photocoagulation for retinopathy first described by Meyer-Schwickerath; the importance of blood pressure control to slow the progression of nephropathy (demonstrated by Mogensen and Parving); the introduction of low-dose insulin in the treatment of diabetic ketoacidosis in the 1970s; and improvements in the care of pregnant women with diabetes pioneered by White and Pedersen.

[1] Prof. David R. Matthews has made small editorial changes to the text.

Textbook of Diabetes, Fifth Edition. Edited by R. Holt, C. Cockram, A. Flyvbjerg and B. Goldstein.

Ancient times

Diseases with the cardinal features of diabetes mellitus were recognized in antiquity (Table 1.1). A polyuric state was described in an Egyptian papyrus dating from *ca* 1550 BC, discovered by Georg Ebers (Figure 1.1), and a clearly recognizable description of what would now be called type 1 diabetes was given by Aretaeus of Cappadocia in the 2nd century AD (Figure 1.2a). Aretaeus was the first to use the term "diabetes," from the Greek word for a syphon, "because the fluid does not remain in the body, but uses the man's body as a channel whereby to leave it." His graphic account of the disease highlighted the incessant flow of urine, unquenchable thirst, the "melting down of the flesh and limbs into urine" and short survival.

Table 1.1 Milestones in the clinical descriptions of diabetes and its complications.

Clinical features of diabetes	
Ebers papyrus (Egypt, 1500 BC)	Polyuric state
Sushrut and Charak (India, 5th century BC)	Sugary urine; thin and obese patients distinguished
Aretaeus (Cappadocia, 2nd century AD)	Polyuric state named "diabetes"
Chen Chuan (China, 7th century)	Sugary urine
Avicenna (Arabia, 10th century AD)	Sugary urine; gangrene and impotence as complications
Diabetic ketoacidosis	
William Prout (England, 1810–1820)	Diabetic coma
Adolf Kussmaul (Germany, 1874)	Acidotic breathing
Hyperlipidemia	
Albert Heyl (Philadelphia, 1880)	Lipemia retinalis
Retinopathy	
Eduard von Jaeger (Germany, 1855)	General features
Stephen Mackenzie and Edward Nettleship (England, 1879)	Microaneurysms
Edward Nettleship (England, 1888)	New vessels, beading of retinal veins
Julius Hirschberg (Germany, 1890)	Classification of lesions; specific to diabetes
Neuropathy and foot disease	
John Rollo (England, 1797)	Neuropathic symptoms
Marchal de Calvi (France, 1864)	Neuropathy is a complication of diabetes
William Ogle (England, 1866)	Ocular nerve palsies in diabetes
Frederick Pavy (England, 1885)	Peripheral neuropathy
Julius Althaus (Germany, 1890)	Mononeuropathy
Thomas Davies Pryce (England, 1887)	Perforating foot ulcers
Nephropathy	
Wilhelm Griesinger (Germany, 1859)	Renal disease in people with diabetes
Paul Kimmelstiel and Clifford Wilson (USA, 1936)	Glomerulosclerosis associated with heavy proteinuria

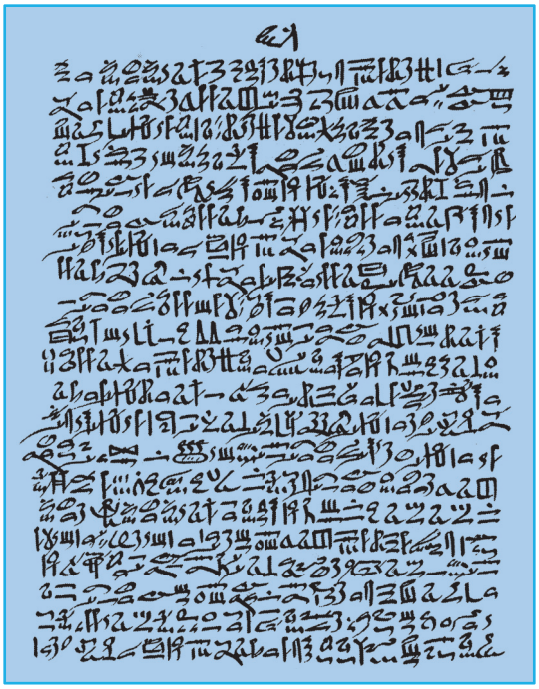


Figure 1.1 The Ebers papyrus. Source: Courtesy of the Wellcome Library, London.

The Hindu physicians, Charak and Sushrut, who wrote between 400 and 500 BC, were probably the first to recognize the sweetness of diabetic urine (Figure 1.2b). Indeed, the diagnosis was made by tasting the urine or noting that ants congregated round it. Charak and Sushrut noted that the disease was most prevalent in those who were indolent, overweight, and gluttonous, and who indulged in sweet and fatty foods. Physical exercise and liberal quantities of vegetables were the mainstays of treatment in the obese, while lean people, in whom the disease was regarded as more serious, were given a nourishing diet. The crucial fact that diabetic urine tasted sweet was also emphasized by Arabic medical texts from the 9–11th centuries AD, notably in the medical encyclopedia written by Avicenna (980–1037).

The 17th and 18th centuries

In Europe, diabetes was neglected until Thomas Willis (1621–1675) wrote *Diabetes, or the Pissing Evil* [1]. According to him, "diabetes was a disease so rare among the ancients that many famous physicians made no mention of it … but in our age, given to good fellowship and guzzling down of unallayed wine, we meet with examples and instances enough, I may say daily, of this disease." He described the urine as being "wonderfully sweet like sugar or honey" but did not consider that this might be because it contained sugar.

The first description of hyperglycemia was in a paper published in 1776 by Matthew Dobson (1735–1784) of Liverpool (Figure 1.3 and Table 1.2) [2]. He found that the serum as well as the urine of his patient Peter Dickonson (who passed 28 pints of urine a day) tasted sweet. Moreover, he evaporated the urine

(a)

Diabetes is a dreadful affliction, not very frequent among men, being a melting down of the flesh and limbs into urine. The patients never stop making water and the flow is incessant, like the opening of aqueducts. Life is short, unpleasant and painful, thirst unquenchable, drinking excessive, and disproportionate to the large quantity of urine, for yet more urine is passed. One cannot stop them either from drinking or making water. If for a while they abstain from drinking, their mouths become parched and their bodies dry; the viscera seem scorched up, the patients are affected by nausea, restlessness and a burning thirst, and within a short time, they expire.

(b)

Figure 1.2 (a) Clinical description of diabetes by Aretaeus of Cappadocia (2nd century AD). Adapted from Papaspyros NS (1952) *The History of Diabetes Mellitus*. (b) Sushrut (Susrata), an Indian physician who wrote medical texts with Charak (Charuka) between 500 BC and 400 BC.

MEDICAL

OBSERVATIONS

AND

INQUIRIES.

BY

A SOCIETY OF PHYSICIANS IN LONDON.

VOLUME V.

LONDON:
Printed for T. CADELL, in the Strand.
MDCCLXXVI.

XXVII. *Experiments and Obſervations on the Urine in a* Diabetes, *by* Matthew Dobſon, *M. D. of* Liverpool; *communicated by Dr.* Fothergill.

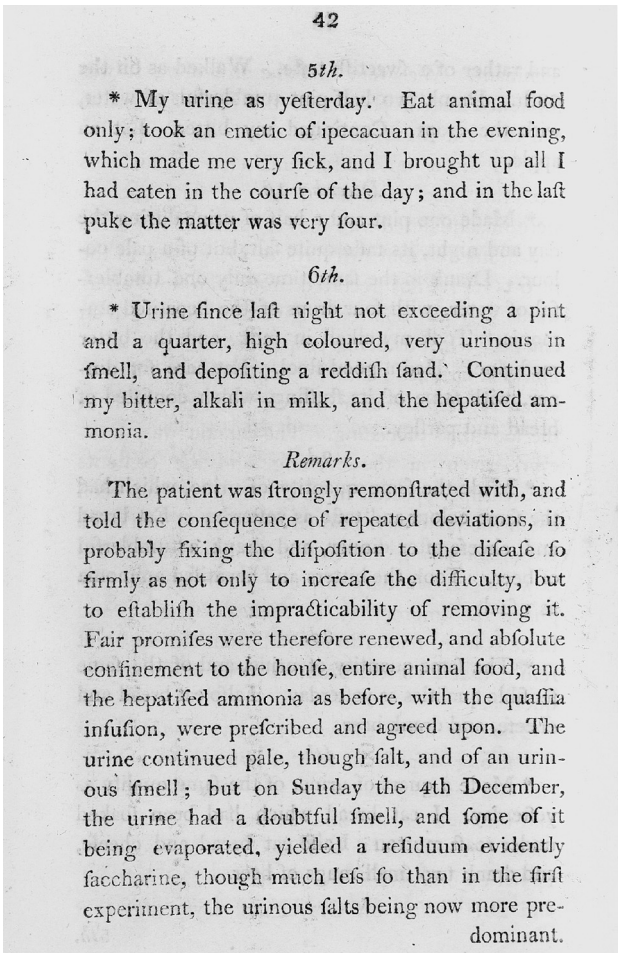
SOME authors, eſpecially the Engliſh, have remarked, that the urine in the diabetes is ſweet. Others, on the contrary, deny the exiſtence of this quality, and conſequently exclude it from being a characteriſtic of the diſeaſe. So far as my own experience has extended, and I have met with nine perſons who were afflicted with the diabetes, the urine has always been ſweet in a greater or leſs degree, and particularly ſo in the caſe of the following patient.

Peter Dickonſon, thirty-three years of age, was admitted into the public hoſpital in Liverpool, October 22, 1772. His diſeaſe was a confirmed diabetes; and he paſſed twenty-eight pints of urine every 24 hours. He had formerly enjoyed a good ſtate of health; nor did it appear what had been the remote cauſes of this indiſpo-

Figure 1.3 Frontispiece and opening page of the paper by Matthew Dobson (1776), in which he described the sweet taste of both urine and serum from a person with diabetes [2].

to "a white cake [which] smelled sweet like brown sugar, neither could it by the taste be distinguished from sugar." Dobson concluded that the kidneys excreted sugar and that it was not "formed in the secretory organ but previously existed in the serum of the blood."

The Edinburgh-trained surgeon, John Rollo (*d.* 1809) was the first to apply the adjective "mellitus" (from the Latin word meaning "honey"). He also achieved fame with his "animal diet," which became the standard treatment for most of the 19th century. Rollo thought that sugar was formed in the stomach from vegetables, and concluded that the obvious solution was a diet of animal food. Thus, the regimen described in his 1797 book, *An Account of Two Cases of the Diabetes Mellitus* [3], allowed his patient Captain Meredith to have for dinner "Game or old meats which have been long kept; and as far as the stomach may bear, fat and rancid old meats, as pork." Rollo was probably the first to note the difficulty that some people with diabetes find in adhering to treatment—a difficulty he blamed for the death of his second patient (Figure 1.4).



42

5*th*.

* My urine as yeſterday. Eat animal food only; took an emetic of ipecacuan in the evening, which made me very ſick, and I brought up all I had eaten in the courſe of the day; and in the laſt puke the matter was very ſour.

6*th*.

* Urine ſince laſt night not exceeding a pint and a quarter, high coloured, very urinous in ſmell, and depoſiting a reddiſh ſand. Continued my bitter, alkali in milk, and the hepatiſed ammonia.

Remarks.

The patient was ſtrongly remonſtrated with, and told the conſequence of repeated deviations, in probably fixing the diſpoſition to the diſeaſe ſo firmly as not only to increaſe the difficulty, but to eſtabliſh the impracticability of removing it. Fair promiſes were therefore renewed, and abſolute confinement to the houſe, entire animal food, and the hepatiſed ammonia as before, with the quaſſia infuſion, were preſcribed and agreed upon. The urine continued pale, though ſalt, and of an urinous ſmell; but on Sunday the 4th December, the urine had a doubtful ſmell, and ſome of it being evaporated, yielded a reſiduum evidently ſaccharine, though much leſs ſo than in the firſt experiment, the urinous ſalts being now more predominant.

Figure 1.4 Extract from John Rollo's account of two cases of diabetes (1797). Rollo was well aware of the problem of non-adherence. Note that "the patient was strongly remonstrated with, and told of the consequences of repeated deviations." Source: Courtesy of the Wellcome Library, London.

The 19th century

In 1815, the French chemist Michel Chevreul (1786–1889) proved that the sugar in diabetic urine was glucose [4]. In the middle of the century, tasting the urine to make the diagnosis was superseded by chemical tests for reducing agents such as glucose as introduced by Trommer in 1841, Moore in 1844 and—the best known—Fehling in 1848. Measurement of blood glucose could only be done by skilled chemists but needed so much blood that it was rarely used in either clinical care or research. It only became practicable with the introduction in 1913 of a micromethod by the Norwegian-born physician Ivar Christian Bang (1869–1918) and it was the ability to measure glucose repeatedly which led to development of the glucose tolerance test between 1913 and 1915.

Glucose metabolism was clarified by the work of Claude Bernard (1813–1878) [5], the Frenchman whose numerous discoveries have given him a special place in the history of physiology (Figure 1.5). When Bernard began work in 1843, the prevailing theory was that sugar could only be synthesized by plants, and that animal metabolism broke down substances originally made in plants. It was also thought that the blood only

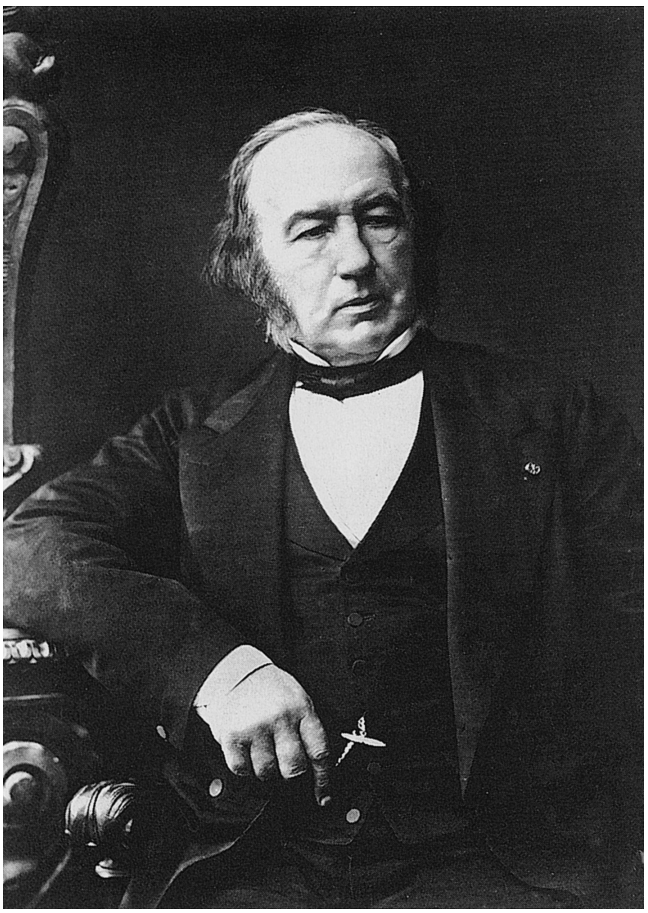


Figure 1.5 Claude Bernard (1813–1878). Source: Courtesy of the Wellcome Library, London.

contained sugar after meals, or in pathologic states such as diabetes. Between 1846 and 1848, Bernard reported that glucose was present in the blood of normal animals, even when starved. He also found higher concentrations of glucose in the hepatic than in the portal vein, and "enormous quantities" of a starch-like substance in the liver which could be readily converted into sugar. He called this "glycogen" (i.e. sugar-forming) and regarded it as analogous to starch in plants. His hypothesis—the "glycogenic" theory—was that sugar absorbed from the intestine was converted in the liver into glycogen and then constantly released into the blood during fasting.

Another discovery by Bernard made a great impression in an era when the nervous control of bodily functions was a scientifically fashionable concept. He found that a lesion in the floor of the fourth ventricle produced temporary hyperglycemia (*piqûre* diabetes) [6]. This finding spawned a long period in which nervous influences were thought to be important causes of diabetes; indeed, one piece of "evidence"—cited by J.J.R. Macleod as late as 1914—was that diabetes was more common among engine drivers than other railway workers because of the mental strain involved [7].

In the first part of the 19th century the cause of diabetes was a mystery, because autopsy usually did not show any specific lesions. A breakthrough came in 1889 when Oskar Minkowski (Figure 1.6) and Josef von Mering (1849–1908) reported that pancreatectomy in the dog caused severe diabetes [8]. This was serendipitous, because they were investigating fat metabolism; it is said that the laboratory technician mentioned to Minkowski that the dog, previously house-trained, was now incontinent of urine. Minkowski realized the significance of the polyuria, and tested the dog's urine (Table 1.3).

Possible explanations for the role of the pancreas were that it removed a diabetogenic toxin, or produced an internal secretion that controlled carbohydrate metabolism. The concept of "internal secretions" had been publicized in June 1889, by the well-known physiologist Charles-Édouard Brown-Séquard (1817–1894), who claimed to have rejuvenated himself by injections of testicular extract [9]. It was given further credence in 1891, when Murray reported that myxedema could be cured by sheep thyroid extract by injection or orally.

In 1893, Gustave Laguesse suggested that the putative internal secretion of the pancreas was produced by the "islands" of cells scattered through the gland's parenchyma [10], which had been discovered in 1869 by the 22-year-old Paul Langerhans (1847–1888) (Figure 1.7). Langerhans had described these clusters of cells, having teased them out from the general pancreatic tissue, but had not speculated about their possible function [11]; it was Laguesse who named them the "islets of Langerhans." At this time, the glucose-lowering internal secretion of the islets was still hypothetical, but in 1909 the Belgian Jean de Meyer named it *insuline* (from the Latin for "island") [12].

It would be wrong to give the impression that Minkowski's experiments immediately established the pancreatic origin of diabetes. In fact, during the next two decades, it was widely agreed that diabetes was a heterogeneous disorder with various subtypes,

Figure 1.6 Oskar Minkowski (1858–1931).

Figure 1.7 Paul Langerhans (1847–1888). Source: Courtesy of the Wellcome Library, London.

and that its pathogenesis involved at least three organs: the brain, pancreas, and liver [13]. The discovery by Blum in 1901 that injection of an adrenal extract caused glycosuria implicated other glands, and led to the "polyglandular theory" of Carl von Noorden (Vienna), who proposed that the thyroid, pancreas, adrenals, and parathyroids controlled carbohydrate metabolism.

Clinical diabetes in the 19th century

Doctors in the 19th century were therapeutically impotent; their main role was as taxonomists who described symptom complexes and the natural history of disease. As a result, most of the major complications of diabetes were well described before 1900.

Eduard von Jaeger (1818–1884) is credited with the first description of diabetic retinopathy, in his beautiful *Atlas of Diseases of the Ocular Fundus*, published in 1869 [14]. In fact, the features illustrated (Figure 1.8), from a 22-year-old man, look more like hypertensive retinopathy. In 1879, Stephen Mackenzie (1844–1909) and Sir Edward Nettleship (1845–1913) found microaneurysms in flat preparations of the retina and, in 1888, Nettleship described new vessels and the beaded appearance of retinal veins [15]. The full picture of diabetic retinopathy was described in 1890 by Julius Hirschberg (1843–1925) who was the first to claim that it was specific to diabetes [16].

Neuropathic symptoms in people with diabetes had been mentioned by Rollo at the end of the 18th century, and in 1864 Charles Marchal de Calvi (1815–1873) concluded that nerve damage was a specific complication of diabetes. In 1885, the Guy's Hospital physician, Frederick Pavy (1829–1911), gave a description of neuropathic symptoms which would grace any modern textbook [17]:

> *The usual account given by these patients of their condition is that they cannot feel properly in their legs, that their feet are numb, that*

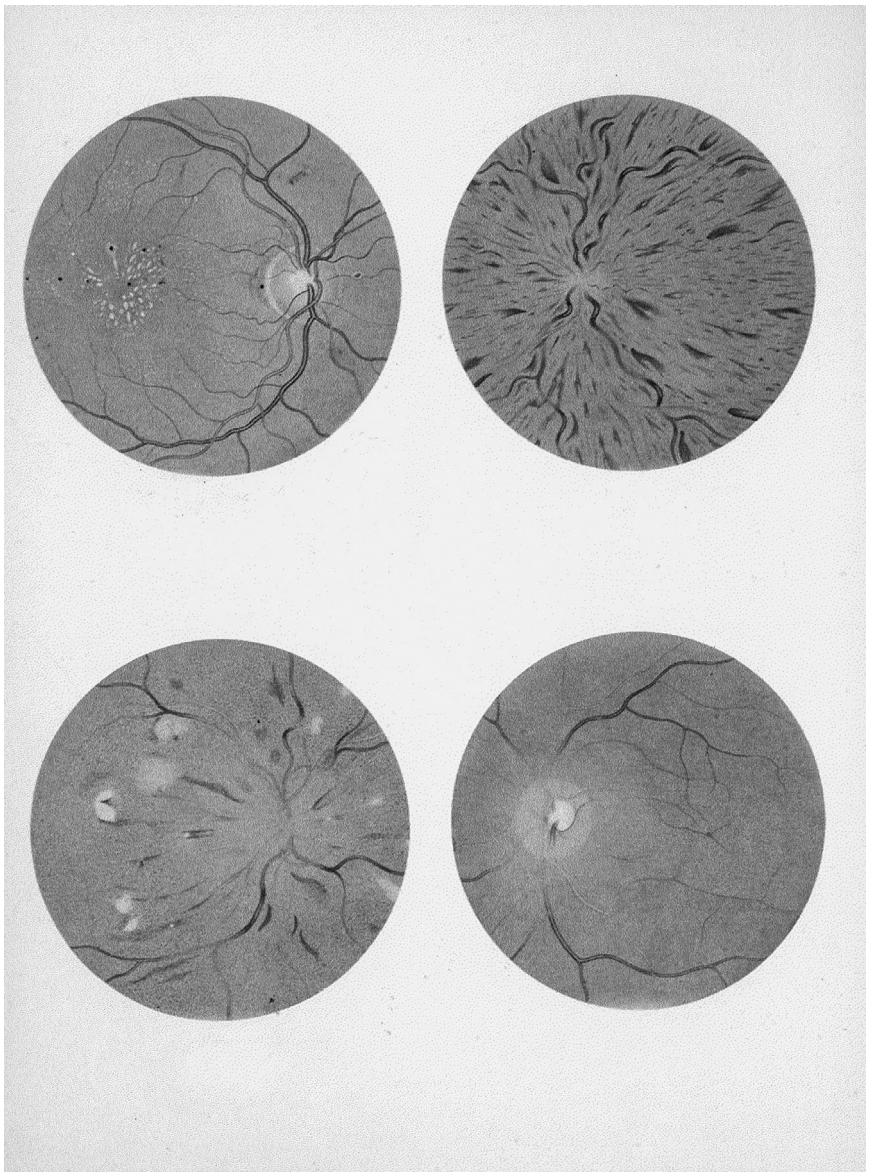


Figure 1.8 Pictures from *Jaeger's Atlas of the Optic Fundus*, 1869 [14]. Top left: Bright's disease. Top right: Jaeger's retinitis hemorrhagica is now recognized as central retinal vein occlusion. Bottom left: A 22-year-old man with suspected diabetes. Bottom right: Central retinal artery occlusion. Source: Courtesy of W.B. Saunders.

their legs seem too heavy—as one patient expressed it, "as if he had 20 lb weights on his legs and a feeling as if his boots were great deal too large for his feet." Darting or "lightning" pains are often complained of. Or there may be hyperaesthesia, so that a mere pinching of the skin gives rise to great pain; or it may be the patient is unable to bear the contact of the seam of the dress against the skin on account of the suffering it causes. Not infrequently there is deep-seated pain located, as the patient describes it, in the marrow of the bones which are tender on being grasped, and I have noticed that these pains are generally worse at night.

Pavy also recorded unusual presentations, including a 67-year-old who complained of "lightning pains on the right side of the waist" and cases in which the third nerve was affected with "dropped lid and external squint" [18].

Kidney disease was known to be relatively common in diabetes. In 1859, Wilhelm Griesinger (1817–1868) reported 64 autopsies in adults, half of whom had renal changes which he attributed to hypertension and atherosclerosis [19]; however, the histologic features of diabetic kidney disease and the importance of renal complications were not reported until the 1930s.

In the latter part of the 19th century it was becoming apparent that there were at least two clinically distinct forms of diabetes. In 1880, the French physician Etienne Lancereaux (1829–1910) identified lean and obese patients as having *diabète maigre* and *diabète gras* [20], and this observation laid the foundations for subsequent etiologic classifications of the disease.

The 20th century

Murray's cure of myxedema in 1891 led to a belief that pancreatic extract would soon result in a cure for diabetes, but, in the face of repeated failures over the next 30 years, even believers in an antidiabetes internal secretion were depressed about the likelihood of isolating it, and diverted their attention to diet as a treatment for the disease.

Best known was the starvation regimen of Frederick Madison Allen (1876–1964), which Joslin (Figure 1.9) described in 1915 as the greatest advance since Rollo's time [21]. This approach was an extreme application of one that had been proposed as early as 1875 by Apollinaire Bouchardat (1806–1886), who

(a)

(b)

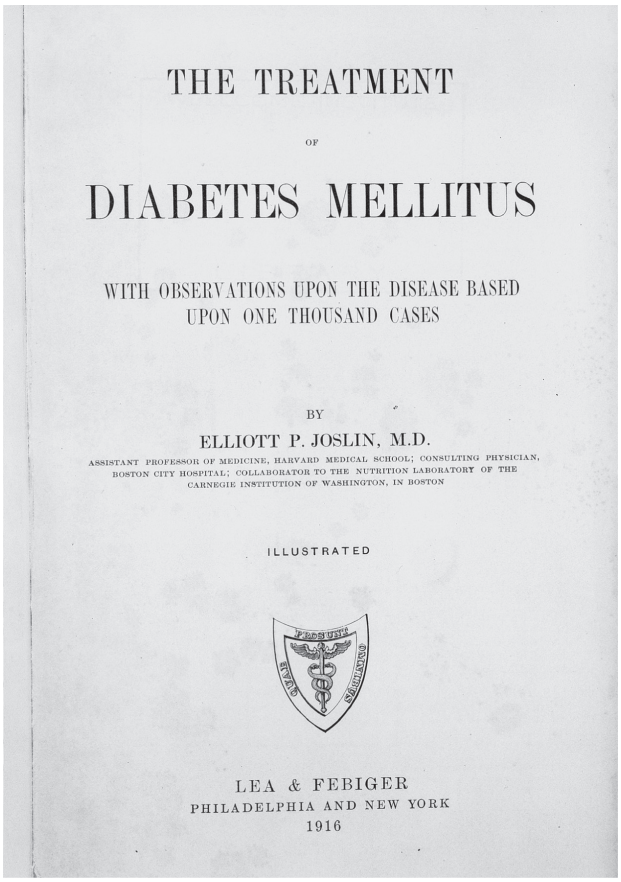


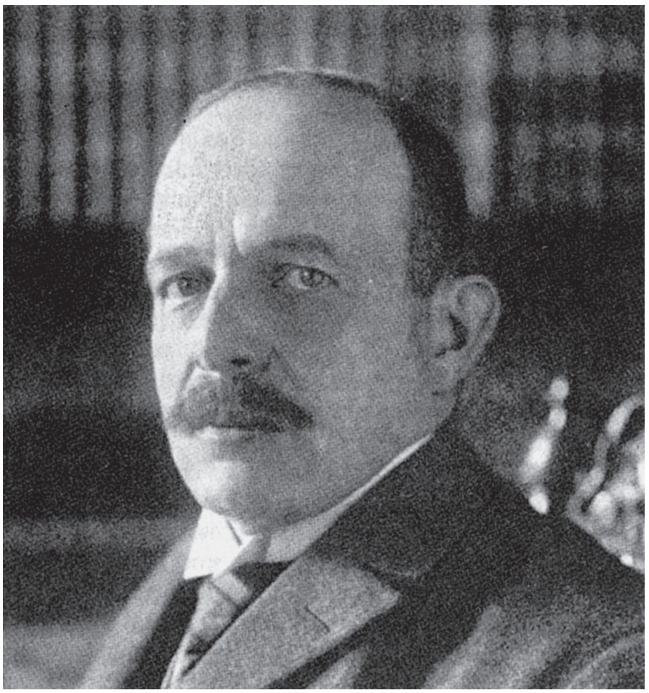
Figure 1.9 Elliott P. Joslin (1869–1962), arguably the most famous diabetes specialist of the 20th century and the frontispiece to his 1916 textbook [22]. Source: Courtesy of the Wellcome Library, London.

advocated intensive exercise and "*manger le moins possible*." Starvation treatment did work in a limited sense, in that some people could survive for many months or even years, instead of a few weeks or months with untreated type 1 diabetes. The quality of life, however, was very poor, and some died of malnutrition rather than diabetes. In 1921, Carl von Noorden (1858–1944)—proponent of the "oatmeal cure"—turned away in disapproval when he saw Joslin's prize patient, 17-year-old Ruth A, who at just over 1.52 m in height weighed only 24.5 kg (a body mass index of 10.6 kg/m^2).

Discovery of insulin

Many attempts were made between 1889 and 1921 to isolate the elusive internal secretion of the pancreas. These largely failed

(a)



(b)

Experimentelle Untersuchungen über den Diabetes.[1])

Kurze Mitteilung.[2])

Von

G. Zuelzer.

F. Blum hat vor einigen Jahren gezeigt, dass subkutane oder intravenöse Injektion von Nebennierensaft bei den verschiedensten Tieren Glykosurie hervorruft, die 48 bis 74 Stunden anhalten kann. Ich, und kurze Zeit darauf Metzger wiesen nach, dass gleichzeitig eine Hyperglykämie besteht, dass es sich beim Nebennierendiabetes also nicht etwa um ein Analogon des Phloridzindiabetes, um einen sogenannten Nierendiabetes handeln könne. Während ich mich dahin aussprach, dass dieser Diabetes seiner ganzen Natur nach dem richtigen Diabetes ähnele, nur durch die Dauer seines Bestehens von ihm unterschieden sei und naturgemäss auch keine Tendenz zum Fortschreiten zeigen, i. e. niemals das Endstadium des gewöhnlichen schweren menschlichen Diabetes darbieten könne, wurde die in Frage stehende Glykosurie von den meisten anderen Autoren als eine ziemlich belanglose toxische Glykosurie aufgefasst.

Es schien mir nicht sehr wahrscheinlich, dass ein Körper, der anscheinend unverändert, wie er normalerweise produziert und dauernd[3]) dem Säftestrom des Organismus zugeführt wird, dass ein solcher, quasi physiologischer Körper eine vollkommen unphysiologische Wirkung sollte hervorbringen können. Ich habe also versucht, den Ort des Angriffs des Nebennierensaftes[4]), sowie die Ursachen seiner toxischen Wirkung näher zu erforschen. Ich folgte dabei, wie gesagt, stets dem Gedanken, in dem Nebennierendiabetes ein, wenn auch nur flüchtiges Bild gewisser menschlicher Diabetesformen zu finden.

So untersuchte ich zuerst, welchen Einfluss hat der Nebennierensaft auf die Leber als dasjenige Organ, welches, allgemein ansgedrückt, mit der Zuckerregulierung im Körper in erster

1) Die Untersuchungen wurden zum Teil mit Unterstützung der Gräfin Bose-Stiftung im physiologischen Institut der Berliner Universität, und zwar noch unter Mithilfe der verstorbenen Proff. I. Munk und Paul Schultz ausgeführt.

2) Diese kurze Mitteilung wurde der Redaktion bereits vor ca. 3 Jahren eingereicht. Die Drucklegung unterblieb auf Wunsch des Verf. in der bisher nicht erfüllten Erwartung, dass es gelingen würde, aus den theoretischen Untersuchungen praktisch-therapeutische Resultate zu erzielen.

3) Durch Versuche von Ehrmann, Archiv f. experim. Pathol. u. Pharmakol., Bd. 55, ist inzwischen der Nachweis erbracht worden, dass die Adrenalinsekretion konstant vor sich geht.

4) In meinen ersten Versuchen bediente ich mich des von mir selbst hergestellten Nebennierensaftes. In den zahlreichen späteren Versuchen habe ich inzwischen genau die gleichen Wirkungen mit den verschiedenartig hergestellten käuflichen Adrenalinpräparaten feststellen können.

(c)

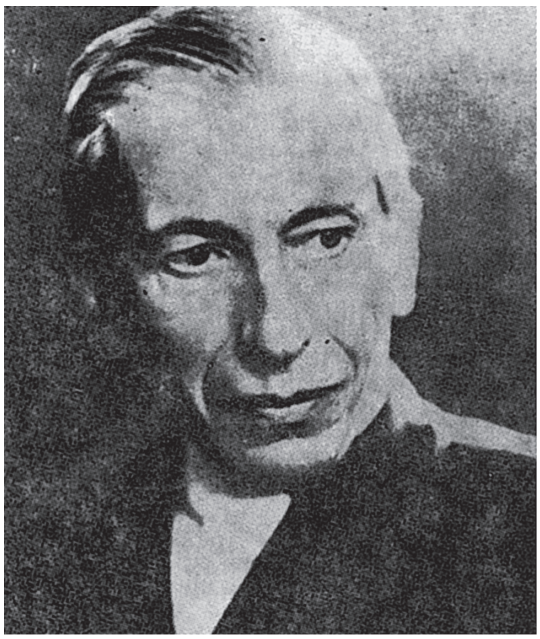


Figure 1.10 (a) Georg Zuelzer (1840–1949) and (b) the title page from his paper (1907) reporting that a pancreatic extract reduced glycosuria in pancreatectomized dogs [23] (top). (c) Nicolas Paulesco (1869–1931).

Figure 1.11 The discoverers of insulin. Clockwise from top left: Frederick G. Banting (1891–1941); James B. Collip (1892–1965); J.J.R. Macleod (1876–1935); and Charles H. Best (1899–1978). Source: Courtesy of the Fisher Rare Book Library, University of Toronto.

because the extracts were inactive or had unacceptable side effects; some preparations may have had limited biologic activity, but this was not recognized, either because hypoglycemia was misinterpreted as a toxic reaction or because blood glucose was not measured. Those who came closest were the Berlin physician, Georg Zuelzer (1840–1949) in 1907 [23], Ernest Scott (1877–1966) in Chicago in 1911 [24], and Nicolas Paulesco (1869–1931) in Romania in 1920–1921 [25] (Figure 1.10).

The story of how insulin was discovered in Toronto in 1921 is well known, at least superficially (Figure 1.11). A young orthopedic surgeon, Frederick Banting, inspired after reading an article by the pathologist Moses Barron (1884–1975), wondered whether the antidiabetes pancreatic principle was digested by trypsin during extraction, and decided to prevent this loss by ligating the pancreatic duct, thus causing the exocrine tissue to degenerate. He approached the Professor of Physiology in Toronto, J.J.R. Macleod, an authority on carbohydrate metabolism, who poured scorn on the idea and suggested that the only likely outcome would be "a negative result of great physiological importance."

Eventually, Macleod relented and installed Banting in a rundown laboratory, later leaving for Scotland and a fishing holiday. A student, Charles Best, was chosen by the toss of a coin to help Banting. Within 6 months of this unpromising start, Banting and Best (referred to in Toronto academic circles as B^2) had discovered the most important new therapy since the antisyphilitic agent Salvarsan. These events are described in detail in the excellent book by Michael Bliss [26].

Their approach began with the injection of extracts of atrophied pancreas (prepared according to Macleod's suggestions) into dogs rendered diabetic by pancreatectomy. Subsequently, they discovered that active extracts could be obtained from beef pancreas which Best obtained from the abattoir. The extraction procedure (using ice-cold acid-ethanol) was greatly refined by James B. (Bert) Collip, a biochemist who was visiting Toronto on sabbatical leave.

The first clinical trial of insulin (using an extract made by Best) took place on January 11, 1922, on 14-year-old Leonard Thompson, who had been on the Allen starvation regimen since 1919 and weighed only 30 kg (Figure 1.12). After the first injection, his blood glucose level fell slightly, but his symptoms were unchanged and he developed a sterile abscess. On January 23, he was given another extract prepared by Collip, and this normalized his blood glucose by the next morning; further injections over the next 10 days led to marked clinical improvement and complete elimination of glycosuria and ketonuria. Initial clinical results in seven cases were published in the March 1922 issue of the *Canadian*

Figure 1.12 Leonard Thompson, the first person to receive insulin, in January 1922. Source: Courtesy of the Fisher Rare Book Library, University of Toronto.

Medical Association Journal [27], which concluded dramatically that:

1 Blood sugar can be markedly reduced, even to normal values;
2 Glycosuria can be abolished;
3 The acetone bodies can be made to disappear from the urine;
4 The respiratory quotient shows evidence of increased utilization of carbohydrates;
5 A definite improvement is observed in the general condition of these patients and, in addition, the patients themselves report a subjective sense of well-being and increased vigor for a period following the administration of these preparations.

The term "insulin" was coined by Macleod, who was unaware of de Meyer's earlier suggestion of *insuline*. News of its miraculous effects spread astonishingly rapidly [28]. In 1922, there were only 19 references in the world literature to "insulin" or equivalent terms such as "pancreatic extract"; by the end of 1923, there were 320 new reports, and a further 317 were published during the first 6 months of 1924.

By October 1923, insulin was available widely throughout North America and Europe. International recognition followed rapidly for its discoverers, and the 1923 Nobel Prize for Physiology or Medicine was awarded jointly to Banting and Macleod. Banting was angered by the decision, and announced publicly that he would share his prize with Best, whereupon Macleod decided to do the same with Collip.

The postinsulin era

It was confidently anticipated that insulin would do for diabetes in the young what thyroid extract had done for myxedema, but it soon became obvious that insulin was a very different type of treatment. Thyroid was given once a day by mouth and at a fixed dosage. Insulin had to be injected in measured amounts which varied from day to day, and carried the ever-present danger of hypoglycemia. One often reads that insulin "revolutionized" the treatment of diabetes; it did so in the sense that it saved the lives of many who would otherwise have died, but its unforeseen effect was to transform an acute, rapidly fatal illness into a chronic disease with serious long-term complications. For example, only 2% of deaths among Joslin's young patients with diabetes before 1937 were caused by kidney disease, while over 50% dying between 1944 and 1950 had advanced renal failure. Strategies to avoid and prevent the chronic complications of diabetes remain important scientific and clinical priorities today.

The rest of this chapter highlights some developments that can be regarded as landmarks in the understanding and management of the disease: to some extent, this is a personal choice, and it is obvious from the other chapters in this book that the "history" of diabetes is being rewritten all the time.

Causes and natural history of diabetes

The recognition that diabetes was not a single disease was important in initiating research that has helped to unravel the causes of hyperglycemia.

The broad etiologic subdivision into type 1 (juvenile-onset, or insulin-dependent) and type 2 diabetes (maturity-onset, or non-insulin-dependent) stemmed ultimately from Lancereaux's *diabète maigre* and *diabète gras* distinction, as well as observations soon after the discovery of insulin that some individuals did not react "normally" to insulin. In the 1930s, Wilhelm Falta (1875–1950) in Vienna [29] and Harold Himsworth (1905–1993) in London [30] proposed that some individuals with diabetes were more sensitive to the glucose-lowering effects of insulin, whereas others were insulin-insensitive, or insulin-resistant. The former were usually thin and required insulin to prevent ketoacidosis, while the latter were older, obese, and ketosis-resistant.

The "insulin clamp" technique developed in the 1970s by Ralph DeFronzo *et al.* [31] in the USA was the first to measure rigorously the hypoglycemic action of insulin, and has led to countless studies of insulin resistance and its relationship to type 2 diabetes and vascular disease. Various groups, including DeFronzo's, have helped to clarify the role of β-cell failure in type 2 diabetes, and how it relates to insulin resistance. Maturity-onset diabetes of the young (MODY) was recognized in 1974 by Robert Tattersall (*b.* 1943) as a distinct, dominantly inherited subset of type 2 diabetes [32]; since 1993 a variety of different molecular defects have been identified in this condition.

The causes of the profound β-cell loss that led to the severe insulin deficiency of type 1 diabetes remained a mystery for a long time. "Insulitis", predominantly lymphocytic infiltration of the islets, was noted as early as 1901 by Eugene L. Opie (1873–1971) and colleagues [33], but because it was apparently very rare,

found in only six of 189 cases studied by Anton Weichselbaum (1845–1920) in 1910, its importance was not appreciated. The possible role of insulitis in β-cell destruction was not suggested until 1965, by the Belgian Willy Gepts (1922–1991) [34]. The theory that type 1 diabetes results from autoimmune destruction of the β cells was first made in 1979 by Deborah Doniach (1912–2004) and GianFranco Bottazzo (*b.* 1946) [35]. Unlike other autoimmune endocrine diseases where the autoantibody persists, islet cell antibodies turned out to be transient and disappeared within a year of the onset of diabetes. An unexpected finding from the Barts–Windsor prospective study of the epidemiology of diabetes in childhood started by Andrew Cudworth (1939–1982) was that islet cell antibodies could be detected in siblings of young people with diabetes up to 10 years before they developed apparently acute-onset diabetes. This long lead-in period raised the possibility of an intervention to prevent continuing β-cell destruction. Cyclosporine in people with newly diagnosed type 1 diabetes prolonged the honeymoon period but without permanent benefit once the drug was stopped [36]. Nicotinamide and small doses of insulin (together with many other interventions) prevented diabetes in the non-obese diabetic (NOD) mouse but were without effect in relatives of people with type 1 diabetes with high titers of islet cell antibodies [37,38].

From 1967, when Paul Lacy (1924–2005) showed that it was possible to "cure" diabetes in inbred rats with an islet cell transplant, it always seemed that the problem of islet cell transplantation in humans was about to be solved. Hope was rekindled in 2000 by a team in Edmonton, Canada. After 5 years 80% of those who had received a transplant were producing some endogenous insulin but only 10% could manage without any injected insulin [39].

Chronic diabetic complications

It had been assumed that arteriosclerosis caused chronic diabetic complications, but this notion was challenged by two papers published in the mid-1930s, which pointed to specific associations of diabetes with retinal and renal disease (Table 1.2). In 1934, Henry Wagener (1890–1961) and Russell Wilder (1885–1959) from the Mayo Clinic reported people who had retinal hemorrhages but no other clinical evidence of vascular disease [40], and concluded that "The very existence of retinitis in cases in which patients have no other signs of vascular disease must mean that diabetes alone does something to injure the finer arterioles or venules of the retina, probably the latter."

In 1936, Paul Kimmelstiel (1900–1970) and Clifford Wilson (1906–1997) described the striking histologic finding of "intercapillary glomerulosclerosis"—large hyaline nodules in the glomeruli—in the kidneys of eight people at autopsy (Figure 1.13) [41]. Seven of the eight individuals had a known history of diabetes, and Kimmelstiel and Wilson noted the common features of hypertension, heavy albuminuria with "edema of the nephrotic type," and renal failure. In fact, this paper led to considerable confusion during the next 15 years: according to one writer, the "Kimmelstiel–Wilson syndrome" came to mean all things to all men [42]. Nonetheless, it was significant because it drew attention to a specific diabetic renal disease.

Table 1.2 Milestones in the scientific understanding of diabetes and its complications.

Matthew Dobson (England, 1776)	Diabetic serum contains sugar
Michel Chevreul (France, 1815)	The sugar in diabetic urine is glucose
Claude Bernard (France, 1850s)	Glucose stored in liver glycogen and secreted during fasting
Wilhelm Petters (Germany, 1857)	Diabetic urine contains acetone
Paul Langerhans (Germany, 1869)	Pancreatic islets described
Adolf Kussmaul (Germany, 1874)	Describes ketoacidosis
Oskar Minkowski and Josef von Mering (Germany, 1889)	Pancreatectomy causes diabetes in the dog
Gustave Edouard Laguesse (France, 1893)	Glucose-lowering pancreatic secretion produced by islets
M.A. Lane (USA, 1907)	Distinguished A and B islet cells
Jean de Meyer (Belgium, 1909)	Hypothetical islet secretion named "*insuline*"
Frederick Banting, Charles Best, J.J.R. Macleod, James Collip (Canada, 1922)	Isolation of insulin
Richard Murlin (USA, 1923)	Discovered and named glucagon
Bernado Houssay (Argentina, 1924)	Hypophysectomy enhances insulin sensitivity
Frederick Sanger (England, 1955)	Determined primary sequence of insulin
W.W. Bromer (USA, 1956)	Determined primary sequence of glucagon
Rosalyn Yalow and Solomon Berson (USA, 1959)	Discovered radioimmunoassay for insulin
Donald Steiner (USA, 1967)	Discovered proinsulin
Dorothy Hodgkin (England, 1969)	Determined three-dimensional structure of insulin
Pierre Freychet (USA, 1971)	Characterized insulin receptors
Pedro Cuatrecasas (USA, 1972)	Isolated insulin receptor protein
Axel Ullrich (USA, 1977)	Reported sequence of rat insulin
Ralph DeFronzo and Reuben Andres (USA, 1979)	Invented insulin clamp technique
Graham Bell (USA, 1980)	Reported sequence of human insulin gene

Acceptance of the concept that diabetic angiopathy was specific to the disease owed much to the work of Knud Lundbæk of Aarhus in Denmark (Figure 1.14), who published his findings in a book in 1953–1954 and a paper in the *Lancet* in 1954 [43,44]. His key arguments were that long-standing diabetic vascular disease differed fundamentally from atherosclerosis, in that both sexes were equally affected and that microaneurysms, ocular phlebopathy, and Kimmelstiel–Wilson nodules were unique to diabetes and usually occurred together.

The molecular and cellular mechanisms underlying diabetic tissue damage remain controversial after decades of intensive research. One of the early landmarks in this field was the work of

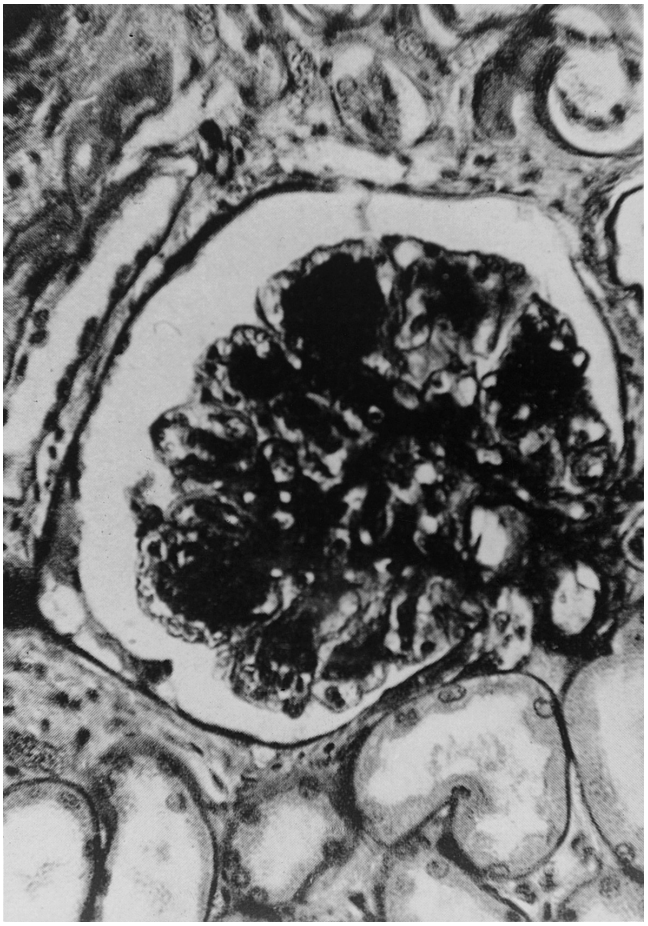


Figure 1.13 Nodular glomerulosclerosis. Figure from the paper by Kimmelstiel and Wilson, 1936 [41]. Source: Courtesy of the British Medical Association Library.

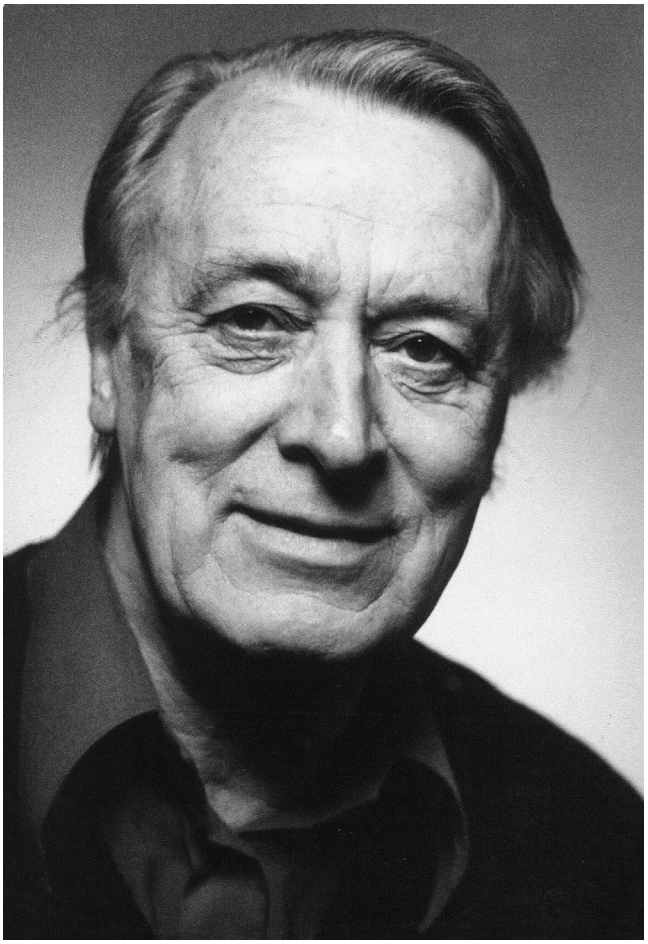


Figure 1.14 Knud Lundbæk (1912–1995). Source: Courtesy of Dr. Carl Erik Mogensen.

J.H. Kinoshita (*b.* 1922) during the early 1970s, which pointed to the involvement of the polyol pathway in the formation of diabetic cataracts [45].

Physiology

In 1907, M.A. Lane, a student of Robert Bensley (1867–1956), Professor of Anatomy in Chicago, used conventional histologic techniques to distinguish two different cell types in the islet of Langerhans, which he termed A and B [46]. The hormones secreted by these respective cell types were not identified until much later (Table 1.2). Frank Young (1908–1988) and colleagues reported in 1938 that injections of anterior pituitary extract could induce permanent diabetes in the dog, and that this was accompanied by selective degranulation and loss of the β cells [47]; it was surmised that these cells produced insulin, and this was finally confirmed using immuno-histochemistry by Paul Lacy in 1959 [48]. Glucagon was similarly localized to the α cells in 1962 by John Baum and colleagues [49].

Table 1.3 Milestones in the understanding of the causes of diabetes.

Thomas Willis (England, 17th century)	Overindulgence in food and drink
Thomas Cawley (England, 1788)	Pancreatic stones cause diabetes
Oskar Minkowski and Josef von Mering (Germany, 1889)	Pancreatectomy causes diabetes in the dog
Etienne Lancereaux (France, 1880)	Lean and obese diabetic subtypes distinguished
Eugene Opie (USA, 1900)	Hyaline degeneration (amyloidosis) of islets (type 2 diabetes)
Eugene Opie (USA, 1910)	Lymphocytic infiltration of islets ("insulitis"; type 1 diabetes)
Wilhelm Falta (Vienna) and Harold Himsworth (England, early 1930s)	Distinguished insulin-resistant and insulin-sensitive forms of diabetes
Willy Gepts (Belgium, 1965)	Suggested that insulitis caused β-cell destruction (type 1 diabetes)
Deborah Doniach and GianFranco Bottazzo (England, 1979)	Suggested that insulin-dependent diabetes is an autoimmune disease
Andrew Cudworth and John Woodrow (England, 1975)	Insulin-dependent diabetes associated with specific HLA antigens

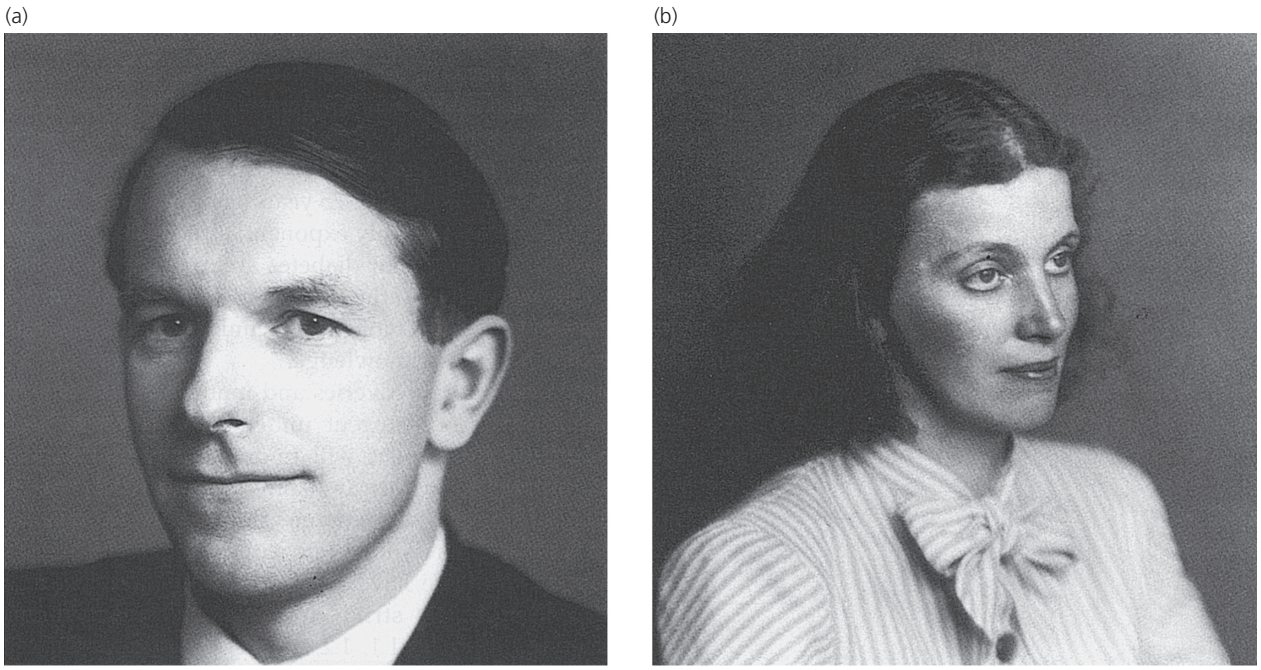


Figure 1.15 Frederick Sanger (1918–2013) and Dorothy Hodgkin, née Crowfoot (1910–1994). Source: Courtesy of Godfrey Argent Studio, London.

The amino acid sequence of insulin was reported in 1955 by Frederick Sanger in Cambridge, UK [50], and the three-dimensional structure of the molecule in 1969 by Dorothy Hodgkin, in Oxford [51]; both discoveries were recognized by the award of Nobel Prizes (Figure 1.15). The complete insulin molecule was synthesized from amino acids by Wang Ying-lai (1908–2001) and colleagues in Shanghai in 1965 [52]. The insulin precursor, proinsulin, was described in 1967 by Donald Steiner (1930–2014) in Chicago [53]. The first bioassay for insulin, based on the hormone's ability to lower blood glucose in the alloxan-diabetic rat, was reported in 1950 by the Australian Joseph Bornstein (1918–1994), working in London with Robin D. Lawrence (see Figure 1.20) [54]. This method was superseded in 1956 by Rosalyn Yalow and Solomon Berson in the USA, who discovered that insulin was antigenic; they exploited the binding of the hormone to anti-insulin antibodies to develop the first radioimmunoassay [55]. This assay method revolutionized endocrinology—and indeed, many areas of physiology and medicine—and was also rewarded with a Nobel Prize (Figure 1.16).

The sequence of rat insulin genes was described in 1977 by Axel Ullrich (*b.* 1945) and colleagues [56], and the human sequence by Graham Bell (*b.* 1948) and his group in 1980 [57]. The existence of insulin receptors was inferred from the insulin-binding characteristics of liver-cell membranes by Pierre Freychet (*b.* 1935) and colleagues in 1971 [58], and the receptor protein was isolated by Pedro Cuatrecasas (*b.* 1936) in the following year [59]. The gene encoding the insulin receptor was cloned and sequenced in 1985 by two groups [60, 61]. In recent years, numerous advances have helped to clarify how insulin exerts its biologic actions. Among these was the discovery in 1985 of the first of the glucose transporter (GLUT) proteins by Mueckler and colleagues in the USA [62].

Management of diabetes

An objective observer surveying clinical diabetes during the half-century after the discovery of insulin and the "resurrection" (a word used by Joslin) of young people with diabetes would have been dismayed by what he saw (Table 1.4). In particular, young people were dying of complications that had previously been assumed to be the preserve of the elderly. Two particularly depressing papers were published in 1947 and 1950. First,

Figure 1.16 Solomon Berson and Rosalyn Yalow.

Table 1.4 Selected milestones in the management of diabetes.

Lifestyle modification	
Li Hsuan (China, 7th century)	Avoid wine, sex, and salty cereals
Thomas Willis (England, 17th century)	Food restriction
John Rollo (England, 1797)	Animal diet
Apollinaire Bouchardat (France, 1875)	Food restriction and increased exercise
Carl von Noorden (Germany, 1903)	"Oatmeal" cure
Frederick Allen (USA, 1913)	Starvation diet for early-onset diabetes
Karl Petrén (Sweden, 1915)	High-fat, low-carbohydrate diet
Insulin treatment	
Georg Zuelzer (Germany, 1907) and Nicolas Paulesco (Romania, 1921)	Isolated pancreatic extracts with hypoglycemic activity
Frederick Banting, Charles Best, J.J.R. Macleod, and James Collip (Canada, 1922–1923)	Isolation and first clinical use of insulin
Hans Christian Hagedorn (Denmark, 1936)	Protamine insulin, the first long-acting insulin
David Goeddel (USA, 1979)	Synthetic human-sequence insulin produced by recombinant DNA technology
John Pickup (London, 1978)	Described continuous subcutaneous insulin infusion
John Ireland (Scotland, 1981)	Invented pen injection device
Oral hypoglycemic agents	
Avicenna (Arabia, 10th century)	Recommended lupin, fenugreek, and zedoary seeds
Willhelm Ebstein (Germany, 1876)	Recommended sodium salicylate
E. Frank (Germany, 1926)	Biguanide derivative (Synthalin) introduced, but withdrawn because of toxicity
Celestino Ruiz (Argentina, 1930)	Noted hypoglycemic action of some sulfonamides
Auguste Loubatières (France, 1942)	Discovered hypoglycemic action of prototype sulfonylurea
H. Franke and J. Fuchs (Germany, 1955)	Carbutamide introduced
G. Ungar (USA, 1957)	Phenformin introduced
Diabetic monitoring and treatment targets	
University Group Diabetes Program (USA, 1969)	First randomized trial in diabetes
Peter Sönksen and Robert Tattersall (1978)	Introduction of self blood glucose monitoring
R. Flückiger and K.H. Winterhalter (Germany, 1975)	Showed that HbA_{1c} was glycated hemoglobin
World Health Organization (1991)	St. Vincent Declaration identified targets for diabetes care
Diabetes Control and Complications Trial (USA, 1993)	Proved that improved glycemic control prevents and slows progression of microvascular complication in type 1 diabetes
UK Prospective Diabetes Study (UK, 1998)	Proved that improved glycemic and blood-pressure control improve microvascular and macrovascular outcomes in type 2 diabetes
Management of complications	
Gerd Meyer-Schwickerath (Germany, 1964)	Use of xenon arc lamp to treat diabetic retinopathy
University of Minnesota Team (USA, 1966)	First combined kidney–pancreas transplants
Carl-Erik Mogensen and Hans-Henrik Parving (Denmark, 1980s)	Strict blood pressure controls slows progression of diabetic neuropathy

Henry Dolger (1909–1997) in New York described 20 people who fulfilled the then-accepted criteria for excellent diabetic control, but who all developed severe retinopathy after 6–22 years [63]; among these was the first person ever to receive insulin at Mount Sinai Hospital, New York, who also had heavy albuminuria and hypertension by the age of 32. Second, Ruth Reuting reported a cohort of 50 young patients originally identified in 1929 [64]. By 1949, one-third had died (mostly from cardiovascular and renal disease) at an average age of 25 years, after only 18 years of diabetes, and the survivors showed "ominous signs of hypertension, azotemia, and proteinuria in significant numbers." This had occurred despite the introduction of more versatile insulin preparations (see below); the situation was so hopeless that it inaugurated 20 years of treatment with "heroic" measures such as adrenalectomy and hypophysectomy.

These and other studies raised questions about whether lowering blood glucose levels to normal could prevent diabetic complications or reverse them once they had appeared. The hypothesis remained untestable for four more decades, until the means to achieve tight glycemic control and measure it had been devised.

Figure 1.17 Hans Christian Hagedorn (1888–1971) from the Hagedorn Medal. Source: Courtesy of C. Binder, Steno Institute, Hvidovre, Denmark.

Insulin

For the first decade after its discovery, insulin was available only in its soluble (regular) formulation, whose short-action profile required multiple daily injections. The first delayed-action preparation, protamine insulinate, was introduced in 1936 by Hans Christian Hagedorn in Denmark (Figure 1.17) [65]. This was followed by protamine zinc insulin later the same year, then globin insulin in 1939, NPH (neutral protamine Hagedorn, or isophane) in 1946, and the lente series in 1952. Long-acting insulins were welcomed by diabetes specialists and people with diabetes, but their use as a single daily injection probably produced worse glycemic control than three or four injections of soluble insulin. Indeed, delayed-action preparations were initially condemned by some diabetes specialists, such as Russell Wilder of the Mayo Clinic, because the patient could slip without apparent warning into hypoglycemia.

The number and variety of insulin preparations proliferated, but the main advances were in methods to produce highly purified preparations from porcine or bovine pancreas, which remained the source for therapeutic insulin until the early 1980s. Insulin was the first therapeutic protein to be produced by recombinant DNA technology, initially by David Goeddel (*b.* 1951), who expressed synthetic genes encoding the A- and B-chains separately in *Escherichia coli* and then combined these chemically to produce human-sequence insulin [66]. From there, genetic engineering has been used to produce "designer" insulins such as the fast-acting insulin analogs lispro and aspart and the "peakless" basal insulins such as glargine, detemir, and degludec. These insulins are more expensive than NPH but the evidence suggests that there is less clinical hypoglycemia with their use [67].

Most people with diabetes still inject insulin subcutaneously. From a patient's viewpoint, major milestones were the replacement of glass and steel syringes by disposable plastic syringes with fine-gauge needles, and then by "pen" injection devices invented by John Ireland (1933–1988) in Glasgow, Scotland, in 1981 [68]. Portable insulin infusion pumps were developed by John Pickup (*b.* 1947) and colleagues in London during the late 1970s [69], and have become progressively smaller and more sophisticated. Both people with diabetes and manufacturers hope that there will eventually be an insulin that can be given without injection. The first inhaled insulin was marketed in 2006 but withdrawn a year later because of lack of demand and concerns about safety [70], but other products have more recently reached the market.

Oral antidiabetes agents

The first orally active glucose-lowering drug, synthalin, a guanidine derivative, was developed by Frank and colleagues in Breslau in 1926 [71], but had to be withdrawn because of toxicity (a recurrent problem for oral antidiabetes drugs). The sulfonylureas originated from the work of Auguste Loubatières (1912–1977) in France during the early 1940s on the glucose-lowering action of a sulfonamide derivative, 2254RP. Loubatières made the crucial observations that proved that these drugs act as insulin secretagogues and that they were effective in intact, but not in pancreatectomized, animals [72]. In 1955 carbutamide was the first sulfonylurea to enter clinical practice and tolbutamide followed in 1957. Phenformin, the first biguanide, was introduced in 1959 following research into the metabolic effects of guanidine derivatives which had built on Frank's initial studies [73]. Metformin appeared on the European market in 1960 but was not marketed in the USA until 1994. Troglitazone, the first of a class of antidiabetes drugs—the glitazones—was also marketed in 1994 but withdrawn because of liver damage. It was followed by rosiglitazone and pioglitazone. Another class of drugs, acting on the incretin system, were introduced in 2005. These are either glucagon-like peptide 1 (GLP-1) receptor agonists (such as exenatide) or inhibitors of the enzyme dipeptidylpeptidase-4 (DPP-4) which breaks down GLP-1 (gliptins).

In 2010 another class of agents, the SGLT2 inhibitors—the gliflozins—became widely available with action blocking the renal sodium-glucose co-transporters and thereby causing glycosuria—with effects on lowering plasma glucose, reducing blood pressure, and causing weight loss. A landmark trial using empagliflozin in high-risk people with existing cardiovascular disease showed a marked reduction in mortality [74].

Tolbutamide, phenformin, and insulin were compared in the treatment of "maturity-onset" diabetes in the first randomized controlled trial, the University Group Diabetes Program [75–77]. This much-criticized study concluded that the death rate was higher for both oral agents than for placebo, and that insulin (whether given in a fixed or variable dose) was no better than placebo [77]. These findings were interpreted by some as suggesting that treatment of maturity-onset diabetes was a waste of time—a myth that was only laid finally to rest by the UK Prospective Diabetes Study [78].

Glucose control and treatment targets

During the 1920s, opinion leaders advocated normalizing blood glucose in young people with diabetes, the rationale being to "rest"

the pancreas, in the hope that it might regenerate. The only way of monitoring diabetic control was by testing the urine for glucose, and attempts to keep the urine free from sugar inevitably resulted in severe hypoglycemia and often psychologic damage. This led to the so-called "free diet" movement—linked particularly with Adolf Lichtenstein (Stockholm) and Edward Tolstoi (New York)—which encouraged people with diabetes to eat whatever they liked and not to worry about glycosuria, however heavy. Tolstoi's view [79] was that a life saved by insulin should be worth living, and that people with diabetes should be able to forget that they had diabetes after each morning's injection; it seems likely that many physicians followed this policy for the next 40 years.

Adult physicians were similarly ambivalent about the importance of good glycemic control. Only one-third of diabetes physicians questioned in England in 1953 thought that normoglycemia would prevent diabetic complications, and only one-half advised urine testing at home [80].

Practical monitoring of diabetic control became feasible in the late 1970s with the introduction into clinical practice of test strips for measuring blood glucose in a fingerprick sample and the demonstration that most people with diabetes could use them at home [81, 82]. The discovery of hemoglobin A_{1c} by Samuel Rahbar (1929–2012) paved the way for glycated hemoglobin (HbA_{1c}) assays which gave an objective measure of overall glucose control [83]. These methods in turn made possible the North American Diabetes Control and Complications Trial, which in 1993 finally established that good control prevents and delays the progression of microvascular complications in type 1 diabetes [84]. For type 2 diabetes, the importance of good glycemic control was definitively proved by another landmark study, the UK Prospective Diabetes Study (UKPDS), masterminded in Oxford, UK, by Robert Turner (Figure 1.18). The UKPDS reported in 1998, and not only showed a beneficial effect of improved glycemic control on microvascular complications [78], but also established the importance of treating hypertension [85]. By the late 1990s it was clear that reducing glucose levels, high blood pressure, or cholesterol separately would reduce the frequency of heart disease and death and it was natural to wonder whether tackling them simultaneously (multiple risk factor intervention) would be even better. The Steno 2 study, which began in Denmark in 1992, enrolled people with type 2 diabetes with microalbuminuria and after 13 years of follow-up showed that multiple risk factor intervention reduced the risk of death by 20% and the risk of developing nephropathy, retinopathy, and neuropathy by 50% [86].

Diabetic complications

Apart from the general benefits of controlling blood glucose, some specific treatments have emerged for certain chronic complications. Well-conducted clinical trials during the late 1970s showed the effectiveness of laser photocoagulation in preventing visual loss from both maculopathy and proliferative retinopathy [87]. This technique was derived from the xenon arc lamp originally described in the late 1950s by Gerd Meyer-Schwickerath (1921–1992) of Essen, Germany [88].

Figure 1.18 Robert Turner (1939–1999), instigator of the UKPDS, the first study to show that good control of blood glucose and blood pressure was beneficial in type 2 diabetes. Source: Courtesy of the British Diabetic Association.

The importance of blood pressure control in preventing the progression of nephropathy is now fully recognized, and blockade of the renin-angiotensin system may be particularly beneficial; that blood pressure control slowed the progression of nephropathy was shown in studies by Carl-Erik Mogensen (*b.* 1938) and Hans-Henrik Parving (*b.* 1943) published in the early 1980s [89]. The detection of very low albumin concentrations in urine (microalbuminuria), now used throughout the world to screen for and monitor the course of diabetic nephropathy, is derived from a radioimmunoassay developed in 1969 by Harry Keen and Costas Chlouverakis, at Guy's Hospital in London [90].

Diabetic ketoacidosis

The introduction of insulin was only one aspect of the management of this acute and previously fatal complication of diabetes. Of the first 33 cases treated by Joslin and his colleagues between January 1, 1923 and April 1, 1925, 31 survived—an excellent

outcome, even by modern standards, which Joslin [91] attributed to: "Promptly applied medical care, rest in bed, special nursing attendance, warmth, evacuation of the bowels by enema, the introduction of liquids into the body, lavage of the stomach, cardiac stimulants, and above all the exclusion of alkalis."

Sadly, other centers did not pay so much attention to detail. In 1933, the death rate from ketoacidosis in Boston was only 5%, but elsewhere in North America and Europe it averaged 30% and could be as high as 75%. An important advance in management was the acceptance of relatively low-dose insulin replacement, following the example of Ruth Menzel and colleagues in Karlsburg, Germany [92]. This broke with the tradition of high-dose regimens such as that proposed by Howard Root in the USA, which had recommended an average of 1200 units of insulin during the first 24 hours of treatment [93]. Another step forward was the recognition by Jacob Holler in 1946 of the danger of hypokalemia [94]. Holler's observation helped to establish the need for monitoring plasma potassium levels, which became feasible with the introduction of the flame photometer, and replacing potassium accordingly.

Diabetic pregnancy

As late as 1950, the outcome of pregnancy in women with diabetes was still very poor in most units, with perinatal fetal losses of 45–65%, some 10 times higher than in the general population. Exceptions to this depressing rule were the units run by Priscilla White at the Joslin Clinic in Boston, who had published excellent results as early as 1935 [95], and by Jørgen Pedersen in Copenhagen (Figure 1.19). Pedersen identified the common features underpinning success as good diabetic control and care provided by an experienced and dedicated team consisting of a physician, obstetrician, and pediatrician [96]. Pedersen's target of a fetal mortality rate of 6% was not achieved in most European or US units until the 1980s.

(a)

(b)

Figure 1.19 Jørgen Pedersen (1914–1978) and Ivo Drury (1905–1988), pioneers, with Priscilla White (1900–1989), in the management of pregnancy in women with type 1 diabetes. Source: Courtesy of Dr. Carl Erik Mogensen and the Royal College of Physicians of Ireland.

(a)

(b)

Figure 1.20 Ernesto Roma (1887–1978) and (right) Robin D. Lawrence (1892–1968). Source: Photograph of Dr. Roma by courtesy of Manuel Machado Sá Marques and the Associação Protectura das Diabéticos de Portugal.

Delivery of care for people with diabetes

From the earliest days of insulin injection and urine testing, it was apparent that people with diabetes needed knowledge and practical skills to manage their disease effectively. Lip-service was often paid to the importance of diabetes education, but most patients were badly informed. In 1952, Samuel Beaser (1910–2005) questioned 128 people with diabetes attending the Boston Diabetes Fair, and found that "all were distinctly deficient in knowledge of their disease" [97]; he felt that responsibility lay with both doctors and administrators. Further studies during the 1960s by Donnell Etzwiler (1927–2003) in Minneapolis showed that many doctors and nurses were also ignorant about managing diabetes. Since the 1980s, diabetes specialist nurses and nurse educators have been appointed in increasingly large numbers—thus fulfilling a suggestion originally made by Joslin in 1916.

National and international diabetes associations have also played an important part by supporting scientific and clinical research, providing practical and moral help for people with diabetes, and lobbying governments on their behalf. The first of these organizations was the Portuguese Association for the Protection of Poor Diabetics, founded in 1926 by Ernesto Roma of Lisbon after an inspiring visit to Joslin's clinic in Boston (Figure 1.20). The Association's aim was to provide free insulin and education for people with diabetes and their families. In the UK, the Diabetic Association (later the British Diabetic Association, and now Diabetes UK) was established in 1934 by Robin Lawrence of King's College Hospital, London, helped by the novelist H.G. Wells (Figure 1.20). Similar organizations were later founded in France (1938), the USA (1940), and Belgium (1942), and now exist in most countries.

On a wider scale, the International Diabetes Federation was established in 1950 and the European Association for the Study of Diabetes (EASD) in 1964. These organizations are devoted to the practice of diabetes care as well as the basic and clinical science of the disease, and have been valuable in coordinating treatment targets and strategies at international level; an important example was the St. Vincent Declaration, issued jointly in 1990 by the EASD and the World Health Organization [98].

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Archives

The notebooks and personal papers of the discoverers of insulin are preserved at the Thomas Fisher Rare Book Library, University of Toronto, Canada.

2 Classification and Diagnosis of Diabetes

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Key points

- Diabetes is a group of metabolic diseases characterized by hyperglycemia resulting from defects in insulin secretion, insulin action, or both.
- There is a general agreement that there are three main types of diabetes and the fourth type includes the less common specific types of varied etiology.
- Although blood glucose remains the main stay for diagnosis of diabetes, HbA_{1c} is now approved as an alternative diagnostic test for hyperglycemia.
- Diagnostic criteria for gestational diabetes (GDM) are modified.
- Impaired glucose tolerance (IGT) is a predictor for subsequent development of type 2 diabetes and is also a cardiovascular risk factor.

Introduction

Diabetes is one of the most common metabolic diseases with a complex, multifactorial etiology and has varied clinical and biochemical manifestations. Multiple therapeutic approaches are required for glycemic management of its different groups. The main cause of the disease is inadequate secretion and/or impaired action of insulin on the target tissues. Severity of the resultant hyperglycemia and the symptoms and signs vary widely. The vascular damage resulting in microvascular and macrovascular complications depends largely on the degree and duration of hyperglycemia.

Diabetes mellitus has been known since ancient times. The term "diabetes" was probably first used by Apollonius of Memphis around 250 BC, which literally meant "to go through" or siphon as the disease drained more fluid than a person could consume. The Latin word "mellitus" was added later as the urine of people with diabetes was sweet (Chapter 1) [1].

In 1500 BC, Hindu scholars described "a mysterious disease causing thirst, enormous urine output, and wasting away of the body with flies and ants attracted to the urine of people" [2]. At the same period, an Egyptian physician, Hesy-ra and the Greek physician Arateus also documented similar symptoms of a mysterious disease which also caused emaciation. If urine tasted sweet diabetes was diagnosed. It was only in the 1800s that chemical tests were developed to detect the presence of sugar in the urine. The early descriptions were probably related to severe forms of the disease, either type 1 diabetes (T1DM) or late type 2 diabetes (T2DM) [3].

In the late 19th century, two categories were recognized, one category was described as occurring in young people with a short time course before ketoacidosis occurred and the second one was described as common in older and obese people. In 1936, Himsworth showed that diabetes could be divided into insulin-resistant and insulin-sensitive types and the former was more common among the maturity-onset variety [4].

Definition

Diabetes is a group of metabolic diseases characterized by hyperglycemia resulting from defects in insulin secretion, insulin action, or both. The chronic hyperglycemia of diabetes is associated with long-term damage, dysfunction, and failure of different organs, especially the eyes, blood vessels, heart, nerves, and kidneys [5,6].

Diabetes is characterized by disturbances in carbohydrates, fat, and protein metabolism. The clinical symptoms include polyuria, polydipsia, polyphagia, weight loss, and blurring of vision which usually occur when prolonged hyperglycemia is severe. It exacerbates to uncontrolled diabetes namely ketoacidosis or hyperosmolar non-ketotic coma. Often symptoms are mild or absent among people with T2DM for many years especially when hyperglycemia is mild. The disease may remain undetected, but tissue damage may develop and therefore vascular complications may be present at the time of diagnosis [6]. Chronic hyperglycemia may cause impairment of growth and increase the susceptibility to certain infections in some people with diabetes. In addition to the classic symptoms, people with diabetes may present with vague

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symptoms such as unexplained weight loss, fatigue, restlessness, and body pain. A few persons in the early stages of hyperglycemia present with symptoms of reactive hypoglycemia.

Long-term complications of diabetes are mainly of two types: (1) microvascular complications which include retinopathy with potential loss of vision, nephropathy leading to renal failure, peripheral neuropathy with risk of foot ulcers, amputations, and Charcot joints; and (2) autonomic neuropathy causing gastrointestinal, genitourinary, and cardiovascular symptoms, and sexual dysfunction [5, 6]. The macrovascular complications include cardiovascular diseases with increased incidence of atherosclerotic cardiovascular, peripheral arterial, and cerebrovascular diseases. Hypertension and dyslipidemia often coexist in people with diabetes.

Classification of diabetes

Diabetes has been known for many centuries and the variations in the severity of diabetes was also described. However, a clear distinction between two types of diabetes emerged only in the 20th century. The first real attempt to classify diabetes was by the World Health Organization (WHO) Expert Committee on Diabetes Mellitus which classified diabetes based on the age of onset of the disease, mainly juvenile-onset diabetes and maturity-onset diabetes [7]. Although at that time other phenotypes such as the brittle, gestational, pancreatic, endocrine, insulin-resistant, and iatrogenic varieties were described, there was no clear understanding of etiology [3].

Glucose measurements in blood became common but no standard criteria for diagnosis were used. Diagnosis was usually made if there were clinical symptoms with high blood glucose and glycosuria. In juvenile-onset diabetes ketonuria was noted to be common. Later on with the availability of insulin measurement using radioimmunoassay, insulin deficiency or lack of insulin secretion in juvenile-onset diabetes and apparently normal or raised levels in maturity-onset diabetes could be demonstrated. This was a major breakthrough in the history of diabetes.

The WHO has published several guidelines for diagnosis of diabetes since 1965 [6–9]. The second report of the WHO published in 1980 [8] marked the beginning of the modern classification which was a revision of the criteria published by the National Diabetes Data Group (NDDG) [10]. For the first time the four major groups were defined: (i) insulin-dependent diabetes mellitus (IDDM, type 1); (ii) non-insulin-dependent diabetes mellitus (NIDDM, type 2); (iii) the "other types"; and (iv) gestational diabetes mellitus (GDM). Two risk classes: previous abnormality of glucose intolerance, and potential abnormality of glucose tolerance were also suggested in place of the terms "prediabetes" or "potential" diabetes. Both diagnosis and classification were reviewed in 1985 [9] and 1999 [6]. At the same time the American Diabetes Association (ADA) also published a report of an expert committee on the diagnosis and classification of diabetes [11]. Both the classifications attempted to encompass both etiology and clinical stages of the disease based on the suggestions of Kuzuya and Matsuda [12]. It was recognized that diabetes may progress through several clinical stages from normoglycemia to ketoacidosis. With the discovery of human leucocyte antigen (HLA) genotypes and also the islet cell antibodies, it was clear that juvenile-onset diabetes or the younger people with diabetes who were insulin-dependent had an autoimmune etiology. Maturity-onset diabetes was considered to be a milder form of the disease.

It was also recognized that people with T2DM can move from one to another stage of varying severity of hyperglycemia, from an insulin requiring stage to non-pharmacological intervention with modification of lifestyle. The etiological classification of glycemia was described by WHO [6] and also approved by ADA [13]. Table 2.1 shows the classification as recently described by ADA [5].

The classification of T2DM is largely characterized by exclusion. As new causes are discovered they are included as "other specific types" such as the maturity-onset diabetes of the young (MODY) [3]. WHO revisited the classification in 2006 [14] and 2010 and no major modifications were made. Impaired glucose tolerance (IGT) was removed from the formal classification of T2DM but was retained as a risk state. A new category of risk status, impaired fasting glucose (IFG), was introduced.

Methods and criteria for diagnosing diabetes [5, 6]

An HbA_{1c} of ≥6.5% (≥48 mmol/L) is recommended as the cut point for diagnosing diabetes [15]. A value less than 6.5% (<48 mmol/mol) does not exclude diabetes diagnosed using glucose tests. The expert group concluded that currently there is insufficient evidence to make any formal recommendation on the interpretation of HbA_{1c} levels below 6.5%. The diagnostic criteria currently recommended by WHO, the International Diabetes Federation (IDF), and also by ADA (with minor variations) are shown in Table 2.2.

Fasting glucose may not be as accurate and equivalent to the use of an OGTT in identifying persons with diabetes. Studies in Asian populations [16] and the European DECODE study [17] showed that if only a fasting blood glucose was used, nearly one-third of cases with diabetes might be missed and vice versa at the point of diagnosis. However, with time, the three groups of people identified by the different tests coalesce so that those diagnosed by only one method will be identified by the other tests in due course.

Glycated hemoglobin (HbA_{1c}) for diagnosis of diabetes

Blood glucose measurement has been the mainstay for diagnosis and monitoring glycemic control in diabetes for many decades. Use of OGTT is a comparatively inexpensive, sensitive index of hyperglycemia including impaired glucose homeostasis. However, several disadvantages such as wide biological variability, poor

Table 2.1 Classification of diabetes (adapted from ADA).

I. Type 1
(β-cell destruction, absolute insulin)
- **A. Immune-mediated**
- **B. Idiopathic**

II. Type 2 diabetes
(Predominantly insulin resistance with relative insulin deficiency to a predominantly secretory defect with insulin resistance)

III. Other specific types
- **A. Genetic defects**
  - MODY 3 (Chromosome 12, HNF-1α)
  - MODY 1 (Chromosome 20, HNF-4α)
  - MODY 2 (Chromosome 7, glucokinase)
  - Other very rare forms of MODY (e.g. MODY 4: Chromosome 13, insulin promoter factor-1; MODY 6: Chromosome 2, NeuroDl MODY 7: Chromosome 9, carboxyl ester lipase)
  - Transient neonatal diabetes (most commonly ZAC/HYAMI imprinting defect on 6q24)
  - Permanent neonatal diabetes (most commonly KCNJ11 gene encoding Kir6.2 subunit of (β-cell KATP channel)
  - Mitochondrial DNA
  - Others
- **B. Genetic defects in insulin action**
  Type A insulin resistance, Leprechaunism, Rabson–Mendenhall syndrome
  Lipoatrophic diabetes and others
- **C. Diseases of the exocrine pancreas**
  Pancreatitis, Trauma/pancreatectomy, Neoplasia, Cystic fibrosis, Hemochromatosis, Fibrocalculous pancreatopathy, and others
- **D. Endocrinopathies**
  Acromegaly, Cushing's syndrome, Glucagonoma, Pheochromocytoma, Hyperthyroidism, Somatostatinoma, Aldosteronoma, and others
- **E. Drug- or chemical-induced**
  Vacor, Pentamidine, Nicotinic acid, Glucocorticoids
  Thyroid hormone, Diazoxide, β-Adrenergic agonists, Thiazides
  Dilantin, γ-Interferon, and others
- **F. Infections**
  Congenital rubella, Cytomegalovirus, and others
- **G. Uncommon forms of immune-mediated diabetes**
  Stiff-man syndrome, Anti-insulin receptor antibodies, and others
- **H. Other genetic syndromes sometimes associated with diabetes**
  Down syndrome, Klinefelter syndrome, Turner syndrome, Wolfram syndrome, Friedreich ataxia, Huntington chorea, Laurence–Moon–Biedl syndrome, Myotonic dystrophy, Porphyria, Prader–Willi syndrome, and others

IV. Gestational diabetes mellitus

reproducibility, influenced by acute factors such as stress, food, and exercise, and also by some medications, are the main disadvantages of using blood glucose [18].

Glycated hemoglobin (HbA_{1c}) initially identified as an index of chronic hyperglycemia has now evolved as a valuable tool to monitor glycemic control, for screening and diagnosis of diabetes and prediabetes and as a predictor of micro- and macrovascular complications [18, 19]. Assays of HbA_{1c} have multiple advantages over that of blood glucose including its preanalytical and analytical stability, its independence of the prandial status, and the assays are well standardized with high precision and accuracy. Presently the results are traceable to the Diabetes Control and

Table 2.2 Criteria for the diagnosis of diabetes (adapted from ADA).

Test	Description	Diagnostic cut-off
HbA_{1c}	The test should be performed in a laboratory using a method that is NGSP certified and standardized to the DCCT assay*	≥6.5% (48 mmol/mol)
OR		
Fasting plasma glucose	Fasting is defined as no caloric intake for at least 8 h*	≥126 mg/dL (7.0 mmol/L)
OR		
Two-hour plasma glucose during an oral glucose tolerance testing (OGTT)	The test should be performed as described by the World Health Organization, using a glucose load containing the equivalent of 75 g anhydrous glucose dissolved in water*	≥200 mg/dL (11.1 mmol/L)
OR		
Random plasma glucose	The test is advised for people with classic symptoms of hyperglycemia or hyperglycemic crisis	≥200 mg/dL (11.1 mmol/L)

*In the absence of unequivocal hyperglycemia, criteria 1–3 should be confirmed by repeat testing.

Complications Trial (DCCT) assay values (measured as %) [20] and can also be compared to the highly accurate International Federation of Clinical Chemistry (IFCC)-standardized values (mmol/mol) [18]. High cost of the assay and its instrumentation, lack of awareness regarding its utility among the medical practitioners and the assay interferences (hematological abnormalities, hemoglobinopathies, factors influencing erythropoiesis), limit its application in many countries. Healthcare professionals using the test should be aware of these limitations and use their discretion in interpreting the results. Several lacunae still exist in the understanding of the relationship between HbA_{1c} and glycemia [18]. These include the relationship in children and the elderly, in pregnancy, in chronic liver and renal disease, the effect of HIV, the understanding of the genetic influences on HbA_{1c} variance, and ethnic influences [21].

Type 1 diabetes (T1DM) [5, 6]

Formerly known as insulin-dependent diabetes mellitus or juvenile-onset diabetes, TIDM occurs due to cellular-mediated autoimmune destruction of pancreatic β cells, causing an absolute deficiency of endogenous insulin. Persons with T1DM are dependent on exogenous insulin for survival and are ketosis-prone. Markers of the immune destruction of the β cell include islet cell autoantibodies, autoantibodies to insulin, autoantibodies to glutamic acid decarboxylase (GAD-GAD65), and autoantibodies to the tyrosine phosphatases IA-2 and IA-2β. One or more of these autoantibodies are present in 85–90% of individuals when fasting hyperglycemia is initially detected. The disease also has strong HLA associations, with linkage to the DQA and DQB genes, and is influenced by the DRB genes.

The rate of destruction of β cells is rapid mainly in infants, young children, and adolescents and they may present with ketoacidosis at the time of first presentation. Some persons with T1DM, mostly adults, may have slow deterioration of β cells and show detectable levels of plasma C-peptide for many years. Some people with T1DM are also prone to other autoimmune disorders such as Graves' disease, Hashimoto's thyroiditis, Addison's disease, vitiligo, celiac-sprue, autoimmune hepatitis, myasthenia gravis, and pernicious anemia.

About 2–12% of persons diagnosed with diabetes show phenotype characteristics of T2DM and have good glycemic control with oral antidiabetes agents, but rapidly progress to requiring insulin. They also show the presence of autoimmune markers of β-cell destruction, such as GADA-65. This subgroup is termed "latent autoimmune diabetes of adults" (LADA) [22].

A few people with T1DM may have no evidence of autoimmunity, but are prone to episodic ketoacidosis and may exhibit varying degrees of insulin deficiency and insulin dependency during those periods. This form, termed "idiopathic diabetes" is commonly seen in persons of African and Asian ethnicity and is strongly familial.

Type 2 Diabetes (T2DM)

T2DM, previously known as non-insulin-dependent diabetes, constitutes more than 95% of the total population with diabetes. Its prevalence is increasing globally but the most striking changes are now seen in the low- and middle-income countries. T2DM remains asymptomatic for many years and therefore remains undetected in nearly 50% of persons affected by the disease [5, 6,23]. T2DM is commonly diagnosed incidentally when a medical checkup is done for other reasons. Individuals with T2DM have a relative insulin deficiency; they secrete insulin but not enough to overcome insulin resistance. Though most of them require only lifestyle changes and oral antidiabetes agents to maintain glycemic control, many of them become insulin-requiring over a period of time. Chronic exhaustion of β-cell function is a major cause of this.

Although research studies have focused on the molecular mechanisms underlying T2DM, only modest success has been achieved in unraveling the genetic abnormalities. In the past two decades

T2DM in children and adolescents has become common in Asian populations which could be partly attributed to the rising rates of obesity in children. A study from Taiwan has reported T2DM to be the commonest form of diabetes in children aged 6–18 years. Signs associated with insulin resistance are also common among these children [24].

Other specific types

These forms of diabetes are relatively less common. The underlying defects of the disease processes can be identified in these forms, such as those listed below. Some of these defects are remediable and types of glycemia can also be cured [5, 6].

- Genetic defects in β cells such as MODY.
- Genetic defects in insulin action, such as Leprechaunism.
- Diseases of the exocrine pancreas, such as cancer of the pancreas, cystic fibrosis, and fibrocalculous pancreatopathy (a form of diabetes, which was formerly classified as one type of malnutrition-related diabetes mellitus).
- Endocrinopathies, such as Cushing syndrome, acromegaly, and pheochromocytoma.
- Drug-induced, such as steroid and thiazides.
- Infections, such as rubella, cytomegalovirus; immune-mediated diabetes such as seen in cases with insulin-receptor antibodies; a number of genetic syndromes as shown in Table 2.1 are associated with diabetes.

Gestational diabetes (GDM)

GDM is a state of carbohydrate intolerance resulting in hyperglycemia of variable severity, with onset or first recognition during pregnancy. It does not exclude the possibility that the glucose intolerance may antedate pregnancy but has previously gone unrecognized. The definition applies irrespective of whether or not insulin is used for treatment or whether the condition persists after pregnancy [5, 6].

Women who have diabetes and subsequently become pregnant are termed as having "diabetes mellitus and pregnancy" and should be treated accordingly during and after the pregnancy. GDM may develop at any stage of pregnancy. Hyperglycemia may resolve after the delivery. However, 5–10% of women may continue to have diabetes, often T2DM and will require treatment with lifestyle changes and appropriate hypoglycemic agents.

Women with GDM should be screened for diabetes 6–12 weeks postpartum, using non-pregnant OGTT criteria. Diagnosis using HbA_{1c} at the postpartum screening is not recommended but may be considered beyond 12 weeks postpartum. Women who show impaired glucose regulation at this stage should be treated with lifestyle interventions and in some circumstances metformin.

Women with any of the following risk factors should be screened with an appropriate blood test as shown in Table 2.3, during the first prenatal visit; if the result is found to be normal, they should be tested again between 24 and 28 weeks of pregnancy [5, 6]. The risk factors for GDM include older age, obesity, history of elevated blood glucose levels or GDM during previous pregnancy, women who had large-for-gestational age babies, strong family history of diabetes, and women from high-risk ethnic groups such as Asians.

The criteria used for diagnosis of GDM are shown in Table 2.3.

Different criteria are now used to diagnose GDM. Establishing a uniform approach to diagnosis will have extensive benefits for patients, caregivers, and policy makers [5].

Table 2.3 Screening for and diagnosis of GDM (adapted from ADA).

Test	Cut-off values	Diagnosis
"One-step" (IADPSG consensus) The test is performed at 24–48 weeks of gestation in women with no history of overt diabetes. 75-g Oral glucose tolerance test (fasting for minimum 8 hours)	Fasting: >92 mg/dL (5.1 mmol/L) 1 h: >180 mg/dL (10.0 mmol/L) 2 h: >153 mg/dL (8.5 mmol/L)	Diagnosis of GDM is made when any of the plasma glucose value exceeds the cut-off values
"Two-Step" (NIH consensus) The test is performed at 24–48 weeks of gestation in women with no history of overt diabetes. **Step 1:** 50-g Oral glucose tolerance test (non-fasting) **Step 2:** 100-g Oral glucose tolerance test (fasting for minimum 8 hours)	1 h post glucose: ≥140 mg/dL* (7.8 mmol/L) 3 h post glucose: ≥140 mg/dL (7.8 mmol/L)	If plasma glucose measured 1 h post load is ≥140 mg/dL* (7.8 mmol/L) proceed to Step 2. Diagnosis of GDM is made when plasma glucose measured 3 h after the test is ≥140 mg/dL (7.8 mmol/L)

*The American College of Obstetricians and Gynecologists (ACOG) recommend a lower threshold of 135 mg/dL in high-risk ethnic minorities with higher prevalence of GDM.

Intermediate hyperglycemia or impaired glucose regulation (prediabetes)

Prediabetes is typically defined as blood glucose levels above normal, but below diabetes thresholds and is a risk state that increases the chance of developing diabetes. About one-third of persons with IGT develop T2DM; the annual incidence rate ranges between 2% to 10% per year depending on the population and presence of risk factors [14].

T2DM goes through several subclinical stages of abnormalities before its clinical manifestations occur. IGT is a postprandial abnormality of glucose tolerance where the 2-hour plasma glucose value after 75 gm glucose intake is between 7.8–11.1 mmol/L (140–199 mg/dL). Nearly 20–30% of people with IGT will also have IFG. The values for IFG are a fasting plasma glucose concentration of ≥6.1 mmol/L (110 mg/dL), but <7.0 mmol/L (126 mg/dL). IFG can also exist as an isolated condition [14]. The ADA applies the same threshold for IGT, but uses a lower cut-off value for IFG, that is, fasting plasma glucose of 5.6–6.9 mmol/L (100–125 mg/dL) [5]. The ADA has also introduced the use of HbA_{1c} levels of 5.7–6.4% (38.8–46.4 mmol/mol) as a new category of high diabetes risk. It is possible to prevent the development of diabetes in these people by lifestyle modification.

Use of the term prediabetes has been criticized on the basis that not all people with this condition progress to T2DM and the term "intermediate hyperglycemia" is preferred.

Conclusion

Over the past two decades significant clarity has been achieved in both the classification of diabetes mellitus, and in the diagnostic criteria. This has helped to establish some uniformity in data collection and has also allowed comparison of the international profile of the disease.

However, consensus is still lacking in many areas, for example the diagnostic criteria for GDM. Moreover, sufficient importance is not being given to identifying prediabetes states, which are the strongest predictors of incident T2DM. Conversion of prediabetes to T2DM can be prevented or delayed in a large proportion of individuals by healthy lifestyle modification.

The classification of diabetes continues to evolve as underlying genetic, and other, factors become identified with increasing precision.

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3 Epidemiology of Type 1 Diabetes

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Keypoints

- Type 1 diabetes mellitus (T1DM) develops in genetically susceptible individuals after a preclinical phase of variable length usually with immune-mediated destruction of pancreatic β cells, and requires lifelong treatment with insulin.
- The disease can occur at any age, but the incidence peaks around puberty. Classification of T1DM versus type 2 diabetes mellitus (T2DM) becomes increasingly difficult with age.
- In childhood, the incidence is similar in females and males, but there is a 1.3–2.0-fold male excess in incidence after about 15 years of age in most populations.
- The incidence in childhood varies enormously between countries. Some Asian and South American populations have low incidences (~0.1–8 per 100,000/year), whereas Finland (>40 per 100,000/year), Sardinia (~38 per 100,000/year), and Sweden (~30 per 100,000/year) have high incidences. North America (15–25 per 100,000/year) and Australia (~15 per 100,000/year) have moderate to high incidences, while eastern countries in Europe have low to moderate incidences (4–10 per 100,000/year).
- About 10–20% of newly diagnosed childhood cases of T1DM have an affected first-degree relative. Those with an affected sibling or parent have a cumulative risk of 3–7% up to about 20 years of age, compared with cumulative risks of 0.2–0.8% in the respective general populations. The cumulative incidence among monozygotic co-twins of persons with T1DM is less than 50%, even after >30 years' follow-up.
- Some of the geographic differences and familial aggregation may be explained by human leukocyte antigen haplotypes.
- The incidence of childhood-onset T1DM has increased by 3–4% per year, and there is a tendency towards younger average age at onset over time, which cannot be explained by genetic factors. The causes of this increasing trend are not known.
- Virus infections and nutritional factors have been implicated, but no specific environmental factor has been established as a risk factor.
- Even though insulin replacement therapy and other advances in the management of T1DM have improved the prognosis of persons with T1DM, their mortality is still at least two times (~2–8-fold) higher than in the background population. This is because of both acute and chronic complications of the disease, including cardiovascular disease, after about 30 years of age.

Introduction

Type 1 diabetes mellitus (T1DM) requires lifelong treatment with insulin, and in the majority of cases results from a cell-mediated autoimmune destruction of the β cells in susceptible individuals. This occurs after a preclinical period of months to years when islet autoantibodies to insulin, glutamic acid decarboxylase (GAD), and insulinoma-associated antigen 2 (IA-2) and other autoantigens can be detected [1]. Autoantibodies are not thought to cause the disease, but are markers of ongoing β-cell destruction. Persistent positivity for two or more islet autoantibodies in early life is associated with a high probability of developing T1DM within the following months to years in genetically susceptible individuals—a more than 60% cumulative incidence after 10 years [2].

Genetic factors influence the susceptibility to T1DM, particularly human leukocyte antigen (HLA) genes [3, 4]. The combination of HLA class II haplotypes DR3-DQ2 and DR4-DQ8 confers a very high risk of T1DM, whereas those who carry only one of the two risk haplotypes have moderately increased risk. Several other alleles, including those in class I loci, further influence the genetic risk. More details on the role of genetic factors and the pathological process are covered elsewhere in this volume. Diagnosis of T1DM among children is considered relatively simple, typically

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with very high glucose levels and clear dependence upon insulin, but classification and early detection become increasingly difficult with increasing age.

Occurrence of T1DM by age, sex, place, and time

The World Health Organization (WHO) DIAMOND Study (Multinational Project for Childhood Diabetes) [5] and the EURODIAB ACE Study [6] have collected standardized incidence data for T1DM among children aged under 15 years, based on notification by the diagnosing physician and date of diagnosis, defined as the date of first insulin injection. In both projects, the degree of undercounting of cases has been estimated using a second source of information.

Incidence rates are calculated as the number of new cases per 100,000 person-years. Person-years are typically estimated by the mean population size in each calendar year, sex, and age group. The proportion of the population expected to develop the disease by a certain age, the cumulative incidence, can be approximated by multiplying the average incidence rate in an age group by the number of years covered by the age group. For instance, if the average incidence rate among 0–14-year-olds is 20 per 100,000 person-years, then ([20/100,000] × 15 = 0.003) 0.3% of children in that population will develop disease before they reach 15 years of age. Note that this corresponds closely to the prevalence at age 15 years (assuming no mortality), while the prevalence in the age group 0–14 years will be substantially lower.

Most of the incidence data available today come from studies of children in European countries. Incidence data from Africa are still sparse, but increased information on the incidence of T1DM among Asian and South American populations has changed the understanding of the global patterns in variation in incidence.

Occurrence of T1DM by age

In principle, T1DM may occur at any age, but it is very rare in the first year of life and becomes increasingly difficult to distinguish from other types of diabetes after about 30 years of age. Essentially all populations display a steady increase in incidence rate with age up to around 10–15 years [5], but more recent data from Finland indicate an incidence in 0–4-year-olds that is nearly as high as that in 10–14-year-olds [7]. The incidence rate increases from birth to peak at around puberty (Figure 3.1) and in most populations is lower among 15–29-year-olds than among 0–14-year-olds [8–12]. In some populations there seems to be a second rise in incidence after the age of about 25–30 years [13–15].

In the Swedish nationwide prospective incidence study of 15–34-year-olds, 78% of the newly diagnosed participants were classified as having T1DM and 15% as having type 2 diabetes mellitus (T2DM) at the time of the diagnosis [16]. The follow-up showed that 92% of participants diagnosed before 30 years of age were treated with insulin at a later date [17]. These findings are consistent with incidence data from Finland among 15–39-year-olds [18, 19]. In these studies, the incidence of T2DM exceeded that of T1DM by the age of about 30 years. By contrast, in Turin, Italy, which has a much lower incidence of T1DM, the incidence of T2DM is about three times higher than that of T1DM at the age of 30 years [13]. Although beyond the scope of this chapter, it is important to consider the possible clinical heterogeneity and increasing difficulty of classification of diabetes with increasing age, and also potential monogenic diabetes among those with very early onset [20]. A proportion of the apparent heterogeneity may represent extremes within a continuum.

There is a lack of population-based incidence data for age groups above 35 years of age. The only published population-based incidence studies covering the incidence of T1DM over the whole age span is one from Rochester, Minnesota, 1945–1969 [21]

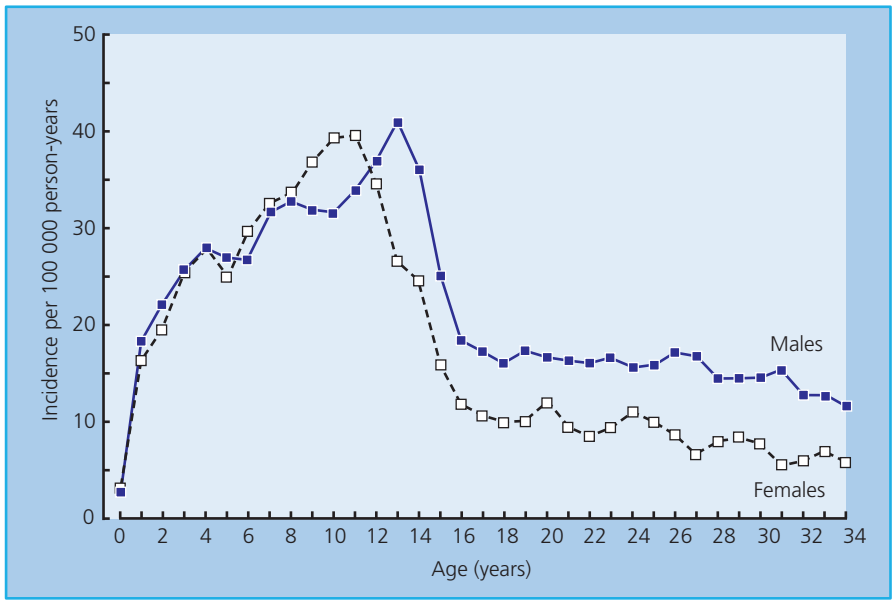

Figure 3.1 Incidence rate of type 1 diabetes per 100,000/year in Swedish males and females by age during 1983–1998. Source: Pundziute-Lyckå et al. 2002 [11]. Reproduced with permission of Springer.

and from Denmark, 1973–1977 [22]. The latter study indicated that the cumulative probability of developing T1DM before age 80 years is in the range 1–1.5%.

Incidence by sex

The peak in incidence rate among children occurs slightly earlier in girls than boys (Figure 3.1), suggesting an influence of puberty. During the 1970s, there was a male excess of T1DM in children in populations of European origin and a female excess in populations of African and Asian origin [23]; however, during the early 1990s, the sex-specific pattern in incidence among children changed towards more modest differences. Of 112 centers with data during 1990–1999, only six showed a significant excess of females (Beijing, Hong Kong, and Zunyi in China, New South Wales in Australia, Puerto Rico, and the African American ethnic group in the United States) and six centers showed a significant male excess (West Bulgaria, Finland, and Attica in Greece, Switzerland, Oxford in the United Kingdom, and the Dominican Republic), and all differences were generally of modest magnitude [5]. The general impression is still that it is the high-incidence countries that tend to have a slight male excess, whereas the opposite is seen in low-incidence countries. Many studies have shown a male excess in the incidence of T1DM among young adults. Whereas the male : female ratio among children in most populations is 0.9–1.1 [5], the male : female ratio among young adults ranges from about 1.3 up to 2.0 in many populations [12, 24].

Incidence by country

The incidence rate of T1DM among childhood populations shows a vast geographic variation worldwide (Figure 3.2) [5, 25–27]. Over the period 1990–1999, the age-adjusted incidence rate of T1DM ranged globally from 0.1 in Zunyi (China) and Caracas (Venezuela) to 37.8 in Sardinia and 40.9 per 100,000/year in Finland [5]. The most recent data from Finland indicate an incidence rate of nearly 60 per 100,000 in 2006 [7], the highest incidence ever recorded.

European countries are well represented with registries, and there is an ~10-fold difference between highest and lowest incidence countries in Europe [26], with the apparently lowest rate of 3.6 per 100,000/year in Macedonia during 1989–1994. Sweden has a high incidence rate (30 per 100,000/year). Centers in France and mainland Italy, for instance, report intermediate incidence rates of ~10 per 100,000/year, whereas some other European countries have intermediate to high incidence rates [5]. In general, the incidence rates are low in Eastern European countries, although the most recent EURODIAB data show that for several countries where the incidence rate previously was below 10 per 100,000/year, during 1999–2003 it increased to 10 per 100,000/year or more, for example, in Lithuania, Bucharest in Romania, and in Katowice in Poland [27].

Standardized data for the age group 15–29 years from European centers (in Belgium, Lithuania, Romania, Sardinia, Slovakia, Spain, Sweden and the UK) during 1996–1997 showed incidence rates between 5 and 12 per 100,000/year [12]. Incidence rates among 15–29-year-olds within this range have also been reported, albeit from earlier time periods, in other European centers, such as 5.5 per 100,000/year in Rzeszow, Poland, in 1980–1992 [28], ~7 per 100,000/year in Turin, Italy, in 1984–1991 [13, 29], and ~13 per 100,000/year in two regions of Denmark in 1970–1976 [8].

Although Sweden and Sardinia had higher incidence rates among children, the incidence rate among young adults was not much higher there than in the other centers in the multicenter study [12]. Older data from Norway (1978–1982) [10] indicated a higher incidence rate of 17 per 100,000/year and more recent data from Finland (1992–2001) [18] indicated 8 per 100,000/year among 15–29-year-olds. Recent data on new users of insulin (and no other hypoglycemic agents) indicated stable incidences over 30 per 100,000/year among 15–29-year-olds in Norway during 2006–2010 [30]. In addition to problems with correct classification of type of diabetes in adults mentioned above, incomplete ascertainment may also be a greater problem for young adults than among children [31], whereas incomplete ascertainment is not a likely problem with the insulin use data. Differences between countries in the incidence among young adults should be interpreted with caution until more data are collected using comparable methodology.

The USA is represented with the data collected during the 1990s from Allegheny County in Pennsylvania, Chicago in Illinois, and Jefferson County in Alabama, with incidence rates in the range 11–18 per 100,000/year among children. Alberta and Calgary in Canada had slightly higher rates (~23 per 100,000/year; Figure 3.2) [5], while the data from the Avalon Peninsula, Newfoundland, indicated a higher incidence rate of 35.9 per 100,000/year [32].

In South America, children in centers in Venezuela, Paraguay, and Colombia had incidence rates of <1 per 100,000/year, Chile (Santiago) had ~4 per 100,000/year, and Argentina and Brazil had an average of ~8 per 100,000/year. Many centers in Central America and the West Indies (except Puerto Rico and St. Thomas) generally had low to intermediate incidence rates, with indications of decreasing time trends [5].

Data from New Zealand and parts of Australia show moderate to high incidence rates (15–25 per 100,000/year) among children [5]. Data from other Pacific Island countries are lacking, and would be difficult to interpret because the populations in most island countries are small. In Asia, the mean incidence rate among the 23 centers in China during the early 1990s was 0.8 per 100,000/years. Japan had a slightly higher average incidence rate of 1.7 per 100,000/year among three centers, and Kuwait stood out with a high incidence rate of 22 per 100,000/year.

There is limited information on the incidence rate of T1DM from sub-Saharan Africa [33]. The five DIAMOND centers are all in North Africa (Algeria, Libya, Sudan, and Tunisia) or Mauritius, an island off the coast of Madagascar. Incidence rates reported from these centers range from low to intermediate, but these countries cannot be said to be representative of Africa.

Additional incidence data from other regions are discussed in sections below.

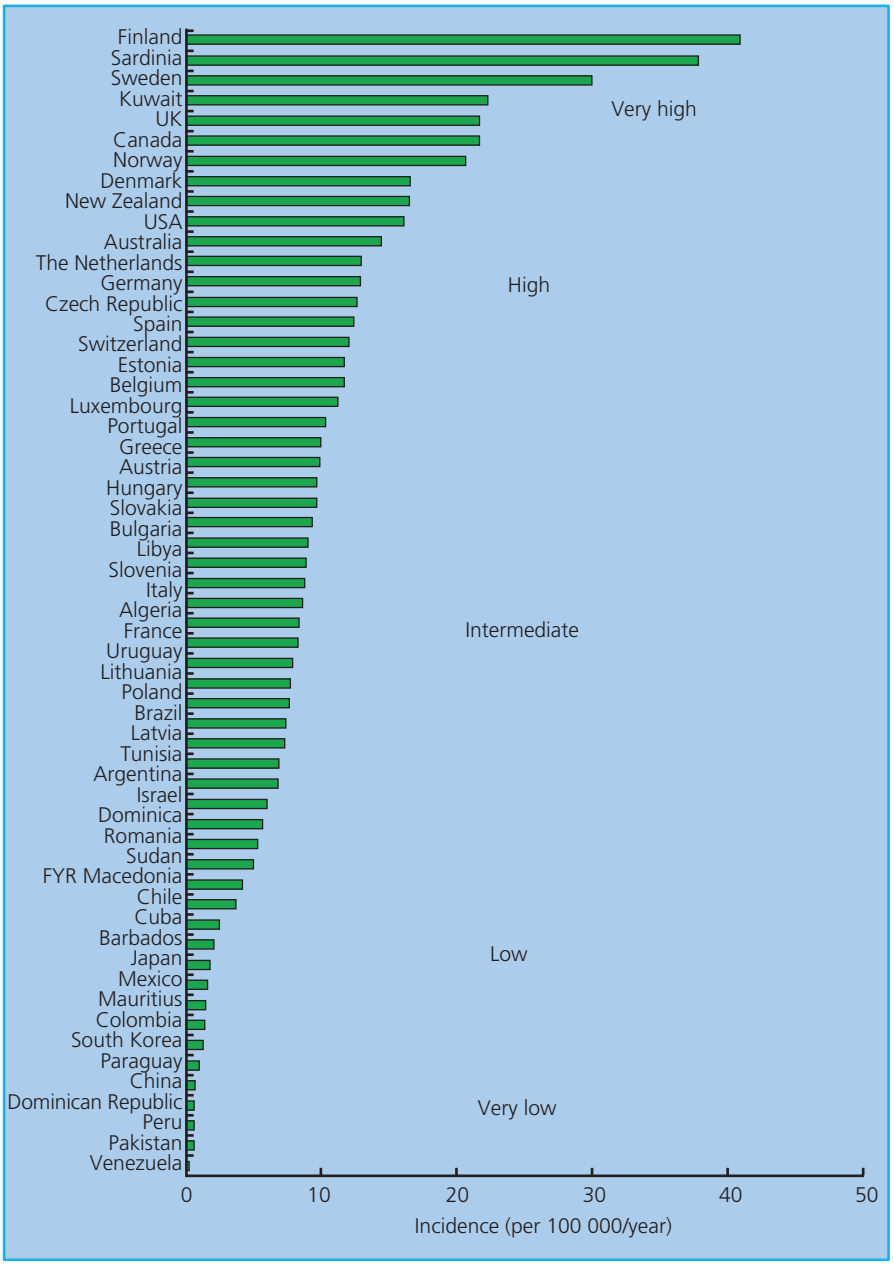

Figure 3.2 Geographic variation in childhood onset type 1 diabetes incidence rates, 1990–1999. Note that most registries were not nationwide and that several countries display within-country variation. Source: The DIAMOND Project Group 2006 [5]. Reproduced with permission of John Wiley & Sons.

Trends in incidence over time

The methodology for population-based incidence registries was not standardized until the late 1980s, but a number of older data sources have been reviewed to assess possible time trends. There is a general impression that the incidence of T1DM increased strongly after the middle of the 20th century [34, 35], although in Denmark the incidence among 0–29-year-olds seemed stable from 1924 to the 1970s [8]. An analysis of incidence trends of more standardized registry data from 1960 to 1996 in 37 populations worldwide showed a significant increase in incidence rate over time in the majority of populations, with a steeper relative increase in low-incidence than in high-incidence populations [36].

In the 103 centers participating in the WHO DIAMOND project for at least 3 years during 1990–1999, the overall relative increase in incidence rate was 2.8% per year [5]. By continent, overall increasing trends per year were estimated at 5.3% in North America, 3.2% in Europe and 4.0% in Asia [5]. The only regions with an overall decreasing trend were Central America and the West Indies [5].

In general, the increasing trend appeared to be strongest in the centers with high and very high incidence rates during the 1990s. In the centers with low and very low incidence rates, there were no significant increases in incidence rates over time. However, the 15-year (1989–2003) time trends in Europe reported to EURODIAB indicated an overall mean increase in incidence

rate of 3.9% per year, with a tendency towards stronger relative increases in the countries with the lowest average incidence rates during the first 5 years (1989–1994) [27].

Overall, the relative increase over time during the 1990s among the DIAMOND centers was most pronounced in the younger age group: 4.0% among 0–4-year-olds, 3.0% in 5–9-year-olds and 2.1% in 10–14-year-olds, and was similar for boys and girls in most centers. The pattern of a steeper relative increase among the youngest was seen in Europe and Oceania, but not in Asia and North America [5]. A smaller relative increase in incidence rate over time among older individuals than among younger ones has also been seen in European studies covering wider age ranges [11, 14, 15, 37, 38]. This latter observation is in line with a model where a certain pool of genetically susceptible individuals contract the disease at younger ages [11, 14, 39]. The few available data, however, are not entirely consistent with this idea. An increasing incidence rate has been seen also among older age groups in some populations [15, 19, 29], but the lack of standardized incidence data covering the whole age range makes it difficult to draw firm conclusions. Note that despite the time trends indicated in Sweden with decreasing average age of onset, the peak incidence rate remained around the age of puberty [11].

In Finland, the incidence rate increased linearly from the mid-1960s to the mid-1990s [40] and thereafter even more steeply, reaching almost 60 per 100,000/year in 2006. After a peak in 2006, the incidence among children in Finland seems to have plateaued [41]. However, when considering the year-to-year variation in long-term data from Finland and other Nordic countries, this may well be only temporary (Figure 3.3). Whereas data from the Swedish Childhood Diabetes Register suggested a possible plateau in the incidence in Sweden in 2006 [42], other register data from Sweden showed a continuing increase up to 2009 [43]. Furthermore, data from Germany [44], Israel [45], USA [46], Yorkshire, UK [47], and Shanghai, China [48] show these to be examples of countries or regions with continuing rises in incidence up to recent years. Data from Western Australia suggest a continuing increase over the long term, but that the incidence varies in cycles of ~5 years [49]. Similar patterns have been observed elsewhere, but it does not seem to be a general pattern (Figure 3.3). On the other hand, a plateau in incidence in Norway is strongly suggested from about 2004 to 2012 [50]. Also, in the Czech Republic, the incidence among children seems to have leveled off [51]. We are not aware of countries where consistent and significant decreases in incidence have been observed during the past 2–3 decades. When stratified by sex and age groups, the year-to-year variation in most studies becomes very large and trends should be interpreted with caution. It should be clear from the observed long-term trends (Figure 3.3) that predictions about future trends in incidence rates are more or less futile.

Variation in incidence within countries, including by ethnic group

In several countries, marked within-country variations in the incidence rate of T1DM have been reported, even in relatively homogeneous populations. Marked ethnic variations have also been observed, generally in line with differences in countries or regions discussed above, and some geographic differences may be due in part to differences in the distribution of ethnic groups. Potential methodological problems should be considered when making inferences based on epidemiological studies of different ethnic groups and immigrants. These include differential ascertainment and definition of ethnic group, underestimation of the base population in some ethnic groups, genetic admixture, and possible heterogeneity in clinical presentation [20, 52]. Among childhood-onset cases, however, it seems that the large majority, even in Japan [53], have classic autoimmune T1DM.

Historically, the incidence of T1DM has been higher in populations of European origin, particularly those living in Europe, than that among populations of non-European origin [52, 54]. The incidence rates of T1DM in most South American studies with standardized registries seem to be much lower than those among Latino people in the USA and lower than those among Spaniards living in Spain [52]. Data from the SEARCH study in the USA showed clear ethnic differences in the prevalence of T1DM in 2009 [55]. The highest prevalence was among non-Hispanic white

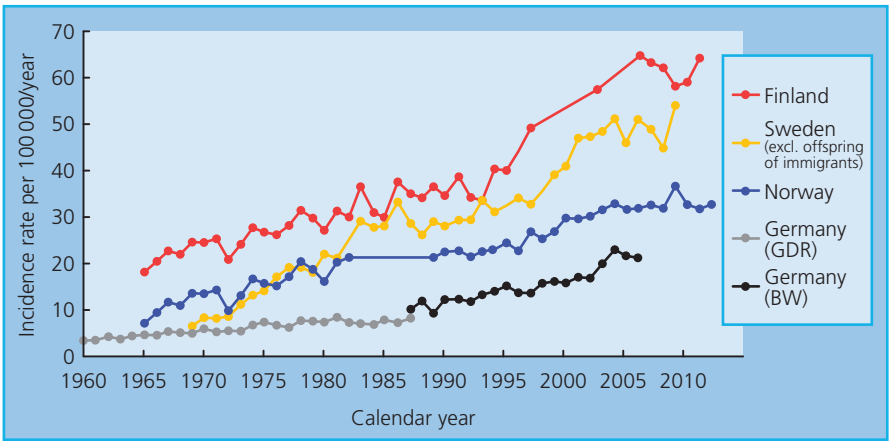

Figure 3.3 Long-term time trends in incidence rate of type 1 diabetes diagnosed before 15 years of age in Finland, Sweden, Norway, and Germany. Source: Data from Tuomilehto et al. 1999 [40], Harjutsalo et al. 2008 [7], Harjutsalo et al. 2013 [41], Hussen et al. 2013 [43], Joner & Søvik 1989 [163], Skrivarhaug 2014 [50], and Ehehalt et al. 2012 [44]. Finish data 1965–1996 are for age group 1–14 years, and thereafter 0–14 years (and data from 1997 to 2005 are averages for three calendar years); all other data are observed incidence per calendar year without smoothing of curves. Nordic data are from nation-wide registries and German data are from former Eastern Germany (GDR) and the Baden-Württemberg registry 1987–2006.

youth, while African American and Hispanic youth had approximately half, Asian Pacific Islanders approximately one-quarter, and American Indian youth approximately one-seventh of the prevalence compared with non-Hispanic white youth. Other studies have indicated that the differences in incidence among ethnic groups in the USA are less dramatic, at least for some groups in some regions of the USA [5, 54]. It is worth noting that many ethnic groups in the USA have considerable admixture with people of European ancestry, which may dilute any potential effect of ethnicity on T1DM risk.

Up to 1.5-fold differences have been described among counties or regions within Finland, Sweden, and Norway [56–58]. In Italy during 1990–2003, the incidence rate among children varied from ~40 per 100,000/year in the island Sardinia, from 11 to 19 per 100,000/year in regions of northern mainland Italy, and from 8 to 12 per 100,000/year in the central-southern part of Italy [59]. Sardinia's population history is different from that for mainland Italy. Children born in families who moved to mainland Italy from Sardinia kept their high T1DM incidence [60]. In New Zealand, the 1.5-fold higher incidence among children in the South Island compared with that in the North Island was largely explained by the 4.5 times higher incidence among children of European origin compared with that among Māoris [61]. In China, there was a 12-fold geographic variation (0.13–1.61 per 100,000/year), generally with higher incidence in the north and east. In addition, there was a sixfold difference between the Mongol (1.82 per 100,000/year) and the Zhuang (0.32 per 100,000/year) ethnic groups [62]. Considering immigrants as a single group, the time trends in incidence differed significantly from "ethnic Swedes" from the late 1980s and onwards [43] (Figure 3.4). In Israel, there was a parallel increase over time, but a consistently lower incidence in childhood-onset T1DM among non-Jews (mainly Palestinians) than among Jews during 1997–2010 [45]. There also seemed to be a systematically lower incidence among South Asian than among non-South Asian children in Yorkshire [47] (Figure 3.4).

The incidence of T1DM among children of immigrant parents in Germany, Sweden, and mainland Italy has been shown to correlate with the incidence in the country or region of origin of their parents, whether the incidence in the country of origin is higher or lower [60, 63, 64]; however, the incidence among immigrants from Pakistan to the UK (or their children) is similar to that among native Britons [65, 66], despite the very much lower incidence recorded in Karachi, Pakistan [5].

In summary, although there are clear ethnic differences in incidence rate of T1DM and strong evidence for a role of genetic factors, some of the above-mentioned studies also suggest a possible role for as yet unidentified environmental factors.

Seasonal variation in diagnosis of T1DM

Several studies have reported a peak in the number of cases diagnosed in the autumn (fall) and winter, and a smaller proportion of cases diagnosed in the spring or summer, consistent in both the northern and southern hemispheres [9, 26]. Although reasonably consistent, there is some variation in exact peak and nadir between countries, age groups, sexes, and periods. Generally, the degree of seasonal variation is stronger among those diagnosed at age 10–14 years than in younger children (Figure 3.5) [26]. Different methods have been used in the analysis of seasonal variations, and often with data covering relatively short periods of time and a limited number of cases; the results are therefore not necessarily comparable. Interpretation of seasonal variation must be carried out in light of the long and variable preclinical period in T1DM, and it is speculated that viral or other periodic factors have a role in the timing of the precipitation or onset of the disease in susceptible individuals who would develop it sooner or later.

Familial clustering and twin studies

In addition to providing clues regarding the relative importance of genetic and non-genetic factors in the etiology of disease, data on risk of T1DM among people with affected relatives may also

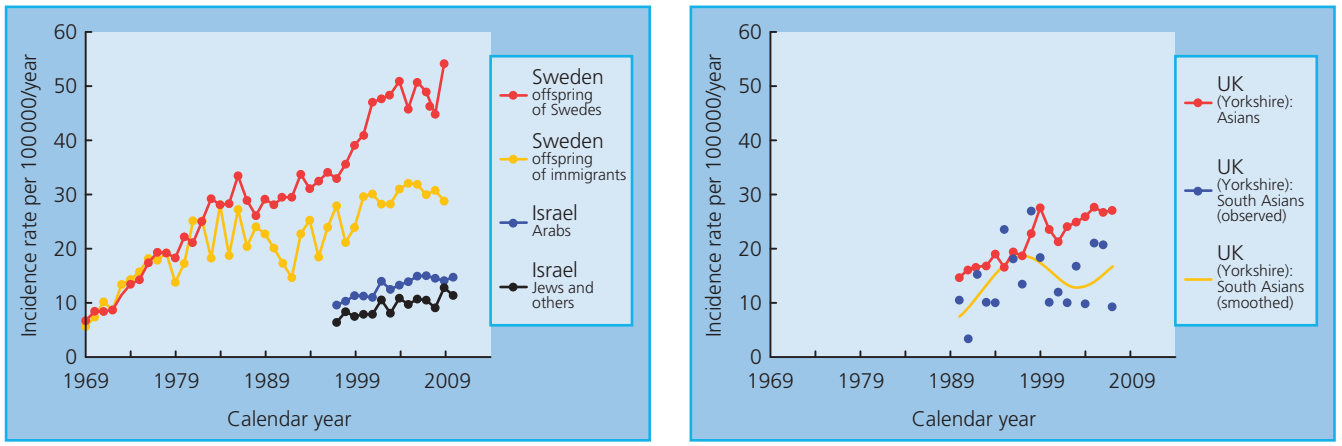

Figure 3.4 Incidence trends in type 1 diabetes among ethnic groups in Sweden and Israel (left panel) and Yorkshire, UK (right panel). Source: Data from Hussen et al. 2013 [43] and Harron et al. 2011 [47]. Note that the data from Israel shown here are for ages below 15 years, as for the Swedish and UK data. R.C. Parslow and O. Blumenfeld kindly provided raw data for UK and Israel, respectively.

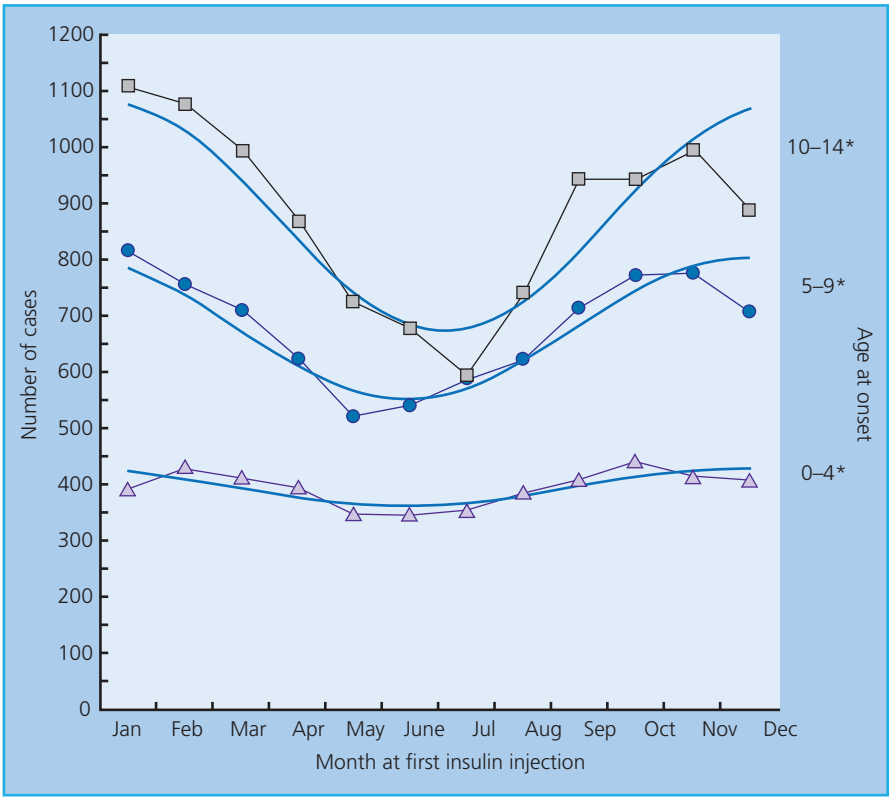

Figure 3.5 Seasonal variation in diagnosis of type 1 diabetes among >22,000 children diagnosed 1989–1998 in European centers, by age at onset. *Age (years) at first insulin injection. Source: Green and Patterson 2001 [26]. Reproduced with permission of Springer.

aid the clinician in counseling family members of newly diagnosed individuals. Around 80–90% of people with newly diagnosed T1DM do not have any affected siblings or parents, but first-degree relatives of a person with T1DM are at increased risk. By the age of 20 years, ~4–6% of siblings of T1DM probands have been reported to develop T1DM in populations of European origin [67–69], compared with around 0.2–1.0% in the corresponding background populations. The offspring of affected fathers have a 1.5–3-fold increased risk of T1DM compared with the offspring of affected mothers [70, 71]. By 20 years of age, 5–8% of the offspring of men with diabetes, but only 2–5% of the offspring of women with diabetes, have been found to be affected. There is currently no accepted explanation for this phenomenon.

Given the well-established effect of genetic factors, it is no surprise that the concordance rate for T1DM in monozygotic (MZ) twins is much higher than that in dizygotic (DZ) twins [72, 73]. In one study from North America, the estimated cumulative risk 10 years after onset in the proband (diagnosed before age 40 years) was about 25% in MZ twins and about 11% in DZ twins [74]. Corresponding 10-year cumulative risks from Finland were estimated as 32% for MZ twins and 3.2% for DZ twins [73]. Comparable estimates were also found in the Danish twin registry, although the exact age at onset was not known in this study [72]. In general, the risk for the co-twins was higher and the discordance time shorter the earlier the onset in the proband [73–75]. In a long-term follow-up of discordant MZ twins from the USA and the UK, more than 50% of MZ pairs remained discordant for T1DM (Figure 3.6) [75]. Because MZ twins share 100% of their genomic DNA, this suggests that genetic susceptibility is in most cases not sufficient for the development of disease.

Despite the relatively high proportion of MZ twins being discordant for clinical T1DM, many of the non-diabetic co-twins of persons with T1DM develop islet autoimmunity [76]. Together with the limited variation in prevalence of positivity for islet autoantibodies between countries [39] and animal studies suggesting a two-stage disease process [77], this supports the idea that environmental factors may have an important role in the progression from islet autoimmunity to overt disease.

Environmental risk factors for T1DM: clues from epidemiological studies

The time trends described above must be ascribed to some change in the environment, even in the event that the increase is brought about by a change in the age distribution. Some of the variation in incidence rate between European countries can be explained by differences in the frequency of HLA susceptibility genotypes [78], but clearly not all [79]. It has been suggested that the proportion of persons with newly diagnosed T1DM who carry the highest risk genotype (DR3-DQ2/DR4-DQ8) has decreased over time (reviewed in [80]). It may be speculated that increased exposure to some risk factor or decreased exposure to some protective factor have caused more individuals with moderate risk

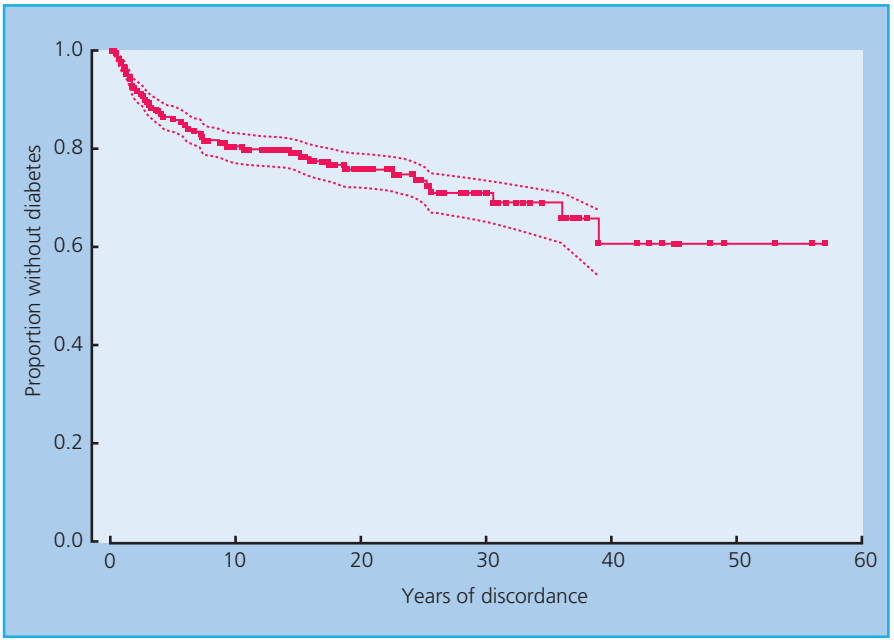

Figure 3.6 Diabetes-free survival in non-diabetic monozygotic twins whose co-twin had type 1 diabetes, after several years of follow-up. Dotted lines represent 95% confidence intervals. Source: Redondo et al. 2001 [75]. Reproduced with permission of Springer.

("permissive") genotypes (e.g. either DR3-DQ2 or DR4-DQ8, but not both) to develop T1DM in recent years. Although there is overwhelming evidence for an essential role of genetic factors in the etiology of T1DM, available evidence strongly suggests that one or more non-genetic factors are also involved; however, the nature of these putative factors is not well known.

In general, environmental factors may be envisioned to have a role in the following:

1 initiating of the autoimmune disease process;

2 modulating the progression from islet autoimmunity to clinical T1DM; or

3 "precipitating" disease in individuals with advanced preclinical disease.

Little is known about the initiation of autoimmunity in humans [81], but some form of immune-mediated mechanism leading to the breakdown of self-tolerance is likely to be involved. An incidence peak in islet autoimmunity in the second year of life and instances of very early seroconversion for islet autoantibodies among children who develop T1DM suggests that potential environmental factors influencing step 1 are likely to operate very early in life [82]. Limited geographic variation in the prevalence of islet autoimmunity despite the large differences in incidence of T1DM between countries suggests a major importance of environmental factors in the progression from islet autoimmunity to T1DM [39], although the hypothesis that there are environmental triggers of autoimmunity cannot be discarded [83]. Responsible factors may operate by modulating the immune system and metabolism. *In vitro* experiments have suggested that actively insulin-secreting β cells hyperexpress islet autoantigens such as GAD, and are more susceptible to toxic effects of the cytokine interleukin-1β [84]. It may be speculated that factors that increase the stress on β cells may contribute non-specifically to the precipitation of clinical disease [84]. This includes insulin resistance or other mechanisms implied in infections, puberty, and growth spurts. Insulin resistance is not easy to measure reliably in humans, but several studies have found measures of insulin resistance relative to first-phase insulin response to an intravenous glucose tolerance test to be predictive of progression to T1DM (reviewed in [85]). Below, some of the most frequently studied non-genetic factors with a potential role in the etiology of human T1DM are discussed.

Specific putative environmental factors

Viral infections

There is a large body of literature linking infections and T1DM [86], but the link has not been established as causal in humans. Studies vary in design, ranging from *in vitro* studies [87], experiments with various animal models [88], studies of people with disease including of pancreatic tissue [87, 89–92], and epidemiological case–control and cohort studies [9, 93–95]. Congenital rubella syndrome has been associated with a several-fold increase in the incidence of T1DM [96]. Although not contributing to the incidence of T1DM in most countries today, this observation has been cited as a proof of principle that intrauterine factors and viral infections in general can influence the risk of T1DM in humans. It probably remains the best example of a non-genetic factor contributing to increased risk of T1DM in humans, but the consistency of the available evidence and the absolute risk associated with congenital rubella syndrome may have been overstated [97, 98].

Several early studies based on assays for antibodies to enteroviruses in cases with T1DM and controls initially seemed promising, but systematic review of the data showed too much

heterogeneity in the methodology and results to be able to draw any conclusion [93]. Prospective study design and detection of enterovirus RNA represent important contributions to the methodology of such studies in recent years, but a careful review of available data revealed only limited consistency across studies with similar design [95].

Increased risk of childhood-onset T1DM has been associated with evidence of maternal enterovirus infections during pregnancy in some studies, but not in all [95, 99]. Using both serum enterovirus antibodies and RNA as indications of postnatal infection, independent prospective studies from Finland have found enterovirus to be associated with increased risk of islet autoimmunity and T1DM [83], whereas other similar studies did not find any significant association [95]. It seems that the presence of viral particles in the blood is more strongly correlated to T1DM than mere presence in the stool, although still larger studies are needed [94, 95, 100]. An immunohistochemical study of stored sections of pancreatic biopsies obtained post-mortem in young individuals with recent-onset T1DM found that the β cells of multiple islets stained positive for enterovirus capsid protein VP1 in 44 of 72 cases. Very few of the controls in that study stained positive [91]. This study substantiated previous evidence based on one or a few participants [89, 90] and indicated problems with the methods used in a previous study of a similar material where no such evidence was found [101]. Based on early data [89], the Coxsackie B4 serotype of human enterovirus has been suspected to be particularly diabetogenic. Technical difficulties with the detection and interpretation of small quantities of viral particles remain, but a recent study found signs of enterovirus by multiple techniques and in different laboratories in fresh pancreatic tissue obtained from six newly diagnosed young adults with T1DM [92]. Nevertheless, the serotype or other characteristics of the enterovirus could not be determined in this study. Recently, application of serotype-specific neutralizing antibody tests to the prospective DIPP study suggested a novel association between the Coxsackie B1 serotype, and rather a possible protective association with Coxsackie B4, but this needs to be replicated [83].

Enterovirus infections are common and there is evidence that the frequency of infection has decreased with improved hygiene in recent decades, opposite to the trend seen for T1DM. It has been postulated that the increasing incidence of T1DM in children may be explained in part by decreased protection from maternal enterovirus antibodies [102]. A more direct test of this hypothesis is still lacking.

The so-called "hygiene hypothesis" comes in different versions but essentially proposes that the decline in microbial exposure in many populations over the past few decades has caused a concomitant increase in incidence of immune-mediated diseases, including T1DM [103]. Some infections and microbial agents reduce the incidence of autoimmune diabetes in experimental animals [104]. Epidemiological studies have investigated non-specific infections and infectious symptoms, but the results have been inconsistent. Daycare attendance is usually associated with increased exposure to microbial agents, and a meta-analysis concluded that there is some evidence for a lower risk of T1DM among children who attended daycare centers early in life, but the results were not sufficiently homogeneous to allow a strong conclusion [105].

There are many promising observations supporting a possible role of viral infections in the etiology of T1DM, but the current evidence that infections have an important and causal role in human T1DM is not conclusive. Although the problem of identifying the potential strain of enterovirus that might be diabetogenic would pose an additional problem, early work on vaccine development towards such a strain is in progress. Others have suggested that it may be possible to develop a vaccine that can reproduce the potential beneficial effects of viral infections (cf. "hygiene hypothesis") regardless of the existence or identification of one or a few diabetogenic viral serotypes [104]. However, it is currently unknown whether such vaccines will be efficacious and feasible for the prevention of T1DM.

Toxins

A number of other environmental chemicals may influence the immune system and potentially the risk of T1DM [106]. The rodenticide Vacor has been associated with T1DM in humans after ingestion of large doses [107]. There are structural and mechanistic similarities between Vacor and streptozotocin and alloxan [107], which are specifically toxic to β cells, and used to induce diabetes in experimental animals [107, 108]. Some epidemiological studies have assessed the intake of nitrates and nitrites, which may be converted to related *N*-nitroso compounds, but most studies have used ecological study designs and assessed levels in community drinking water, which is probably a poor indicator of total exposure. A potential diabetogenic role of *in utero* exposure to bafilomycin, a toxin produced by bacteria growing on the skin of root vegetables such as potatoes, has been suggested based on experiments with rodents and *in vitro* studies [109]. In a prospective study, there was no support for the idea that frequent potato consumption during pregnancy could increase the risk of islet autoimmunity in the offspring, but it is unknown whether frequency of potato intake really is a marker for bafilomycin exposure [110]. In a case–control study nested within a cohort of pregnant women, persistent organochlorine pollutants in stored sera were not associated with later risk of T1DM in the offspring [111]. If anything, there was a tendency towards inverse associations. In conclusion, few high-quality studies are available on the potential influence of environmental chemicals on T1DM incidence in the population, and there is currently little direct evidence for an important involvement of such factors in human T1DM.

Nutritional factors

Several possible plausible mechanisms have been proposed to link dietary factors to T1DM, including "molecular mimicry" and a detrimental effect of bovine insulin in cow's milk (reviewed in [112]). A reduced risk conferred by prolonged breastfeeding and/or delayed introduction of cow's milk has been suggested in

many case–control studies, but most of these studies were susceptible to recall bias and the issue is controversial [113]. Prospective studies of genetically susceptible children have found mixed results. In the DIPP study, neither multiple islet autoantibodies nor T1DM were associated with duration of exclusive or total breastfeeding [114], whereas the DAISY study found an association between early or late introduction of solid foods and increased risk of T1DM [115]. In MIDIA, there was an inverse association between long duration of any breastfeeding and risk of T1DM, but no association with duration of full breastfeeding, age at introduction of solid foods, or breastfeeding when introducing solid foods [116]. Duration of breastfeeding was not associated with self-reported T1DM up to age 30 years in a prospective population-based study including 61 cases [117]. It is difficult to differentiate the role of breastfeeding versus introduction of weaning foods, but the hypothesis that delaying the introduction of intact cow's milk proteins (regardless of breastfeeding duration) is tested in a large randomized trial called the TRIGR. While results for the primary endpoint (T1DM at age 10 years) are expected in 2017, the intervention showed no significant reduction in positivity for multiple islet autoantibodies [118].

The immunomodulatory effects of vitamin D and the preventive effect of pharmacological (hypercalcemic) doses of 1,25-dihydroxyvitamin D on diabetes development in experimental animals have been documented in several studies [119]. Systemic concentration of 1,25-dihydroxyvitamin D is tightly controlled by hydroxylation of 25-hydroxyvitamin D, and this must be taken into account when evaluating experimental results from animal models. Vitamin D is also produced in the skin upon exposure to ultraviolet light, and no prospective study has yet been published of serum 25-hydroxyvitamin D, which is an established marker of vitamin D status, and risk of T1DM. A multicenter case–control study found a significantly lower risk of T1DM associated with reported use of vitamin D supplement in early life [120], although recall and selection bias may have affected these findings; however, this was also supported by a prospective Finnish study [121]. In the DAISY study of genetically predisposed children followed longitudinally, there was no significant association between 25-hydroxyvitamin D in serum from toddlers and risk of islet autoimmunity or progression from islet autoimmunity to T1DM [122]. The German BABYDIAB study similarly found no significant association between circulating 25-hydroxyvitamin D and progression from islet autoimmunity to T1DM [123]. Prospective studies of maternal intake of vitamin D via food during pregnancy and risk of islet autoimmunity in children have not produced convincing evidence for any relation [124]. However, a study in Norway found a significant association between low 25-hydroxyvitamin D in late pregnancy and higher risk of T1DM in the offspring [125]. A study of serum 25-hydroxyvitamin D in pregnant women collected during the first trimester of index pregnancies did not find any significant association with risk of childhood-onset T1DM in the offspring [126].

A case–control study in Norway found an association between the use of cod liver oil in the first year of life and lower risk of T1DM [127]. Cod liver oil, which is commonly used in Norway, is an important source of both vitamin D and long-chain n-3 fatty acids docosahexaenoic acid (DHA) and eicosapentaenoic acid (EPA) in this population. The lack of association with other vitamin D supplements in these studies supports a role of n-3 fatty acids rather than vitamin D. Recall bias cannot be ruled out entirely from the latter study. Although support for the hypothesis that intake of dietary n-3 fatty acids may prevent islet autoimmunity and/or T1DM came from a prospective study including both dietary assessment and analysis of fatty acid composition of red-cell membranes, which is a biomarker of n-3 fatty acid status [128], a later follow-up of this study did not find any association with progression from islet autoimmunity to T1DM [129].

Despite previous indications from two prospective studies that serum α-tocopherol (vitamin E) could be associated with lower risk of T1DM, there was no association with advanced islet autoimmunity or T1DM in early life in the DIPP study [130]. In conclusion, the role of nutritional factors in T1DM remains uncertain.

Perinatal factors and postnatal growth

Offspring of mothers without diabetes aged 35 years or more when giving birth have a ∼20–30% increased risk compared with offspring of mothers who are aged 25 years or less [131, 132]. Results for birth order and for paternal age have been less consistent [131, 133, 134]. Birth by cesarean section has been associated with a ∼20% increased risk of T1DM in children according to a meta-analysis of 20 published studies [135]. Although there is some potential for selection bias in the case–control studies included, and the mechanism is unknown, it was speculated that delayed colonization of the infant's intestine associated with cesarean section may be involved. On the other hand, a recent study of discordant sibships did not find any association between cesarean section and T1DM [136].

Increased birth weight has been associated with a relatively weak but significant increase in risk of childhood-onset T1DM in large cohort studies based on linkage of population registries, independent of maternal diabetes and other potential confounders [137]. There have also been studies reporting no significant association, but these were generally smaller case–control studies. Birth weight is certainly only a marker of some other phenomenon and the mechanisms involved remain to be defined.

Associated factors such as postnatal growth or excess body weight might be of relevance. A number of studies have indicated that children developing T1DM are taller, heavier, or gain more weight or height prior to diagnosis compared with their peers [138, 139]. However, there was substantial heterogeneity between studies in methodology and results, such as age at measurement of body size, which body size or growth measurement was associated with T1DM, and how data were analyzed statistically. Many of the published studies were case–control studies, which are prone to selection bias. However, two recent large-scale cohort studies found that for each standard deviation (approximately 1 kg) increase in weight or weight gain up to age 12 months, the risk of

T1DM [140] or multiple islet autoantibodies [141], increased by approximately 20%.

In summary, environmental factors may influence individuals very differently, depending on the genetic background, although direct evidence for specific gene–environment interactions from humans is scarce. No specific single factor has been identified thus far. Taking into account the multifactorial nature of T1DM, specific environmental risk factors with sufficiently large impact to be of clinical importance and detectable in epidemiological studies may not exist; however, identification of potential environmental risk factors and their role in the disease process is important in the potential prevention of T1DM in the future, and lack of consistent findings may reflect lack of properly conducted prospective studies. Given the enormous amount of resources necessary for conducting preventive intervention trials, and the negative results of completed trials, it may be wise to initiate future trials based on consistent findings from properly conducted prospective observational studies.

Mortality

Before the discovery of insulin in 1922, T1DM meant an almost certain death soon after its onset. After the initiation of insulin replacement therapy, a dramatic improvement in survival occurred. Another major improvement in survival occurred in people with diabetes diagnosed in the 1950s [142]; however, even today T1DM is associated with a ~2–8-fold excess risk of premature mortality [143] (Figure 3.7). A large variation in relative mortality has been reported from different countries. For instance, the standardized mortality ratio (SMR) for people with T1DM in Finland was lower than that in Lithuania, Estonia, and Japan [144, 145]. A higher mortality in African American compared with white individuals with T1DM in the USA has been reported, and this difference seems to be attributable to acute complications [146].

Data from Europe showed that the short-term mortality was two times higher in people followed from diagnosis of T1DM in childhood than the respective general populations, with variation in the SMR from about 1.1 to 4.7 in different countries [147]. In a nationwide cohort of individuals with T1DM in Norway followed from onset before 15 years of age and up to 40 years' duration (mean 17 years), the SMR was 3.6 [148]. In a UK cohort of more than 7000 prevalent cases of T1DM with a mean age of 33 years at baseline, the SMR after up to 7 years of follow-up (mean 4.5 years) was 3.7 [149]. Many studies have reported that the SMR varies with age and with diabetes duration, or both, but the results are not consistent among studies.

Ascertainment of cause of death is difficult, but around one-third of the early deaths in the European multicenter study were clearly attributable to diabetic ketoacidosis (DKA), and about half of the relatively few deaths among young people with T1DM seem to be unrelated to diabetes [147, 150]. This was consistent also in a recent study where a clinical committee evaluated

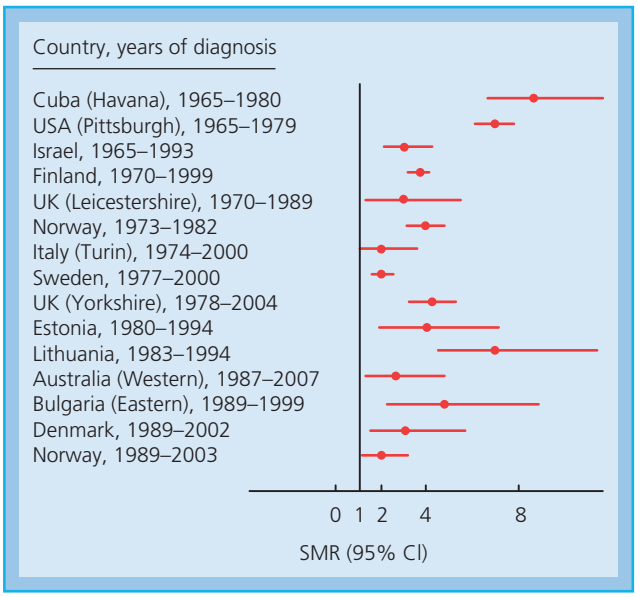

Figure 3.7 Standardized mortality ratios (SMRs) for people followed from diagnosis of childhood-onset type 1 diabetes. Data are from different studies, summarized by Morgan et al. 2015 [143]. Only studies with at least 10 observed deaths are shown. An SMR of 1.0 means a mortality rate among people with type 1 diabetes that is equal to that in the background population for the same age, sex, and calendar period. Studies were sorted by the earliest year of diagnosis of type 1 diabetes, and secondarily by SMR. Note that there were differences in duration of follow-up and other minor methodological differences between studies.

all available death certificates, medical records, autopsy reports, and police reports to adjudicate the cause of death [151]. Hypoglycemia as a cause of death is currently rare compared with DKA, but potentially increasing because of the more vigorous glycemic control suggested for the prevention of long-term complications [152]. After ~10–15 years of diabetes duration, microvascular and macrovascular chronic diabetes complications start to make an impact, and after about 30 years of age cardiovascular causes become increasingly important [153]. The relative mortality from cardiovascular causes is at least as high for women as for men. SMRs for cardiovascular causes of death of 8–40 have been reported in people with T1DM, and the SMR depends strongly on nephropathy [154]. There are some data suggesting that people with T1DM who remain free of nephropathy do not have higher mortality than that in the background population [153, 155], but this has not been confirmed in other studies [156, 157].

There is growing evidence that better glycemic control and improved risk factor control such as lowering of blood pressure and lipids are associated with reduced risk of late complications and improved survival [154]. Long-term follow-up in the DCCT/EDIC showed that multiple daily insulin injections (today's standard mode of treatment) compared with less intensive insulin treatment for 1–15 years resulted in a significant reduction in total mortality [158]. Nevertheless, a large proportion of individuals with T1DM have suboptimal HbA_{1c} levels. Despite the relationship between increased HbA_{1c} and increased mortality,

a Swedish study found that even those with low HbA_{1c} seem to have a significantly higher mortality than people without diabetes [155]. In line with the impression that treatment is gradually improving, people diagnosed with T1DM in more recent years seem to have lower short-term mortality than those diagnosed in earlier time periods [159–161]. Nevertheless, a major gap in mortality compared to the general population remains in recent large-scale studies [162]. A continuing challenge is the deaths of individuals with undiagnosed T1DM and people without access to care in the developing world.

Conclusions

T1DM is one of the most common chronic diseases diagnosed in childhood, but the disease can occur at any age. Its incidence varies drastically between populations and even within populations. T1DM has a strong genetic component and familial clustering, but the majority of cases have no affected siblings or parents. Only a minority of carriers of the susceptibility genes develop T1DM. The incidence of T1DM is increasing in most studied populations at an average rate of ~3–4% per year. The causes of this increase are not known. It is believed that some environmental factors may have contributed to it, but no definite causal environmental factor for autoimmune T1DM has yet been identified.

T1DM was a fatal disease before the insulin era. Although mortality in people with diabetes has decreased drastically, both acute and late complications lead to increased morbidity and premature mortality in T1DM. Primary prevention of T1DM would be the only solution to these problems, but unfortunately no practical preventive measures are currently available.

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4 Epidemiology of Type 2 Diabetes

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Key points

- The prevalence of type 2 diabetes mellitus (T2DM) is increasing worldwide.
- Approximately 415 million people worldwide had diabetes in 2015, making it one of the most common non-communicable diseases globally.
- The largest increase is observed in regions with rapidly developing economies and urbanization.
- The aging population, with an increase in the proportion of people aged >65 years in most countries, has contributed significantly to this increase in prevalence.
- The age of onset of diabetes is also decreasing in many countries, giving rise to an increasing proportion of young people of working age being affected by the disease.
- Several risk factors are known to be associated with increased risk of T2DM. Many of these risk factors are associated with a Westernized lifestyle and increase with urbanization, although novel environmental risk factors have emerged.
- Areas with a high ratio of impaired glucose tolerance (IGT) to diabetes are at an earlier stage of the diabetes epidemic, and thus may be a particular target for preventive strategies.
- The regions with the highest diabetes prevalence rate at present are in the Pacific Islands and Middle East.
- The largest increase in diabetes prevalence is predicted to occur in China and India.
- Diabetes is associated with approximately twofold increased mortality in most populations, with the excess risk decreasing with increasing age.
- The increase in diabetes prevalence, particularly among young adults, along with the increased morbidity and mortality associated with microvascular and macrovascular complications, is likely to lead to an escalation of healthcare costs and loss of economic growth.
- Prevention efforts require widespread public education and coordinated multisectoral efforts to encourage physical activity and a healthy diet.
- Maternal health and the intrauterine environment have also emerged as an important window of opportunity for primordial prevention.

Introduction

Type 2 diabetes mellitus (T2DM) is one of the commonest forms of chronic disease globally and few societies or ethnic groups are spared. It accounts for about 85% of cases of diabetes in white Europeans and virtually all other ethnic groups. In 2015, the International Diabetes Federation (IDF) estimated that 415 million people worldwide had diabetes, of whom 75% live in low- and middle-income countries. Among those aged 20–79 years, about 8.8% had diabetes globally, of whom an estimated 46.5% remain undiagnosed. The highest number of people with diabetes was in the Western Pacific region, with 153.2 million, and the region with the highest prevalence rate, at 12.9%, was North America and the Caribbean [1].

The number of people with diabetes is expected to reach 642 million by 2040, an increase of 55% [1]. The largest increases will be in countries with rapidly growing economies, such as India and China. With the increasing consumption of high-energy food, increasing adoption of sedentary lifestyles and urbanization, increasing numbers of individuals are developing T2DM, and the age at which individuals are diagnosed is decreasing. Individuals exposed to longer periods of hyperglycemia will undoubtedly have increased risks of developing vascular complications related to diabetes. The potential healthcare costs and burden of diabetes in these regions will have a significant impact on the economic growth of these regions, as discussed further in Chapter 5.

The epidemiology and prevalence of diabetes are partly determined by the diagnostic criteria used to diagnose diabetes, and these have been modified on a number of occasions. The diagnostic criteria for diabetes and impaired glucose tolerance are based on epidemiological evidence relating microvascular complications to specific degrees of hyperglycemia, and the fasting glucose cut-off has been modified as new data emerged. These changes have major implications for the interpretations of current and future epidemiological studies on diabetes. In 1999, the diagnostic threshold of fasting glucose was lowered from 7.8 mmol/L (140 mg/dL) to 7.0 mmol/L (126 mg/dL). A fasting glucose level

Textbook of Diabetes, Fifth Edition. Edited by R. Holt, C. Cockram, A. Flyvbjerg and B. Goldstein.

between 6.1 and 6.9 mmol/L (111–125 mg/dL) was considered to be prediabetic and the term "impaired fasting glucose" was used. Subsequent lowering of the "normal" fasting glucose level to 5.6 mmol/L (100 mg/dL) further increases the number of people with "prediabetes." Impaired glucose tolerance (IGT), on the other hand, is another prediabetic state, which is only identified by oral glucose tolerance testing, with a post-load glucose level of 7.8–11.0 mmol/L (140–199 mg/dL). It is estimated that about 318 million people or 6.7% in the 20–79 years age group have IGT [1].

Risk factors for T2DM

Several risk factors are known to be associated with increased risk of T2DM, including increasing age, obesity (especially central obesity), dietary excess, dietary factors such as increased intake of animal fats and sugar-sweetened beverages, sedentary lifestyle, a positive family history, history of gestational diabetes, polycystic ovary syndrome, presence of hypertension, hyperlipidemia, or other cardiometabolic risk factors (Figure 4.1) (see Part 8). Many of these risk factors are associated with a Westernized lifestyle and increase with increasing urbanization and mechanization. The recognition of the role of these factors in the pathogenesis of T2DM has led to recommendations for selective screening for T2DM in people with these risk factors [2, 3].

Several large studies, including the Nurses Health Study in the United States and the InterACT Study in Europe, have contributed to improved understanding of the role of dietary factors and the risk of incident T2DM. Dietary factors that increase the risk for T2DM include the following [4, 5]:

- increased fat intake;
- increased intake of red and processed meat;
- consumption of fried food;
- increased intake of white rice;
- sugar-sweetened beverages.

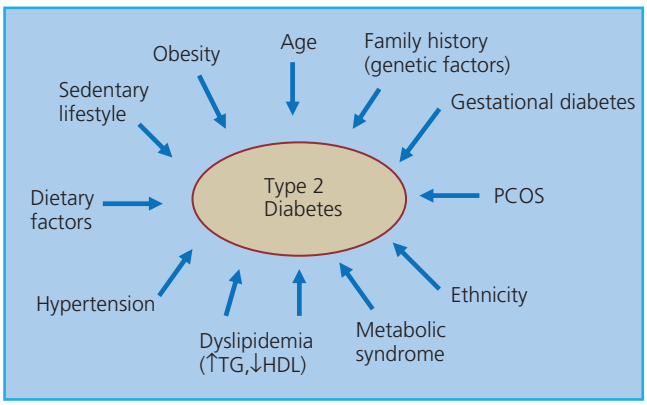

Figure 4.1 Risk factors in the development of T2DM. HDL, high-density lipoprotein cholesterol; PCOS, polycystic ovarian syndrome; TG, triglycerides.

Dietary factors that decrease the risk for T2DM include the following [4, 5]:

- increased fruit and vegetable intake;
- a Mediterranean diet pattern;
- fermented dairy products;
- intake of oily fish;
- tea.

Obesity accounts for 80–85% of the overall risk of developing T2DM, and underlies the current global spread of the disease [6]. The risk of T2DM increases as the body mass index (BMI) increases above 24 kg/m^2, although the risk appears to be present with lower BMI in Asians [7, 8]. Although central obesity is a particularly strong factor, it can impart further risk regardless of the overall level of general obesity. This obesity-related risk is marked in certain ethnic populations such as Pima Indians, black Africans, South Asians, Chinese, and other Asian populations [9–13], and may be related to increased visceral adiposity. Obesity, particularly central adiposity, is associated with insulin resistance, and also β-cell dysfunction, partly through increased free fatty acids and lipotoxicity (see Chapter 16). Obesity is also associated with other metabolic abnormalities such as dyslipidemia and hypertension.

The clustering of some of the risk factors, namely hypertension, elevated blood glucose, elevated triglyceride, low high-density lipoprotein (HDL) cholesterol, and abdominal obesity, is termed the metabolic syndrome. Presence of the metabolic syndrome, according to the definition, is associated with a 2–5-fold increased risk of developing diabetes in most populations [14].

A positive family history is an important risk factor for T2DM. In the InterAct case–cohort study, a family history of T2DM was associated with a 2.7-fold risk of incident diabetes [15]. There have been advances in our understanding of the genetic basis of T2DM over the last few years, with more than 80 genetic variants so far identified as being associated with T2DM (see Chapter 14) [16]. Nevertheless, the identified genetic variants explain <10% of the heritability of T2DM. In the InterAct study, a genetic risk score composed of known genetic variants for T2DM explained only 2% of the family history-associated risk of T2DM, suggesting that there are still unexplained factors that contribute to the association between family history and T2DM, including yet-to-be identified genetic factors, shared environment and behavior, epigenetic factors, and possibly other factors [15]. Most of the known genetic variants for T2DM were identified in European populations. Although several T2DM-associated genetic variants have been identified in other populations including, East Asians and South Asians, our current knowledge of genetic variants associated with T2DM cannot explain the marked geographical and ethnic variations in diabetes prevalence [13, 17].

Traditional risk factors such as increasing age, adiposity, physical inactivity, dietary factors, positive family history, and presence of other cardiometabolic risk factors are well-recognized factors for diabetes and many are considered to be on the causal pathway. Current approaches to diabetes prevention are mostly focused on addressing these risk factors for diabetes, in particular unhealthy

diet and physical inactivity. In the prospective Whitehall II study, it was estimated that traditional modifiable risk factors such as health behavior and obesity, when measured repeatedly over time, explain approximately half of the social inequalities in incidence of T2DM [18].

Recent emerging risk factors

Sugar-sweetened beverages

Consumption of sugar-sweetened beverages is now recognized as an important contributor to the recent rapid escalation in obesity and diabetes [19, 20]. Sugar-sweetened beverages include carbonated soft drinks, fruit juices, iced tea, and energy and vitamin water beverages, and are similar in having high sugar content, low satiety, and low nutritional value. The intake of such beverages has increased markedly over recent decades, and consumption trends often mirror those of obesity and diabetes prevalence in different parts of the world [21]. Sugar-sweetened beverages contain added sugars in the form of fructose, chronic exposure to which can lead to hepatic steatosis, insulin resistance, central obesity, and metabolic abnormalities [22].

Decreased sleep

In addition to changes in diet and physical activity, it has recently been recognized that there is a U-shaped relationship between sleep duration and diabetes risk, with short sleep duration, another facet of our modern lifestyle, being an important contributor to the increasing prevalence of T2DM. Early seminal work highlighted the detrimental effects of sleep deprivation on glucose tolerance and insulin sensitivity [23]. Subsequent cross-sectional studies have suggested an association between short sleep duration and diabetes [24] and obesity [25]. In a prospective study of more than 70,000 women in the Nurses Health Study, short sleep duration was associated with a ~57% increase in diabetes risk over the 10-year study period [26]. Similar data were obtained from the First National Health and Nutrition Examination Survey (NHANES I), which noted that people with a sleep duration of ≤5 h had a 47% increase in incident diabetes over a 10-year period [27]. The exact mechanism whereby sleep restriction increases diabetes risk is unclear, although it may be related to activation of the sympathetic nervous system, decrease in cerebral glucose utilization, changes in the hypothalamic–pituitary–adrenal axis, and other neuroendocrine dysregulation [27]. In addition to short duration, other sleep disturbances, and also altered circadian rhythm, for example during shift work, are associated with increased risk of diabetes [28].

Depression and treatment of depression

There is a bidirectional relationship between depression and diabetes/IGT (see Chapter 57). The incident rate of T2DM is modestly higher among those with baseline depressive symptoms. Once T2DM was diagnosed, there was a positive association with depressive symptoms, illustrating the emotional burden of having diabetes [29]. The use of second-generation antipsychotic agents, commonly referred to as "atypical antipsychotics," has been linked with hyperglycemia and diabetes [30]. A complex association exists between mental illness, use of psychiatric medications, and diabetes [31].

Drug-induced metabolic changes

There is increasing recognition that some commonly used medications may be associated with adverse metabolic effects and increased risk of diabetes (see Chapter 19) [32]. High-dose thiazide diuretics worsen insulin resistance and β-blockers can impair insulin secretion. The increasing use of highly active antiretroviral therapy (HAART) has dramatically reduced the mortality of people with HIV infection. However, protease inhibitors and, to a lesser extent, nucleoside reverse transcriptase inhibitors are associated with insulin resistance, deranged glucose and lipid metabolism, and an increased risk for T2DM. The increasing use of such agents will likely have a significant impact on the epidemiology of diabetes in areas where HIV/AIDS is endemic, such as Africa [33].

Environmental toxins

Whereas most studies on the increasing burden of diabetes with Westernized lifestyle have focused on changes in dietary patterns and the increasingly sedentary lifestyles, some studies suggest that environmental pollutants may represent a previously unrecognized link between urbanization and diabetes [34, 35]. For example, there is strong cross-sectional association between serum concentrations of chlorinated persistent organic pollutants with diabetes [36] and also components of the metabolic syndrome [37]. Brominated flame retardants, bisphenol A, and perfluorinated compounds have emerged as other classes of organic pollutants that are associated with diabetes [38, 39]. These environmental toxins may accumulate in adipose tissue and act as endocrine disruptors, leading to dysregulation of glucose and lipid metabolism.

Low birthweight and fetal malnutrition

There is a relationship between intrauterine environment, fetal malnutrition, and the risk of diabetes and cardiovascular disease later in life [40, 41]. Maternal undernutrition and low infant birthweight, along with rapid postnatal growth, are associated with increased risk of diabetes in the offspring. This "mismatch" of a metabolic phenotype programmed during intrauterine development and the nutritionally rich postnatal environment may be most important in regions that are undergoing rapid economic development, and may be an important factor contributing to the rapid rise in diabetes in Asia and the Pacific region [42].

Maternal obesity, maternal hyperglycemia, and other factors in early development

In addition, offspring of obese women or women with diabetes have an increased risk of diabetes and cardiometabolic abnormalities [43, 44]. This is partly caused by the effects of maternal

overnutrition and effects of intrauterine hyperglycemia on fetal growth, although it may also involve epigenetic changes [45]. With increasing numbers of women with obesity or young-onset diabetes, this is likely to exacerbate the epidemic of diabetes further by setting up a vicious cycle of "diabetes begetting diabetes" [41, 46, 47].

Despite the increasing recognition of these novel risk factors, the main risk factors associated with diabetes remain the traditional ones such as increasing age, adiposity, physical inactivity, dietary factors, positive family history, and presence of other cardiometabolic risk factors, as outlined in Figure 4.1.

Methodological issues in the epidemiology of T2DM

In comparing epidemiological data in T2DM, one must be aware of the importance of the study methodology. Survey methods must be robust, to allow comparison and standardization. A large, truly random sample of a community, with a good response rate, is best; workplace samples may demonstrate "healthy worker" effects, whereas selective samples (e.g. volunteers or people with another disease) are the least useful because of inbuilt recruitment bias. The age distribution of sample populations is crucial in studying T2DM, whose prevalence rises with age; study populations must be age stratified and any comparisons age adjusted, either within the data set or standardized against a reference population. Finally, ascertainment methods are important, for example, whether participants undergo an oral glucose tolerance test, with or without preliminary blood glucose screening. Although reference is often made to the global and national estimates of diabetes prevalence in the *IDF Diabetes Atlas*, one has to be aware of several important limitations of these estimates. For countries in which prevalence studies are available, the data are presented in the *Atlas*. However, for many countries for which no updated prevalence studies are available, the estimates are based on modeled data from nearby countries matched in terms of percentage urbanization, ethnicity, and income group [48]. Owing to these methodological issues, prevalence figures for countries where estimates are based on modeling are not necessarily accurate, and not directly comparable with those from countries in which nationwide epidemiology surveys have been conducted.

As will be discussed later, studies conducted in different regions of the world have highlighted an increase in the prevalence of T2DM. Although few would argue that this translates into increasing burden associated with diabetes, it is important to recognize the factors that have contributed to this increased prevalence. Several factors directly affect the prevalence of diabetes, and may partly account for the increasing prevalence (Figure 4.2). These include:

- changes in the ratio of diagnosed to undiagnosed cases of diabetes;
- population demographic changes with an aging population;
- earlier age at onset of diabetes;

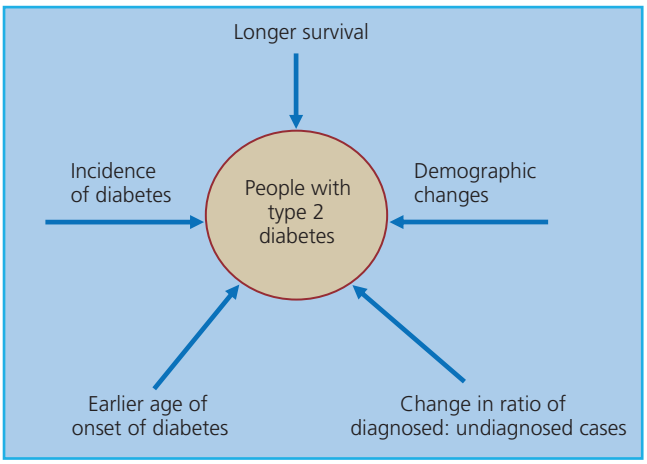

Figure 4.2 Diabetes epidemiological model. Factors directly affecting the prevalence of diabetes included in the present analysis. Source: Adapted from Colagiuri et al. 2005 [49]

- longer survival in people with diabetes;
- increasing incidence of diabetes [49].

The different factors may have different contributions depending on the population being studied, although most if not all are of some importance in most populations. The differences in the contributions of different factors to the prevalence of diabetes is illustrated by the fact that, for example, in Europe the incidence of diabetes has stabilized but longevity and increased case finding now explains the increased numbers, whereas in Africa and parts of Asia there is still a marked increase in incidence [1, 50, 51].

Effects of changes in the definition of diabetes

Although it has long been established that diabetes is a condition associated with hyperglycemia, there was no widespread accepted definition until the 1980s, when the World Health Organization (WHO) Expert Committee on Diabetes Mellitus defined diabetes as a state of chronic hyperglycemia that may result from many environmental and genetic factors often acting together [52]. The precise degree of hyperglycemia that defines diabetes has evolved with time, and relies on epidemiological studies regarding the distribution of glucose levels within various populations.

There are several consequences of the changes in the definition of diabetes with time on the epidemiology of diabetes. First, the American Diabetes Association (ADA) and 1999 WHO classification lowered the diagnostic threshold of fasting glucose from 7.8 to 7.0 mmol/L, thereby increasing the number of individuals in any given population that fulfilled a diagnosis of diabetes mellitus.

It is important to appreciate whether the diagnosis was based on elevated fasting glucose or post-load values during an oral glucose tolerance test. Although the lower fasting glucose level of 7 mmol/L was chosen to resemble the diagnostic significance of the 2-h post-load concentration more closely, numerous studies

Table 4.1 Comparison of WHO and ADA recommendations for the diagnostic criteria for diabetes and intermediate hyperglycemia.

	WHO (2006/2011)	ADA (2003/2010)
Diabetes		
Fasting plasma glucose	≥7.0 mmol/L (126 mg/dL)	≥7.0 mmol/L (126 mg/dL)
	or	
2-h plasma glucose[a]	≥11.1 mmol/L (200 mg/dL)	
HbA_{1c}	(Since 2011)	(Since 2010)
	≥6.5% (48 mmol/mol) (if assay standardized and accurately measured)	≥6.5% (48 mmol/mol) (if assay standardized and accurately measured)
Impaired glucose tolerance (IGT)		
Fasting plasma glucose	<7.0 mmol/L (126 mg/dL)	
	and	
2-h plasma glucose[a]	≥7.8 and <11.1 mmol/L (140 and 200 mg/dL)	
Impaired fasting glucose (IFG)		
Fasting plasma glucose	6.1–6.9 mmol/L (110–125 mg/dL)	5.6–6.9 mmol/L (100–125 mg/dL)
	and (if measured)	
2-h plasma glucose[a]	<7.8 mmol/L (140 mg/dL)	

[a]Venous plasma glucose 2 h after ingestion of 75 g oral glucose load.

have demonstrated that the fasting glucose and post-load criteria identify slightly different people in most populations [53–55]. The use of fasting glucose alone will reduce the overall prevalence of diabetes compared with that identified by 2-h post-load glucose values [56]. Furthermore, there is an increasing number of epidemiological studies that utilize the measurement of HbA_{1c} as an indicator of dysglycemia [57], and several professional organizations, including the ADA in 2010 and the WHO in 2011, have now included HbA_{1c} for the diagnosis of diabetes [58, 59], though this remains an area of debate [60, 61].

The WHO and ADA recommendations for the diagnostic criteria for diabetes and intermediate hyperglycemia are summarized in Table 4.1. Although the lower ADA threshold for diagnosing impaired fasting glucose will result in more people being diagnosed with intermediate hyperglycemia compared with the WHO recommendation, increased diagnostic activity, for example through the use of the oral glucose tolerance test, will increase the ratio of diagnosed to undiagnosed diabetes, and may impact on the prevalence rate reported in epidemiological studies. In a study utilizing 96 population-based cohorts to compare the different diagnostic criteria on population prevalence of diabetes, the prevalence based on HbA_{1c} was in general slightly lower than that based on fasting blood glucose. Furthermore, diabetes diagnosed on HbA_{1c} ≥6.5% had a pooled sensitivity of around 53% (95% confidence interval [CI]: 51.3–54.3%) compared with a definition of fasting glucose of ≥7.0 mmol/L for diagnosing individuals without a previous known history of diabetes [62].

In an earlier comprehensive report on the global prevalence of diabetes [63], it was noted that the most important demographic change to diabetes prevalence across the world was the increase in the proportion of people aged >65 years. Another major factor that has affected the prevalence of diabetes is the increasing age-specific prevalence, especially in the younger age groups [63]. This suggests an earlier age of onset of diabetes, which may be of particular importance in developing countries. It is noteworthy that the tendency is for the prevalence of IGT to decline as that of diabetes rises, suggesting that areas with a high ratio of IGT to diabetes are at an earlier stage of the diabetes epidemic and thus may be a particular target for preventive strategies. Changes and variations in the ratio of IGT to diabetes prevalence, the so-called "epidemicity index," may provide a useful marker for the scale of the epidemic in that particular region [64].

Regional and ethnic patterns of T2DM worldwide

This section considers the geographical distribution and secular changes in the prevalence of T2DM and intermediate hyperglycemia in the major regions of the world. Whenever possible, the most representative recent prevalence studies are presented. In addition, data from the *IDF Diabetes Atlas*, which utilized age- and sex-specific estimates for diabetes prevalence from available epidemiological surveys to extrapolate prevalence in related countries using a combination of criteria including geographical proximity, ethnic, and socioeconomic similarities, are also presented when necessary owing to lack of recent prevalence studies.

Current estimates of the total number of people with diabetes in each region of the world and in those countries with the highest overall numbers are shown in Figure. 4.3. Table 4.2 shows the

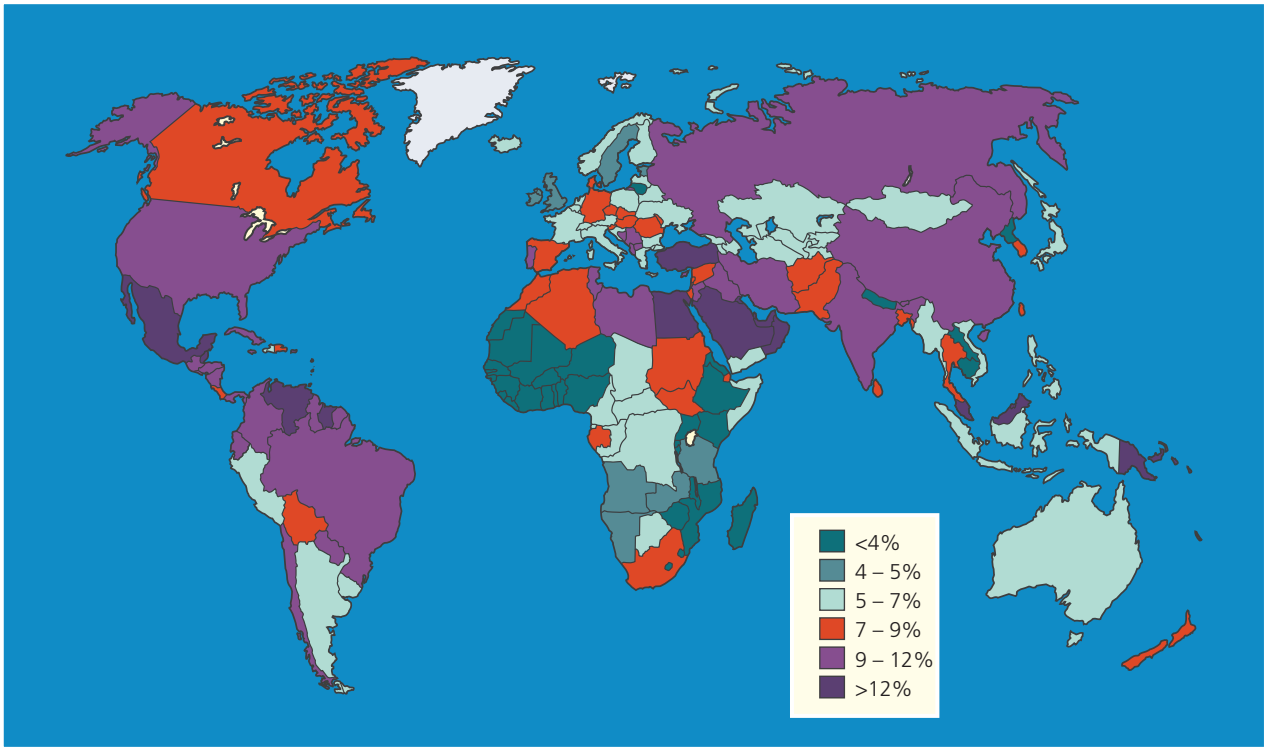

Figure 4.3 Global prevalence of diabetes. Source: Adapted from *IDF Diabetes Atlas*, International Diabetes Federation 2015 [1], Chapter 3, Map 3.1.

countries with the highest prevalence and projected prevalence, and Table 4.3 lists the countries with the greatest number of people with diabetes. These estimates are based on modeling of data available from countries in which prevalence data were obtained from epidemiological surveys, and hence are only estimates that must be treated with caution [48].

Africa

T2DM in the African continent provides contrasting pictures between more urbanized and more rural regions. Whereas poverty and malnutrition are still a major problem affecting sub-Saharan Africa, a region where diabetes is comparatively rare, urbanized areas such as North Africa are reporting increasing prevalence rates [65]. The IDF estimated that overall, ~3.2% of the adult population in the African region are currently affected by diabetes, and is projected to increase to 3.7% by 2040 [1]. Other important epidemiological issues in the region include a low incidence of type 1 diabetes mellitus (T1DM), which is complicated by the occurrence of atypical "ketosis-prone"

Table 4.2 List of countries with the highest prevalence of diabetes (age group 20–79 years, age-adjusted for comparative prevalence) in 2015.

Rank	Country	Prevalence (%)
1	Tokelau	30.0
2	Nauru	24.1
3	Mauritius	22.3
4	Cook Islands	21.5
5	Marshall Islands	21.3
6	Palau	20.9
7	Saudi Arabia	20.0
8	Kuwait	20.0
9	Qatar	20.0
10	United Arab Emirates	19.3

Source: Data from *IDF Diabetes Atlas*, International Diabetes Federation 2015 [1], Appendix: Country summary table: estimates for 2015.

Table 4.3 Top 10 countries with the greatest number of people with diabetes (age range 20–79 years) in 2015.

Rank	Country	Persons (millions)
1	China	109.6
2	India	69.2
3	USA	29.3
4	Brazil	14.3
5	Russian Federation	12.1
6	Mexico	11.5
7	Indonesia	10.0
8	Egypt	7.8
9	Japan	7.2
10	Bangladesh	7.1

Source: Data from *IDF Diabetes Atlas*, International Diabetes Federation 2015 [1], Chapter 3, Table 3.3.

diabetes. This initially presents as T1DM with severe hyperglycemia and ketosis, but subsequently has long-term remission with a clinical course more compatible with T2DM [66]. In addition, there is also a form of early-onset diabetes termed malnutrition-related diabetes mellitus that is associated with past or present malnutrition and sometimes accompanied by pancreatic calcification [33]. Although infective diseases such as HIV infection and tuberculosis are currently the main causes of mortality in sub-Saharan Africa, the increasing prevalence of diabetes and other non-communicable diseases is likely to overtake infections as major causes of mortality. In sub-Saharan Africa, only a small proportion of the population reaches ages at which T2DM becomes a major health problem. Although greater access to HAART has led to markedly reduced mortality, the improvement in life expectancy, coupled with the adverse metabolic effects of HAART, is likely to contribute to further increases in the prevalence of T2DM within the region [33, 67].

Sub-Saharan Africa

There is a paucity of prevalence data from sub-Saharan Africa, with most of the studies coming from Ghana, Cameroon, Nigeria, Tanzania, and South Africa [65, 68]. In a systematic review of prevalence data from Ghanaians and Nigerians, diabetes was rare at 0.2% in urban Ghana in 1963 and 1.65% in urban Nigeria in 1985. The prevalence of diabetes had risen to 6.8% in Nigeria in 2000 (for adults aged ≥40 years) and 6.3% in Ghana in 1998 (for adults aged ≥25 years) [69, 70]. In Cameroon (West Africa), adults aged 24–74 years had an overall diabetes prevalence of 1.1%, with an IGT rate of 2.7%. Prevalence rates in the capital of Cameroon (Yaounde) were 1.3% for diabetes and 1.8% for IGT, compared with rural prevalences of 0.8% for diabetes and 3.9% for IGT [71]. Undiagnosed cases accounted for the majority of cases in these studies, again reflecting a region at the early stages of a looming diabetes epidemic.

In South Africa, both diabetes and IGT are commoner in both urban and rural communities. In Cape Town, age-adjusted prevalences were 8% for diabetes and 7% for IGT [72]. A study conducted in a rural South African community based on a 75-g oral glucose tolerance test and the 1998 WHO criteria reported overall age-adjusted prevalences of diabetes of 3.9%, IGT 4.8%, and IFG 1.5%. Notably, 85% of the cases with diabetes were uncovered by the survey [73].

In addition to exposure to an urban environment, other factors that determine the risk of T2DM in African populations include positive family history, ethnic origin, central adiposity, and physical inactivity [65]. Possible ethnic differences have been examined in several studies. In both Tanzania and South Africa, migrant Asians have higher diabetes prevalence rates than indigenous Africans [74], but this could reflect lifestyle differences. In Tanzania, the difference was particularly marked (1.1% in Africans vs. 9.1% in Asians), which again emphasizes the low prevalence in urban East Africans.

The emerging epidemic of T2DM is further compounded by the various problems hampering the delivery of effective diabetes care within this region. This has resulted in poor glycemic control among most people with diabetes, and also a high frequency of chronic microvascular complications. The rising prevalence of diabetes may also hamper tuberculosis control efforts by increasing the number of susceptible individuals in endemic areas [75]. Better access to healthcare and treatment, improvements in infrastructure to support services (for example, by aligning diabetes care with screening and healthcare delivery for infectious diseases such as HIV and tuberculosis) and healthcare information systems, and also primary prevention measures are urgently needed to reduce the burden of acute and chronic complications of diabetes in the region [33, 65, 67, 76].

North America and the Caribbean

Diabetes and its complications are common and a significant cause of morbidity in North America. The NHANES reported a crude prevalence of total diabetes in 1999–2002 of 9.3%, comprising 6.5% diagnosed and 2.8% undiagnosed [77]. This was significantly increased compared with a crude prevalence of total diabetes in 1988–1994 of 5.1%, mainly through an increase in diagnosed diabetes. There was marked variation in prevalence between ethnic groups, with age- and sex-standardized prevalences of diagnosed diabetes approximately twice as high in non-Hispanic black Americans (11%) and Mexican Americans (10.4%) compared with non-Hispanic white Americans (5.2%). The prevalence of diabetes among the elderly of these minority groups was particularly high, exceeding 30% [77].

The high prevalence rates in US Hispanic people and black Americans are well documented. In 1991, the age-adjusted prevalence of diabetes was 6% in white Americans, 9% in Cubans, 10% in black Americans, 13% in Mexican Americans and 13% in Puerto Ricans [78]. Rates have risen in all groups, but these differences appear to persist. Between 1987 and 1996, the 7–8-year incidence of T2DM approximately tripled in both Mexican Americans and non-Hispanic white Americans, although the absolute rate was twice as high in the Mexican Americans [79]. T2DM is also significantly commoner among older Puerto Ricans (38%) and Dominicans (35%) than among non-Hispanic white Americans (23%) [80]. Economic disadvantage may explain much of the excess prevalence of T2DM among African American women [81].

Other populations in the USA that are particularly at risk of T2DM are the Native American Indian communities, notably the Pima Indians, of whom 50% have diabetes [82]. Reports have highlighted the developing epidemic of T2DM in American Indian youth [83]. Among 15–19-year-olds, diabetes affected 5.1% of Pima Indians (a sixfold increase in prevalence over the previous 20 years) and 0.2% of Canadian Cree and Ojibway Indians. The overall prevalence among all US American Indians of this age is 0.5%. This epidemic of T2DM in young American Indians is supported by secular trends in the incidence rate of T2DM over the previous 40 years in Pima Indians, which showed a more than fivefold increase in incidence rates among Pima Indians aged 5–14 years [84].

A similar situation was seen in Canada, where Aboriginal peoples had more than a twofold increase in prevalence compared with the general population [85]. Other minority groups are also not spared. Among native Hawaiians (Polynesians), the crude (i.e. not age-adjusted) prevalence rates of T2DM and IGT were reported in 1998 to be 20 and 16%, respectively. The age-adjusted rate for T2DM was four times higher than among the US NHANES II study population [86]. In 1991, second-generation Japanese Americans had prevalence rates of 16% (diabetes) and 40% (IGT) [87], and incidence rates remained high at 17.2 per 1000 person-years [88]. This may be due to the increase in visceral adiposity in a population predisposed to impaired β-cell function [89]. Other Asian populations living in the USA that are particularly prone to diabetes include Asian Americans, in whom linguistic difficulties may be a particularly relevant barrier to diabetes education and effective care delivery [90].

It has been estimated that the number of adults in the USA with diagnosed diabetes will rise from 11 million in 2000 (overall prevalence 4.0%) to 29 million in 2050 (overall prevalence 7.2%). The fastest growth is expected to be among black Americans. The projected increase of 18 million is accounted for by approximately similar contributions from changes in demographic composition, population growth, and secular trends [91]. In 2014, it was estimated that 29.1 million people in the USA had diabetes, of whom 8.1 million were undiagnosed. The direct and indirect medical cost attributed to diabetes in the USA in 2012 was $245 billion [92]. Recent data suggest that the percentage of diagnosed people reaching glycemic goals and achieving risk factors control has improved over the last two decades, although only 14% met all three targets regarding glycemic, blood pressure, and lipid control, along with smoking cessation [93]. There has been a substantial reduction in the rates of diabetic complications over the last two decades, especially with regard to myocardial infarction and acute hyperglycemic emergencies [94].

An increasing number of younger people will be affected. In the SEARCH for Diabetes in Youth Study, a multiethnic, population-based study, the incidence of diabetes was 24.3 per 100,000 person-years. The incidence rates of T2DM were highest among American Indians and African American adolescents, varying from 17 to 49.4 per 100,000 person-years, compared with 5.6 per 100 000 person-years in non-Hispanic white Americans [95].

Caribbean

Studies in Jamaica exemplify the secular trend in the West Indies. Rates in the 1960s (underestimated owing to the screening procedure used) [103] were low but rose in the 1970s to 4% in those aged 25–44 years and 8–10% in those aged 45–64 years [104, 105], and to an overall rate of 7.4% in 1996 [106]. A report in 1999 indicated prevalence rates of 16% in women and 10% in men (13% overall). As elsewhere, this exceeds the rate of rise among European-origin populations and parallels the spread of obesity [107].

Central and South America

Data from this region are scarce. In the Mapuche natives in rural Chile, the prevalence of T2DM estimated in 2001 was 3% in men and 5% in women [96], which represents a substantial rise above the very low prevalence of <1% reported in 1985 [97]. Diabetes is clearly much more common in urban communities, for example, 14% in Mexico City in 1994 [98], compared with a 5–10% prevalence nationwide [99]. Surveys in Brazil and Colombia in the early 1990s indicated age-adjusted prevalence rates of ~7% [100, 101]. A recent study in Brazil revealed a rate of self-reported diabetes of 10.1% [102]. A high prevalence of abdominal obesity was noted in these populations, affecting more than 80% of women [99].

Europe

This region contains a diverse mix of countries that have marked differences in affluence, and includes some of the most developed countries in the world. Nevertheless, updated nationwide survey data are only available in some countries. In the *IDF Diabetes Atlas*, only a minority of the 56 European countries had recent published data on national prevalence of diabetes, which ranged from 4.7% in the United Kingdom to 12.8% in Turkey [1, 51] (Table 4.4).

Table 4.4 National estimates of diabetes in Europe in 2015.

	Prevalence of diabetes (%)	
Country	**National population[a]**	**Comparative population[b]**
Albania	12.0	10.3
Austria	9.5	6.9
Belgium	6.7	5.1
Cyprus	10.4	9.6
Denmark	9.9	7.2
Finland	9.0	6.0
France	7.4	5.3
Germany	10.6	7.4
Greece	7.5	5.2
Iceland	7.6	6.1
Ireland	5.3	4.4
Israel	8.5	7.5
Italy	7.9	5.1
Malta	13.9	9.9
The Netherlands	7.9	5.5
Norway	7.8	6.0
Poland	7.6	6.2
Spain	10.4	7.7
Sweden	6.3	4.7
Turkey	12.5	12.8
UK	6.2	4.7

[a] Prevalence based on current age/gender composition.
[b] Prevalence standardized to global age/gender composition.
Source: Data from *IDF Diabetes Atlas*, International Diabetes Federation 2015 [1], Appendix: Country summary table: estimates for 2015.

United Kingdom

T2DM imposes particular burdens in inner cities with multiethnic populations, as those originating from the Indian subcontinent have a high diabetes prevalence. In typical studies [108, 109], the age-adjusted prevalence rates were 3% and 5% in white European men and women, respectively, compared with 12% and 11% in their Asian counterparts in the UK. Asians also show a higher prevalence of IGT, a male preponderance, a younger age at diagnosis, and a lower proportion of undiagnosed diabetes [109].

Poverty and social deprivation apparently contribute to the increasing prevalence of T2DM among inner-city residents; for example, in all ethnic groups in inner-city Manchester there was a surprisingly high age-standardized prevalence, including a rate of 20% among white Europeans [110]. Social deprivation, obesity, physical inactivity, and smoking tend to co-segregate, which may explain this phenomenon. The importance of dietary factors was highlighted by two studies, which demonstrated an association between high dietary energy density or unhealthy dietary patterns characterized by a high intake of sugar-sweetened beverages, burgers, and sausages and snacks with incident T2DM [111, 112]. In the Ely Study, a population-based longitudinal study, the 10-year cumulative incidence of diabetes was 7.3 per 1000 person-years [113].

Scandinavia and Nordic countries

Here, the more homogeneous population may indicate more accurately the true prevalence of T2DM among white Europeans. A survey in northern Sweden revealed a prevalence of diabetes of 8.1% in 2002 [114]. Similar data were obtained in a study in Finland, with age-standardized prevalence of diabetes in 45–64-year-olds being 10.2% for men and 7.4% for women [115]. Lower prevalence data were noted for Iceland [116].

In the early 1990s, T2DM was rare in northern Finland but the prevalence of IGT was 29% in men and 27% in women [117], comparable to that in a homogeneous white female Swedish population aged 55–57 years (28%) [118]. In Denmark, around 15% of the population had IGT in 2003 [119]. The high prevalence of IGT in Finland prompted the Finnish Diabetes Prevention Study [120], which examined whether lifestyle changes could prevent the development of T2DM. Strikingly, nutritional advice and increased physical activity reduced the risk of developing diabetes by 58% in people with IGT, and the effect was sustained over subsequent follow-up [120]. A more recent study in three regions in Finland noted prevalence of IGT of 10.5 and 9.2% in men and women, respectively, which were substantially lower than previously reported figures from northern Finland. It is unclear whether this difference is due to regional differences or to changes in the diabetes to IGT ratio [115].

Using a register of people with diabetes, the calculated incidence rate of diabetes in Denmark was 1.8 per 100,000 at age 40 years and 10 per 100,000 at age 70 years. The incidence rate increased by 5% per year before 2004 but then stabilized. The lifetime risk of diabetes was estimated at 30% [121]. Another study in Finland noted an alarming increase in the incidence of T2DM among young adults, with the age-adjusted incidence of T2DM among 15–39-year-olds being 11.8 per 100,000 per year. The incidence rate increased by 7.9% per year. Interestingly, despite having the highest incidence of childhood T1DM in the world, the incidence of T2DM among young adults in Finland is approaching that of T1DM among the 15–39-year-old age group (age-adjusted incidence of T1DM 15.9 per 100,000 per year) [122].

Continental Europe

A population-based survey in Verona, Italy, revealed an overall prevalence of T2DM of 2.5%, which increased significantly after the age of 35 years [123]. In northern Italy, the age-adjusted prevalence of T2DM was 9% in men and 8% in women over the age of 44 years [124]. In a study that compared the prevalence of diabetes in Casale Monferrato in northwest Italy in 1988 and 2000, the age- and sex-adjusted prevalence of diabetes had increased from 2.1% in 1988 to 3.1% in 2000, with higher age-specific prevalence rates of diabetes in every age group in the later survey, including a twofold increase in the risk for those aged ≥80 years [125].

In France, the MONICA study estimated the adjusted prevalence of T2DM to be 7% in men and 5% in women aged 35–65 years and the adjusted prevalence of impaired fasting glucose to be 12% in men and 5% in women [126]. The prevalence of diabetes increased to 19% in men and 9% in women aged over 60 years [127]. In the more recent French Nutrition and Health Survey conducted between 2006 and 2007, the prevalence of diabetes according to elevated fasting plasma glucose or HbA_{1c} ≥6.5% was 5.6%, with undiagnosed diabetes contributing to fewer than 20% of all cases of diabetes [128].

In The Netherlands, T2DM affects 8% of elderly white Dutch [129]; 65% of those with impaired fasting and post-load glucose levels went on to develop diabetes within 6 years [130]. In a prospective population-based study between 1998 and 2000, the age- and sex-adjusted prevalence of diagnosed diabetes was 2.2% at baseline and 2.9% after 2 years of follow-up, with the elderly aged ≥70 years accounting for 50% of the population with T2DM [131].

In Greece, the prevalence of diabetes increased from 2.4% in 1974 to 3.1% in 1990 [132], as the population aged and became more obese [133, 134]. The prevalence of T2DM was 7.6% in men and 5.9% in women in a survey conducted between 2001 and 2002 [135]. In a follow-up study on those free of cardiovascular disease at baseline, the incidence rate of diabetes within a 5-year period was 5.5% [136]. In Turkey, the overall prevalence rates of T2DM and IGT were 6 and 9%, respectively. Low levels of occupational activity, family history, and obesity were all associated risk factors [137, 138]. Adherence to a Mediterranean diet may have protective effects against diabetes [139].

Prevalence data from Eastern Europe are comparatively sparse. The age-adjusted prevalence of T2DM for men and women in Fergana, Uzbekistan, was estimated to be 8% in both urban men and women, with IGT affecting 5% of men and 6% of women.

Lower prevalence rates for both T2DM and IGT were reported for semirural inhabitants [140]. A survey in the rural area in the Sirdaria province of Uzbekistan confirmed similar age-adjusted prevalence rates of diabetes for men (10%) and women (7.5%). However, prevalence rates of IGT in Sirdaria women (14%) and in men (11%) were higher than for semiurban or urban inhabitants in Fergana [141]. In Russia, the estimated prevalence was 6% in men and 7% in women for diabetes and 6%, and 13%, respectively, for IGT; clustering of hyperlipidemia, obesity, hypertension and low 10-year survival was observed among those with diabetes [142]. A survey conducted in Moscow found a low incidence of reported diagnoses of diabetes (2%) [143], which was supported by another study based on self-reported doctor diagnoses [144]. In addition to underdiagnosis, undertreatment and infrequent insulin use are also likely to contribute to the burden of morbidity [144]. Much of the estimated prevalence data in other East European countries have been extrapolated from data from Poland, where the prevalence of T2DM increased from 3.7 to 10.8% between 1986 and 2000, with a similar increase in prevalence of IGT from 2.9 to 14.5% [145].

Southeast Asia

India

India is the second most populous country in the world and in terms of the number of people with diabetes, with an estimated 69.2 million affected in 2015, a figure that is projected to rise to 123.5 million by 2040 [1]. Sequential surveys in India [146–149] indicate that the prevalence of diabetes has risen steadily since the 1970s, although methodological differences hamper direct comparisons between prevalence studies.

The National Urban Diabetes Survey, carried out in six cities in 2001, found age-standardized prevalence rates of 12% for diabetes (with a slight male preponderance) and 14% for IGT; people ≤40 years old had prevalences of 5% (diabetes) and 13% (IGT) [149]. Diabetes was positively and independently associated with increasing age, BMI, and waist/hip ratio, and a family history of diabetes, a higher monthly income, and physical inactivity. IGT showed associations with age, BMI, and family history of diabetes. Subsequent studies showed an increasing prevalence, with a prevalence rate of 14.3% reported in the Chennai Urban Rural Epidemiology Study (CURES-17) [150], and 18.6% in the city of Chennai in another study [151]. In the large Indian Council of Medical Research-INdiaDIABetes (ICMR-INDIAB) study involving more than 13,000 adults across 188 urban and 175 rural sites in four different regions, the prevalence of diabetes was 10.4% in Tamilnadu, 8.4% in Maharashtra, 5.3% in Jharkhand, and 13.6% in Chandigarh [152]. This gave rise to estimates of 62.4 million people with diabetes and 77.2 million people with prediabetes in India in 2011 [152]. In addition to the increasing prevalence of diabetes, there appears to be a decreasing prevalence of IGT [150]. Another secular trend is the shift towards younger onset of diabetes, especially in urban areas, where up to 36% of those with diabetes are aged ≤44 years [150, 151].

Urban—rural differences in the prevalence of diabetes have been consistently reported in different studies in India. A study in Chennai noted a progressive increase in prevalence rate with increasing urbanization: 2.4% in rural areas, 5.9% in semiurban areas, and up to 11.6% in urban areas [148, 153]. Likewise, more recent data revealed a prevalence of 18.6% in the city of Chennai compared with 16.4% in a town, and 9.2% in periurban villages [151]. In a study of 77 centers in India (40 urban and 37 rural), the standardized prevalence rates for diabetes in the total Indian, urban, and rural populations were 4.3, 5.9, and 2.7%, respectively. Although the prevalence rates of diabetes and IGT are significantly higher in urban than rural areas, it appears that the rural–urban gradient is becoming increasingly attenuated [154].

The Chennai Population Study (CUPS) in 2008 reported alarming rates of incident diabetes (20.2 cases per 1000 person-years) [155]. This has been confirmed by a recent study, which reported an incidence of 22.2 per 1000 person-years, where 59% of those with prediabetes progressed to diabetes during mean follow-up of 9.1 years [156]. Identification of those at high risk and increasing the awareness of the population are much needed. A risk score specific for the Indian population, the Indian Diabetes Risk Score (IDRS), has been developed. It utilizes four clinical variables: age, family history, regular exercise, and waist circumference. A score of >21 identifies those with diabetes with a sensitivity and specificity of close to 60% [157]. This will help target high-risk individuals to early intervention, since lifestyle modification is effective in reducing progression from IGT to diabetes in the Indian population [158]. The pilot phase of a National Program on Diabetes, Cardiovascular Disease, and Stroke (NPCDS) was launched by the Ministry of Health and Family Welfare in January 2008, with the aims of improving awareness of lifestyle-related diseases, disease prevention through screening and targeted intervention, and to coordinating the multisectoral effort that is urgently needed to address the epidemic of obesity and diabetes in India [159].

Pakistan, Bangladesh, and Sri Lanka

The situation in these countries largely mirrors that in India. Diabetes is particularly common (16% of men, 12% of women) in the rural Sindh Province in northern Pakistan [160]. A more recent study in Pakistan indicated similar prevalence rates of 10–11% in urban and rural men and urban women, although lower rates were seen in rural women (5%). However, IGT rates in women were twice those in men [161]. Combining the data from the four provinces of Pakistan, the prevalence of diabetes in the urban areas was 6.0% in men and 3.5% in women, with a total of 22% of the urban population estimated to have some degree of glucose intolerance [162]. In rural Bangladesh, diabetes prevalence was reported in an older study to be 2.1% compared with an IGT prevalence of 13% despite a mean BMI of only 20.4 kg/m^2 [163]. A recent study based on fasting glucose criteria alone that included more than 7000 adults reported a prevalence of 9.7% [164].

In addition to urbanization, the main factor for the high prevalence of diabetes and metabolic abnormalities among Asians is the tendency for central obesity and insulin resistance [148, 165–168].

Despite being born smaller, with lower birth weight, Indian babies have more body fat, which persists into adulthood, thus putting them at increased risk of cardiometabolic complications [169]. Interestingly, one study showed that maternal nutrition and, in particular, low maternal vitamin B_{12} and high folate might be associated with increased adiposity and risk of T2DM in the offspring [170], suggesting that in addition to increased intake of fat and calorie-rich foodstuffs, other dietary factors may play a contributory role.

Mauritius

The high prevalence of diabetes and cardiovascular disease on the island of Mauritius, in the Indian Ocean, has been intensively studied. Here, diabetes is common in an urbanized setting; across several ethnic groups (Asian Indian, Chinese, and Creole), in 1990 the prevalence rates were 10–13%, rising to 20–30% in those aged 45–74 years [171]. A repeat survey in 1998 revealed a rise in prevalence of T2DM to 17.9%. In both studies, the highest prevalence was seen in Asian Indians [171, 172]. The age-standardized prevalence of diabetes was 22.3% in 2009 among men and 20.2% among women, representing an increase of over 60% compared with figures from 1987 [173].

The Middle East and North Africa

Marked socioeconomic changes in many countries in the region, especially among the affluent oil-producing countries, have led to dramatic changes in lifestyle, with changes in nutritional intake, decreased physical activity, and increased obesity and smoking. This, coupled with increasing urbanization and improved life expectancy, has led to a marked increase in the prevalence of diabetes and IGT (Table 4.5). A recent review of prevalence of diabetes in the Middle East highlighted the paucity of data and large differences in prevalence rates among different countries. Obesity and age appeared to be the main driver for high prevalence [174]. Saudi Arabia, Kuwait, and Qatar are among the countries with the highest prevalence rates of diabetes, and Egypt is among the top 10 countries with the highest burden of people with diabetes [1], highlighting this region as one that requires concerted public health action to reduce the potential impact of diabetes [175].

North Africa

Prevalence rates are relatively high (3–8%) in Sudan and Tunisia in addition to Egypt. An Egyptian study of adults aged >20 years showed an IGT prevalence rate of 10% [176]. Urban–rural differences were demonstrated; in Cairo city, diabetes was more common (prevalence 14–20%, depending upon socioeconomic status), whereas the IGT prevalence was lower (6–9%). The converse applied in a rural setting, with a diabetes prevalence of only 5% but a higher IGT prevalence of 13%. As suggested earlier, this may reflect the diabetes epidemic being at an earlier stage in rural populations. In the Tunisian National Nutrition Survey, the prevalence of diabetes was 9.9%, giving an age-adjusted prevalence of 8.5%, with marked urban–rural differences [177].

Table 4.5 Prevalence of diabetes from reported epidemiology studies in selected countries in the Middle East. IGT: Impaired glucose tolerance; IFG: Impaired fasting glycaemia.

		Prevalence (%)	
Year	Country [ref.]	T2DM	IGT
1998	Lebanon [274]	13.2	6.0
2006	Oman [275]		
	Males	11.8	
	Females	11.3	
2000	Oman [276]		
	Males	11.8	7.1 (IFG)
	Females	11.6	5.1 (IFG)
1995	Oman [277]		
	Males	9.7	8.1
	Females	9.8	12.9
2011	Saudi Arabia [278]		
	Males	34.7	
	Females	28.6	
2000	Saudi Arabia [279]		
	Males	26.2	14.4
	Females	21.5	13.9
1995	Saudi Arabia [280]		
	Males	11.8	10.0
	Females	12.8	9.0
1992	Iran [281]		
	Urban males	7.1	8.9
	Urban females	7.6	14.9
	Rural	7.3	7.2
2004	Jordan [282]	17.1	7.8
2009	Qatar [283]	16.7	
	Males	15.2	
	Females	18.1	

Western Pacific region

Australia

The first report of the AusDiab Study [178], published in 2000, provides information about diabetes in a developed country. The overall prevalence of diabetes in Australians aged ≥25 years was 7.5% (8% for men and 7% for women), rising from 2.5% in those aged 25–44 years to 24% among those aged ≥75 years; the prevalence more than doubled since 1981 [179, 180]. About 50% of cases discovered in this survey were previously undiagnosed. The combined prevalence of impaired fasting glucose (IFG) and IGT was 16% (men 17%, women 15%); hence almost 25% of Australians aged ≥25 years have abnormal glucose metabolism. In Australia, T2DM accounts for over 85% of cases and T1DM for 10%. Using data from the AusDiab study, it has been estimated that the prevalence of diabetes is likely to rise from 7.6% in 2000 to 11.4% by 2025 [181]. In the 2012 AusDiab Study Report, the annual incidence of diabetes was reported to be 0.8% per year for men and 0.6% per year for women [182].

T2DM is commoner in native Australian populations, for example, 16–30% of adults in the Aborigine and Torres Strait Islander communities [183]. In this population, diabetes was associated with higher rates of hypertension (69% vs. 21%), obesity (44% vs. 16%), elevated triglyceride, and lower HDL-cholesterol concentrations compared with those who have normal glucose tolerance.

New Zealand

In New Zealand, T2DM is consistently commoner among Polynesians (Māoris and Pacific Islanders) than in white New Zealanders; it accounts for 89% of diabetes in white New Zealanders and 95% in Polynesians. Polynesians are also diagnosed, on average, 5–10 years younger than white New Zealanders and have a 4–8-fold higher prevalence of diabetic nephropathy. Strikingly high prevalence rates of 37–75% were reported for unemployed men, emphasizing again the role of socioeconomic status [184]. In the 2006–2007 New Zealand Health Survey, prevalence rates reported for adults aged >30 years were 4.3% for white New Zealanders, 5.8% for Māoris, 6.5% for Asians, and 10.0% for Pacific Islanders, respectively [185, 186].

Pacific Island countries

The Melanesian, Micronesian, and Polynesian populations of the Pacific Islands show great variations in diabetes prevalence, largely attributable to differences in economic development and lifestyle. Some of the highest prevalence rates worldwide come from this region, notably from Nauru and Papua New Guinea. The Micronesian population of Nauru, made wealthy by bauxite mining and with a longer history of Westernization than other Pacific Island Countries, currently have an age-standardized prevalence rate of 40%. High prevalence rates in Nauru have been maintained since the late 1970s, but now appear to have stabilized as bauxite mining is exhausted [50, 187].

Fiji has a largely bi-ethnic population consisting of native Fijians of Melanesian ancestry together with migrants from India. Recent surveys from Fiji are lacking, but a survey conducted over 30 years ago showed that diabetes prevalence rates were already higher among Indian migrants than in Melanesians. In adults above 20 years of age, crude prevalence rates were 13% among the Indian migrants (with no significant urban–rural gradient), but 7% and 1.7% among urban and rural Melanesians, respectively [188]. At the time, these results were thought to indicate a difference in ethnic (genetic) predisposition, but this conclusion has since been tempered by the finding of high prevalence rates in urbanized Melanesians in Papua New Guinea.

The situation in Papua New Guinea provides an excellent example of the damage inflicted by rapid urbanization: diabetes is virtually non-existent in highland populations [189], in stark contrast to the age-standardized prevalence rate of over 40% among urbanized Koki people (Melanesians) in Port Moresby [190]. Intermediate rates are reported in Austronesians of coastal ancestry.

High prevalence rates of diabetes have been reported in Polynesian populations, conspicuously associated with obesity, both of which are particularly common in Polynesian women. In Western Samoa, diabetes prevalence was reported in 1991 to be 7–9% in two rural communities and 16% in Apia; the prevalence had doubled since 1978 [191]. In the Kingdom of Tonga, situated south of Samoa, the age-standardized prevalence of diabetes was 15.1%, of which 80% was undiagnosed [192].

Diabetes remains undiagnosed in most Pacific Island people with the disease—perhaps 80–100% in some communities, compared with around 25–50% in high-income countries [180]. This is likely to contribute to high rates of complications and frequent presentation with diabetes-related problems, such as foot sepsis [193].

Japan

T2DM has become commoner in Japan since the 1960s, and data from rural parts of Japan suggested a prevalence of 9.1% in men and 10.8% in women, with corresponding IGT prevalences of 12 and 16.5% for Japanese men and women, respectively [194]. A National Diabetes Survey conducted in 2002 estimated a prevalence of 9% [195]. In the National Health and Nutrition Survey in 2007, it was estimated (using HbA_{1c}) that the prevalence of diabetes was 15.3% in men and 7.3% in women [196]. The emerging problem of T2DM among Japanese children is now recognized as a critical problem in that country. T2DM cases outnumber T1DM in children and adolescents by a ratio of 4 :1 [197], and the incidence rate of T2DM for 1981–1990 was 4.1 per 100,000 person-years, approximately twice the incidence rate of T1DM [198]. Nutritional factors are believed to play an important part, with the prevalence of diabetes among Japanese Americans approximately twice that among Japanese in Japan [199].

The causes of death in people with T2DM have also shifted, possibly because of Westernization of diet and increased fat and total calorie intake; higher death rates from renal disease than in white European populations are now being supplanted by rising deaths from coronary artery disease [200]. In order to reduce the burden of diabetes, the Japanese government has launched a large national strategic research project named J-DOIT to reduce diabetes, improve adherence to follow-up, and reduce complications of diabetes [201].

Korea

In the Korean National Health and Nutrition Survey conducted in 2001, the age-adjusted prevalence of diabetes was reported to be 7.6%. The prevalence of impaired fasting glucose was an alarming 23.9% [202], suggesting a future epidemic of diabetes in the Korean population, similar to that in the other Asian countries [203]. In the Korean National Health and Nutrition Survey conducted in 2010–2012, prevalence of diabetes was reported to be 10.1% [204].

China and Chinese populations

The rapid increase in the prevalence of T2DM in China provides one of the most striking examples of the impact of urbanization

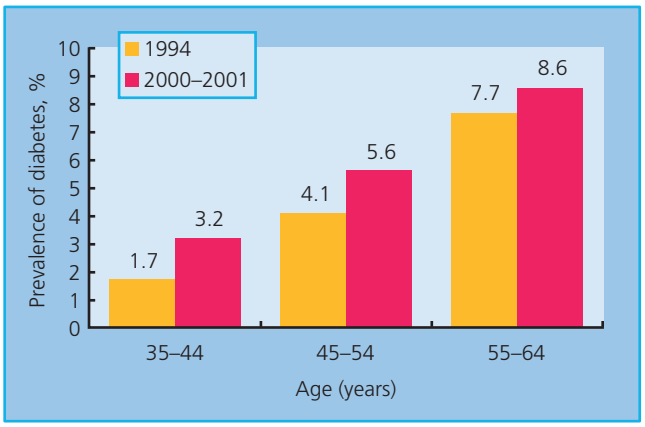

Figure 4.4 Changes in prevalence of diabetes among Chinese adults aged 35–64 years. Source: Data from the 1994 Chinese National Survey and the 2000–2001 InterASIA study (Gu et al. 2003 [209]).

on increasing diabetes prevalence. China, with its current population of nearly 1.4 billion, is the world's most populous country. Diabetes used to be rare: prevalence rates reported between 1980 and 1990 were consistently ≤1.5% even in urban areas such as Shanghai [205], and as low as 0.3% in rural Guangdong Province. Recently, however, the prevalence has risen rapidly, a trend first demonstrated by studies conducted in the Da Qing area of northeastern China. There, the prevalence in 1986 was 1.0%, but by 1994 it had increased over threefold to 3.5% [206, 207]. The 1994 survey of 200,000 people aged 25–64 years in 19 provinces that included Da Qing found overall prevalence rates of 2.3% for diabetes and 2.1% for IGT. A community-based survey of 40,000 people aged 20–74 years in China between 1995 and 1997 confirmed this rising trend and also demonstrated urban–rural gradients in prevalence rates. Age-standardized prevalence rates were 3.2% for diabetes, and 4.8% for IGT, with the highest prevalence in provincial cities and the lowest in rural areas [208]. The International Collaborative Study of Cardiovascular Disease in Asia, conducted in 2000–2001, revealed a further increase in the prevalence of diabetes (undiagnosed and diagnosed) to 5.5%, with another 7.3% affected by IGT [209] (Figure 4.4). Furthermore, amongst the 20 million Chinese people estimated to have diabetes based on fasting blood glucose, only 30% were previously diagnosed [209]. The large proportion of those with IGT is particularly alarming. In the community-based Shanghai Diabetes Study, people with IGT and/or IFG had an 11.7-fold increased risk of diabetes compared with those with normal glucose tolerance over a 3-year follow-up period [210].

Chinese populations in affluent societies such as Hong Kong SAR, Singapore, Taiwan, and Mauritius all show higher prevalence rates compared with mainland China. In Hong Kong, the prevalence of diabetes increased from 8 to 10% between 1990 and 1995 [211, 212]. Studies in Taiwan indicate prevalence rates of 9–11%, although methodological discrepancies make direct comparisons difficult [205]. The annual *incidence* rate in Taiwan was reported in 1997 to be 1.8% [213]. In a review summarizing the findings from prevalence studies conducted in Chinese populations in 1995–2003, it was noted that Chinese people in Hong Kong and Taiwan have a 1.5–2.0-fold increased risk of diabetes adjusted for age and diagnostic criteria compared with their mainland counterparts [214].

The rapid increase in diabetes prevalence in China is likely to have been driven by the increase in obesity, particularly among children and adolescents [168, 215]. Analysis of data from the 2002 National Nutrition and Health Survey noted prevalences of overweight of 4.1%, among children aged 7–12 years and 5.6% among those aged 12–18 years, with obesity prevalences of 2.5 and 1.6%, respectively [216]. In Hong Kong, a community-based study involving more than 2000 adolescents aged 11–18 years found alarming rates of obesity, with 8–10% of those aged 12–13 years fulfilling criteria for obesity [217]. In a national screening program among schoolchildren in Taiwan between 1992 and 1999, the rate of newly identified diabetes was 9.0 per 100,000 for boys and 15.3 per 100,000 for girls. Obesity was found to be the major risk factor for the development of T2DM, where children with BMI in the 95th percentile or higher had an ~19-fold increase in risk of T2DM compared with those with BMI in the <50th percentile [218].

Such alarming data for Chinese populations highlight the potential for further rises within China itself. Unless effective measures can be implemented, given the huge population of China, the consequences could be devastating. Indeed, two recent large nationwide epidemiological studies, involving more than 46,000 and 98,000 adults, respectively, reported diabetes prevalences of 9.7% in 2008 [219] and (if including elevated HbA_{1c} as a diagnostic criterion) 11.6% in 2010 [220]. This translates to a staggering estimate of 92.4 million individuals with diabetes and 148.2 million adults with prediabetes in China in 2008 [219].

South-East Asian peninsula

There is considerable economic diversity within this region, although the recent emerging data showed that despite the relatively traditional lifestyle in many of the countries, diabetes is increasingly common within the region. A survey performed in two villages in Cambodia in 2004 revealed a diabetes prevalence rate of 5% in the rural community in Siem Reap but up to 11% in a semi-urban community [221]. A study conducted in adults in Ho Chi Minh City in southern Vietnam indicated that the prevalence of diabetes increased substantially from 2.5% in 1993 to 3.8% in 2001 [222]. A more recent study using data from 2013 reported an age-standardized prevalence of 6.0% [223]. Similar increases have been reported in Indonesia [224] and the Philippines [225]. Prevalence rates in Thailand appear to be approaching those reported in Malaysia and Singapore, with prevalence of diabetes and IGT in a 2004 national survey reported to be 6.7 and 12.5%, respectively [226].

In Singapore, serial studies since 1975 showed a rising prevalence of diabetes from 2% in 1975 to 4.7% in 1984, 8.6% in 1992, and 9% in 1998. Two more recent surveys indicate that the rate of rise may have stabilized. Ethnic Indians and Malays (especially

Malay women) have the highest rates of diabetes (16.7–14.3%) and also the highest rates of obesity. A further 15% of the adult population have IGT. In a survey conducted in 2004 by the Ministry of Health, Singapore, the prevalence of diabetes among the adult population was estimated to be 8.2% [227]. A more recent survey conducted by the Ministry of Health in 2010 noted a diabetes prevalence of 11.3% [228]. Obesity and adoption of a Westernized diet and lifestyle are again closely associated. T2DM in childhood is also highlighted as an emerging problem. The prevalence of diabetes increased by more than twofold over 20 years in Malaysia, with the most recent nationwide survey reporting a prevalence of 22.6%, compared with a prevalence of 11.6% in 2006 [229].

Impact of diabetes

The epidemic of diabetes has major impact on both personal and societal aspects. The major burden of diabetes stems from the treatment cost of its complications, such as stroke, blindness, coronary artery disease, renal failure, amputation, and infection. In 2015, about 5 million people died of diabetes and its related diseases [1, 230]. Most people die from cardiovascular disease (particularly coronary artery disease and stroke) and end-stage renal disease. In a recent study on the trends in the incidence of diabetes-related complications in the USA, the rates of lower extremity amputations, end-stage renal disease, acute myocardial infarction, stroke, and death from hyperglycemic crisis declined from 1990 to 2010, although there remains a substantial healthcare burden due to the rising diabetes prevalence [94].

There are geographic differences in both the magnitude of these problems and their relative contributions to overall morbidity and mortality [231]. In white European and American populations, macrovascular complications, such as coronary artery disease and amputation, are major causes of disability. In contrast, end-stage renal disease and stroke are more prevalent among Chinese and Asian ethnic groups [13].

It is well established that the occurrence of vascular complications of diabetes is related to the duration of hyperglycemia. With the earlier onset of T2DM, most people will have an increased risk of developing these complications. Despite the high prevalence of complications of diabetes and, hence, the high costs of management, simple, inexpensive measures are effective in preventing the development of diabetes and its vascular complications. Rather than merely focusing on the control of hyperglycemia, global risk reduction with attention on cardiovascular risk factors has been found to be the most effective way of reducing the burden of diabetes. The challenge is to provide a platform whereby effective care can be delivered at an affordable cost.

Mortality and morbidity

Diabetes is associated with approximately twofold increased mortality in most populations, with the excess risk decreasing with increasing age [232–234]. Although initial data suggest that the excess mortality associated with diabetes may be higher in Asian populations, this is probably related to differences in death certificate coding practices [235–237]. It was recently estimated that diabetes accounted for 14.5% of global all-cause mortality among people aged 20–79 years, with close to half of deaths due to diabetes being in people under the age of 60 years [1].

The most systematic comparative data, using standardized methodology, originate from the WHO Multinational Study of Vascular Disease in Diabetes, which has drawn from 14 centers in 13 countries since the 1980s. A follow-up report from 10 of these centers [238] shows that coronary heart disease and limb amputation rates varied 10–20-fold among different centers; there was also marked variation in prevalence of clinical proteinuria and renal failure, but less variation in retinopathy and severe visual impairment. Striking features include the relative rarity of ischemic heart disease and lower extremity amputation in Hong Kong and Tokyo, contrasting with a high incidence of stroke, especially in Hong Kong. A high incidence of stroke was also found in Arizona and Oklahoma, the two Native American Indian centers. The highest rates of ischemic heart disease were seen in the European centers, notably among women in Warsaw. Myocardial infarction was also common in Native American Indians, especially among men, while renal failure and proteinuria rates were highest among Native American Indians and in Hong Kong.

Other issues include the apparent vulnerability of Pacific Island populations to diabetic foot problems associated with neuropathy and of South Asians to coronary heart disease [42]. Importantly, the risk of coronary heart disease is already increased twofold at the stage of IGT [239].

Another cause of morbidity and mortality that is increasingly recognized is the increased risk of cancer in people with diabetes. Various epidemiological studies in different populations have suggested a link between diabetes and increased risk of pancreatic, hepatocellular, endometrial, breast, and colorectal carcinoma [240–242]. Although some of this may be due to presence of common risk factors such as obesity and dietary factors, it has been shown in a large prospective study that cancer risk increases with increasing fasting glucose at baseline [243]. In a large population-based study in Australia, both T1DM and T2DM were found to be associated with increased risk of incidence and mortality for overall and a number of site-specific cancers [244].

Intensive multifactorial interventions to reduce cardiovascular risk factors are effective in reducing cardiovascular mortality in diabetes [245, 246]. Although intensive blood glucose control does not lower cardiovascular mortality in the short term [247, 248], it may have beneficial effects in reducing cardiovascular and total mortality in the longer term, as suggested by long-term follow-up data from UKPDS [249]. It appears that the relative mortality of diabetes is decreasing in some countries [250, 251], and this may be related to the increased utilization of drugs to control hyperlipidemia, hyperglycemia, and hypertension [252].

Healthcare burden and economic costs

The increase in the prevalence of diabetes, particularly among young adults, along with the increased morbidity and mortality

associated with microvascular and macrovascular complications, is likely to lead to an escalation of healthcare costs and reduced economic growth. The IDF estimated that in 2015, diabetes-related health expenditure would reach 320 billion International Dollars (ID) in the USA, 90 billion ID in China, 33 billion ID in Germany, 38 billion ID in Japan, and 29 billion ID in Brazil [1]. The global health expenditure for diabetes in 2015 was estimated to be US$673 billion, of which half would have been spent in North America (around $348 billion), and one-quarter in Europe ($156 billion). In the USA, the estimated total costs (direct and indirect) of diabetes increased from $23 billion in 1969 to $132 billion in 2002 [253, 254]. The cost of diabetes in the USA in 2007 was estimated by the American Diabetes Association to be $174 billion, which includes $116 billion in excess medical expenditures and $58 billion in reduced national productivity [255]. These estimates were revised in 2012 to a total estimated cost of diagnosed diabetes of $245 billion, including $176 billion in direct medical costs and $69 billion in reduced productivity [92]. The largest components of medical expenditures attributed to diabetes are hospital inpatient care, accounting for 43% of total costs, and medications to treat complications of diabetes (18%) and antidiabetes medications and diabetes supplies (12%) [92]. However, the actual burden is likely to be even greater, since other nonmonetary effects such as changes in quality of life, disability and suffering, care provided by unpaid caregivers, and other factors cannot be included in such analyses. The burden of diabetes affects all sectors of society, including higher insurance premiums paid by employees and employers, reduced earnings through productivity loss, and reduced overall quality of life for people with diabetes and their families and friends. The cost of medical care for diabetes varies greatly among the different regions (Table 4.6). Although diabetes is a very costly disease, interventions used to prevent or control diabetes differ greatly in their cost-effectiveness [256]. The cost-effectiveness and feasibility of diabetes interventions in developing countries, as assessed by the World Bank, are listed in Table 4.7. Cost-effective interventions that are technically and culturally feasible should be implemented with the highest priority [257].

Table 4.6 Estimated direct medical costs of diabetes by region, 2003.

Region	Direct medical costs ($ millions)	
	Low estimate	High estimate
Developing countries	12304	23127
East Asia and the Pacific	1368	2656
Europe and Central Asia	2884	5336
Latin America and the Caribbean	4592	8676
Middle East and North Africa	2347	4340
South Asia	840	1589
Sub-Saharan Africa	273	530
Developed countries	116365	217760
World	128669	240887

Source: Adapted from Venkat Naryan KM, Zhang, P, Kanaya AM, et al. In: Jamison DT, Breman JG, Measham AR, eds. *Disease Control Priorities in Developing Countries*, 2nd edn. Washington, DC: International Bank for Reconstruction and Development/The World Bank Group, 2006, Table 30.1.

Prevention of T2DM

"There are entirely too many diabetic patients in the country. Statistics for the last thirty years show so great an increase in the number that, unless this were in part explained by a better recognition of the disease, the outlook for the future would be startling. Therefore, it is proper at the present time to devote attention not alone to treatment, but still more, as in the campaign against the typhoid fever, to prevention. The results may not be quite so striking or as immediate, but they are sure to come and to be important."

[Elliot Joslin, 1921]

Given the cost of diabetes, it is essential to prevent or delay the onset of diabetes and its associated complications. With improved understanding of the natural history of the development of T2DM and the role of various modifiable risk factors in its pathogenesis, a number of randomized clinical trials have examined the effect of lifestyle intervention to prevent T2DM. A large body of evidence has accumulated from these studies on the effectiveness of lifestyle measures in the prevention of diabetes, as summarized in Table 4.8. Most of these interventions include structured education and exercise programs, reducing fat intake and increasing fiber intake, moderate exercise for at least 30 min per day, and moderate weight reduction of ≥5%. Importantly, in addition to being highly cost-effective, the effect of structured lifestyle intervention on reduction of diabetes risk appears to be maintained over a long duration of follow-up [258, 259]. In a follow-up of the China Da Qing Diabetes Prevention Study, participants who received lifestyle intervention had a 51% lower incidence of diabetes during the 6-year active intervention period and 43% lower incidence of diabetes over 20 years [259]. Furthermore, with follow-up extended to 23 years, those randomized to lifestyle intervention had a 41% reduction in cardiovascular mortality and a 29% reduction in all-cause mortality [260].

In addition to lifestyle intervention, several drugs used in the treatment of T2DM and obesity have been evaluated in clinical trials and are effective in preventing diabetes, including metformin, the thiazolidinedione class of compounds, acarbose, orlistat, and insulin itself, as summarized in Table 4.9. The largest body of evidence for pharmacological prevention of diabetes is with metformin treatment, which was associated with an ~40% reduction in risk of diabetes in a meta-analysis [261]. In addition, several clinical trials indicated that angiotensin-converting enzyme (ACE) inhibitors and angiotensin receptor blockers may reduce incident diabetes in high-risk people with hypertension [262–266]. A large randomized clinical trial compared the ACE inhibitor ramipril with placebo in people with IGT or IFG. It did not show a significant reduction in incident diabetes after a

Table 4.7 Summary of cost-effectiveness of interventions for treatment and prevention of diabetes.

Intervention	Cost/QALY (2001 US$)						Feasibility[a]	Implementing priority[b]
	East Asia and the Pacific	Europe and Central Asia	Latin America and the Caribbean	Middle East and North Africa	South Asia	Sub-Saharan Africa		
Level 1								
Glycemic control in people with HbA_{1c} ≥9%	Cost saving	Cost saving	Cost saving	Cost saving	Cost saving	Cost saving	++++	1
Blood pressure control in people with pressure >160/95 mmHg	Cost saving	Cost saving	Cost saving	Cost saving	Cost saving	Cost saving	++++	1
Foot care in people with a high risk of ulcers	Cost saving	Cost saving	Cost saving	Cost saving	Cost saving	Cost saving	++++	1
Level 2								
Preconception care for women of reproductive age	Cost saving	Cost saving	Cost saving	Cost saving	Cost saving	Cost saving	++	2
Lifestyle interventions for preventing T2DM	80	100	130	110	60	60	++	2
Influenza vaccinations among the elderly for T2DM	220	290	360	310	180	160	++++	2
Annual eye examination	420	560	700	590	350	320	++	2
Smoking cessation	870	1170	1450	1230	730	660	++	2
ACE inhibitor use for people with diabetes	620	830	1020	870	510	460	+++	2
Level 3								
Metformin intervention for preventing T2DM	2180	2930	3630	3080	1820	1640	++	3
Cholesterol control for people with total cholesterol >200 mg/dL	4420	5940	7350	6240	3680	3330	+++	3
Intensive glycemic control for people with HbA_{1c} ≥8%	2410	3230	4000	3400	2000	1810	++	3
Screening for undiagnosed diabetes	5140	6910	8550	7260	4280	3870	++	3
Annual screening for microalbuminuria	3310	4450	5510	4680	2760	2500	++	3

[a]Feasibility was assessed based on difficulty of reaching the intervention population (the capacity of the healthcare system to deliver an intervention to the targeted population), technical complexity (the level of medical technologies or expertise needed for implementing an intervention), capital intensity (the amount of capital required for an intervention), and cultural acceptability (appropriateness of an intervention in terms of social norms and/or religious beliefs). ++++ indicates feasible for all four aspects, +++ indicates feasible for three of the four, ++ indicates feasible for two of the four, and + indicates feasible for one of the four.
[b]Implementing priority was assessed by combining the cost-effectiveness of an intervention and its implementation feasibility; 1 represents the highest priority and 3 represents the lowest priority.
Source: Venkat Naryan KM, Zhang, P, Kanaya AM, et al. In: Jamison DT, Breman JG, Measham AR, eds. *Disease Control Priorities in Developing Countries*, 2nd edn. Washington, DC: International Bank for Reconstruction and Development/The World Bank Group, 2006, Table 30.3.

Table 4.8 Summary of randomized clinical trials using lifestyle intervention in the prevention of T2DM.

Study	No of participants	Study participants	Duration (years)	Incidence in control (%)	RRR (%)	Ref.
Da Qing (1997)	577	IGT	6	15.7	38	[284]
			Extended follow-up 23 years after randomization	89.9	45	[260]
DPS (2001)	522	IGT, BMI >25 kg/m^2	3.2	6	58	[120]
			Extended follow-up 7 years after start of study	7.4	43	[258]
DPP (2002)	3234	IGT, BMI >24 kg/m^2, FG >5.3 mmol/L	3	10	58	[285]
			Extended follow-up 10 years after randomization	5.3 per 100 person-years	34	[286]
Indian IDPP-1 (2006)	531	IGT	3	18.3	29	[158]
Japanese (2005)	458	IGT (men), BMI >24 kg/m^2	4	9.3	67	[287]

BMI, body mass index; DPP, Diabetes Prevention Program; DPS, Diabetes Prevention Study (Finland); FG, fasting glucose; IDPP-1, Indian Diabetes Prevention Program ; IGT, impaired glucose tolerance; RRR, relative risk reduction.

median follow-up of 3 years, although ramipril was associated with increased regression to normoglycemia [267]. A large number of pharmacological agents are currently in development or undergoing clinical trials for the treatment of T2DM or obesity, which should provide a constant supply of promising agents for evaluation in their effectiveness for preventing T2DM. At present, however, lifestyle intervention remains more cost-effective as a strategy for diabetes prevention. Recent prevention studies have also demonstrated the effectiveness of using mobile phone messaging or other aids to deliver support for lifestyle modification or patient empowerment [268]. Among those who have morbid obesity, bariatric surgery has a significant impact on glycemic control and more than 60% of severely obese individuals with diabetes experience remission after gastric bypass surgery [269]. In the 3-year follow-up of people with severe obesity who underwent bariatric surgery in the USA, incidence of diabetes was 0.9% after Roux-en-Y gastric bypass and 3.2% after laparoscopic gastric banding [270].

Given the increased appreciation of the important role of the intrauterine environment and early development in modifying the risk of non-communicable diseases, it is increasingly recognized that pregnancy represents a critical period that requires optimal maternal nutrition [271], and also has long-term consequences for the health of the offspring. Therefore, diabetes and non-communicable disease prevention efforts now include considerations of primordial prevention, whereby measures

Table 4.9 RCT assessing the effect of pharmacological interventions in the prevention of T2DM.

Drug	Trial	*n*	Follow-up (years)	Total dose	RR (95% CI)	Ref.
Biguanides						
Metformin	DPP (2002)	2155	2.8	1700 mg/day	0.69 (0.57–0.83)	[285]
	CDPS (2001)	261	3	750 mg/day	0.23	[288]
	IDPP-1 (2006)	531	2.5	500 mg/day	0.74 (0.65–0.81)	[158]
Thiazolidinediones						
Troglitazone	TRIPOD (2002)	236	2.5	400 mg/day	0.45 (0.25–0.83)	[289]
	DPP	585	0.9	400 mg/day	0.25	
Rosiglitazone	DREAM (2006)	5269	3.0	8 mg/day	0.40 (0.35–0.46)	[290]
α-*Glucosidase inhibitors*						
Acarbose	STOP-NIDDM (2002)	1368	3.2	300 mg/day	0.75 (0.63–0.9)	[291]
Insulin						
Insulin glargine	ORIGIN	1456	6	Dose titrated up according to target, mean dose 0.4 units/kg/day	0.72 (0.58–0.91)	[292]

CI, confidence interval; *n*, number; RR, relative risk; CDPS, Chinese Diabetes Prevention Study; DPP, Diabetes Prevention Program; DREAM, Diabetes Reduction Assessment with ramipril and rosiglitazone Medication; IDPP-1, Indian Diabetes Prevention Program 1; ORIGIN, Outcome Reduction with Initial Glargine Intervention; STOP-NIDDM, Study TO Prevent Non-Insulin-Dependent Diabetes Mellitus; TRIPOD, TROglitazone in the Prevention Of Diabetes;

to avoid the establishment of different environmental, social, behavioral, and physical exposures that may impair long-term health start early, including preconception and the pregnancy period [272].

More detailed discussion on epidemiological aspects of diabetes can be found elsewhere [273].

Conclusions

The interaction between genetic predisposition, the popularization of fast food and a sedentary lifestyle, in addition to aging of the general population, plays a major role in the increase in the prevalence of impaired glucose tolerance and T2DM globally. Countries in the Asia–Pacific regions and with a growing economy will bear the major burden in the increase in number of people with diabetes. The significant increase in macro- and microvascular complications of diabetes places a heavy burden on healthcare resources. Studies have confirmed the benefit of intensive multifactorial risk management in reducing all-cause mortality and cardiovascular adverse events. Measures such as weight reduction and exercise are effective in preventing the progression of IGT to diabetes. Hence, despite being one of the commonest chronic diseases, diabetes can be prevented or controlled effectively with interventions that are relatively cost-effective compared with the cost of treating the micro- and macrovascular complications.

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5 The Global Burden of Diabetes

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Key points

- Diabetes results in a range of distressing symptoms, altered daily functioning (requiring attentive self-care, health monitoring, and treatments), changed family roles, higher healthcare costs, lost productivity, disability, and premature mortality, which are felt by individuals, households, communities, and national economies.
- The prevalence of diabetes has grown worldwide, with no country or region spared. With time, the availability of data regarding diabetes burdens has improved; importantly, the prevalence and absolute number estimates for diabetes have consistently outpaced each previous projection. There are still major gaps in data, particularly for incidence, prevalence in some parts of the world, and rate and absolute numbers of people experiencing diabetes complications and mortality in several countries.
- Diabetes is a leading cause of death in the world (5.1 million deaths annually), outnumbering global deaths due to HIV/AIDS, and 75% of this mortality occurs in low- and middle-income countries, disproportionately affecting the young and economically-active populations.
- Cost appraisal methods require epidemiological, clinical, and economic data, and utilize different approaches to calculate the direct medical costs (of treatment, self-management and monitoring, outpatient follow-up, inpatient stays, diagnostic tests, and procedures), indirect costs (of lost outputs due to disability and premature death), and intangible losses (psychosocial burdens) attributable to diabetes.
- Even though there are large variations in methods of cost appraisal, cost items incorporated, and purchasing power, and also accessibility to and patterns of clinical care, together resulting in widely varied between-country per capita expenditures, it is clear that the presence of diabetes results in excess consumption of resources worldwide.
- Progressive severity of diabetes complications, long duration of disease, comorbidities, and complexity of therapy all increase the monetary, infrastructural, and human resource costs of care.
- Individuals in vulnerable subpopulations are at an elevated risk of developing diabetes and progression towards significantly harmful outcomes, and a large proportion of resources is devoted to their therapies and diabetes care; confronting the increased susceptibility and burdens will require addressing the underlying political, socioeconomic, biological, and behavioral factors that perpetuate disparities.

Introduction

Diabetes has emerged as a major health problem worldwide, with serious health-related and socioeconomic impacts on individuals and populations alike. Pandemic growth of diabetes is being spurred on by transitioning demographic (e.g. population aging), socioeconomic, migratory (e.g. between or within countries; urbanization), nutritional and lifestyle patterns, and an affiliated proliferation of overweight and obese adults and children [1–3]. The International Diabetes Federation estimates that there were 415 million people with diabetes worldwide in 2015, and projects that the absolute number will reach 642 million by 2040 [1]. The overwhelming majority of this escalation will be attributable to growth of type 2 diabetes (T2DM). Rapid socioeconomic transformations globally will also result in a parallel growth of diabetes precursors (impaired fasting glucose [IFG] and impaired glucose tolerance [IGT]) and ensuing health consequences [4–6].

Current estimates suggest that three-quarters of those affected by diabetes live in low- and middle-income countries (LMICs) [1, 7]. This challenges traditional paradigms that segregated chronic non-communicable diseases (NCDs) as problems of affluent countries alone. Although this burden of greater absolute numbers may be partially explained by larger population size, the incidence rates for NCDs in rapidly transitioning LMICs are

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much steeper than those in more affluent high-income counties (HICs) [8]. For example, it was previously estimated that by 2025, the number of diabetes cases will increase by 170% in LMICs, compared with a 41% increase in HICs [9].

Thus far, the attention on health burdens in LMICs has justifiably focused on the persistence of infectious diseases, reproductive health problems, and nutritional deficiencies. However, these same countries must also contend with 80% of the global mortality associated with chronic diseases [10, 11]. Projections suggest that this already overwhelming "double-burden" will be exacerbated by the growth of NCDs such as diabetes. Altogether, projected increases in diabetes in all corners of the globe will result in a corresponding escalation of burdens in the form of serious morbidity, disability, diminished life expectancy, reduction in quality of life, loss of human and social capital, and individual and national income losses. This chapter describes these burdens in a global context, and systematically introduces data regarding regional patterns and associated themes.

Distribution

Epidemiological evidence quantifies the impacts and predictors of disease, identifies vulnerable populations and their needs, and facilitates the formulation of appropriate disease prevention and control strategies. However, there is still limited representative epidemiological data, and very few prospective studies, originating from a great many LMICs – the parts of the world that together contribute to the greatest diabetes burdens. Moreover, the utility of currently available estimates is hampered by methodological deficiencies (inconsistent diagnostic criteria, poor standardization of methods) and limited coverage (regional sampling with a predominance of urban studies even though most of the populations in question are rural inhabitants) [12, 13]. To address these barriers, the International Diabetes Federation and World Health Organization use sophisticated modeling approaches to provide global estimates, by country, for diabetes prevalence. Despite many intra-region differences, there are notable patterns for different income-group regions, which are described here.

In Africa:

- There is a general lack of awareness about chronic diseases and their risk factors [12]. For example, three out of five people with diabetes in Africa remain undiagnosed [1], and a mere 25–35% of people with hypertension were aware of their elevated blood pressure status [13].
- There are limited data originating from a few localized centers in certain parts (western, eastern, and southern) of the continent, and prevalence estimates vary widely, between 0–3% in rural areas and 6–10% in urban environments [12, 14]. Since prevalence estimates are largely based on fasting blood glucose levels, diabetes defined by post-prandial hyperglycemia is largely being missed.
- Although urbanization, socioeconomic development, epidemiological transition, and increases in overweight and obesity are cited as factors leading to growth of diabetes [15], data on population-level dietary and physical activity patterns are severely lacking in African countries; also, the prevalence of overweight and obesity is highest among peri-urban low socioeconomic status dwellers, and consequent diabetes risk may also be higher, although again, there are limited data among this population.
- Although HIV/AIDS overshadows NCDs such as diabetes in African countries [14, 16, 17], diabetes and other metabolic factors may be a future concern in this population for various reasons: first, demographic projections alone suggest that the prevalence of diabetes will continue to grow in this region; and second, as HIV mortality declines owing to more widespread use of anti-retroviral therapies, there will be direct (in the form of pancreatic dysfunction associated with therapy) and indirect (increasing longevity of life) impacts that may be associated with increased diabetes prevalence [18]. More data are needed to comprehend fully the relative impacts of HIV infection, anti-retroviral therapy, life expectancy, and contemporary sociodemographic and epidemiological transitions.
- There is variation in risk by ethnicity with higher prevalence of diabetes noted among people of Egyptian and Asian Indian origin than among indigenous African communities [12, 19].

In Europe, the United States, and Canada:

- Available data are derived from population studies, records of insulin and other medication sales, and/or reimbursement claims; estimates still suggest that 30% of people in these HICs have undiagnosed diabetes [1, 4, 20].
- Prevalence of type 1 diabetes (T1DM) is highest in Europe and incidence continues to increase in Europe and North America [21–23].
- Prevalence of T2DM is highest and growing fastest in vulnerable subgroups—lower socioeconomic groups and the elderly [4].
- Life expectancy of people with diabetes, although reduced compared with the general population [24], is markedly higher than in LMICs of the world.
- Therapies are associated with inflated and growing health expenditures [25].

In Central and Latin America:

- The average prevalence of diabetes is 8% [1], although there is variation in diabetes prevalence reflecting the diversity of ethnicities and stage of development between countries [7]. Indigenous populations are estimated to have a high prevalence of metabolic dysfunction and diabetes, as has been noted in Brazil [26], but the patterns and proportions of indigenous peoples in each country are not clearly documented [27].
- The pattern of T1DM incidence seems to correspond to the size of the population of white European ancestry [28, 29].
- Poor accessibility to health services continues to be a problem for many of those affected [28].
- Countries such as Mexico are starkly affected as diabetes has climbed the list of leading causes of mortality over the past three

decades [30], and is now one of the top two causes of death for Mexicans [31].

Asia is emerging as the epicenter of the cardiometabolic pandemic [32, 33] since:

- Populous countries in this region (India and China are estimated to have 66 and 96 million people living with diabetes, respectively) are confronted with diabetes risk being manifest at younger ages and at lower body mass indices compared with populations in other regions [32].
- Patterns of genetic/ethnic propensity and phenotypes are diverse:
  - South Asians have lower BMIs but susceptibility to low β-cell output (low insulin secretion) and also a tendency to deposition of metabolically active visceral adiposity; together, these may explain the greater vulnerability to diabetes in this population [34–36].
  - Peninsular Arabs and Pacific Islanders exhibit a very high prevalence of obesity and diabetes (estimated to be ~20% and ~25–35%, respectively) [1, 37].
  - There are also still rural–urban differences in prevalence of diabetes among Asians, which suggests genetic, environmental, and "thrifty" genotype factors, and their interactions all have a role to play [38].
- More epidemiological data, especially from longitudinal studies, are needed that can inform our understanding of pathophysiology, and also data on best practices and interventions to screen, prevent, and control diabetes cost-effectively.

Diabetes is renowned as a "silent epidemic" [39]. The slow progression and lack of symptoms in the early stages of disease often delays people seeking a glucose test, preventive care, and/or medical attention. As such, self-reported prevalence often reflects an underestimation of the number of cases because it does not account for undiagnosed cases. Almost half of all people with diabetes worldwide (~192 million) remain undiagnosed [1], and the prevalence of undiagnosed diabetes is much higher in low-income than lower- and upper-middle income countries (75% vs. 46%, respectively) [40]. Overall, it is estimated that 84% of all cases of undiagnosed diabetes are in LMICs, with Pacific Island nations showing the highest prevalence [41]. This is particularly concerning because, as the pathophysiology of diabetes sets in, diabetes-related complications such as nerve, eye, kidney, and/or vascular diseases can already manifest before diagnosis occurs [42–44]. Target organ damage of this nature can be life threatening and/or seriously disabling [45].

The traditional socioeconomic gradient associated with chronic diseases may itself be transitioning. As the world's urban population size begins to outnumber those living in rural areas, many LMICs face enormous challenges related to growth of peri-urban slums and squatter settlements, disparities in provision of basic amenities, and poor sanitation and nourishment along with subsequent exposure to contemporary dietary choices, tobacco use, and mechanization of transport with consequent growth in incidence of NCDs. Thus, the paradigm is shifting *globally* towards the inverse relationship found in established market economies where the greatest burdens of NCDs are felt by the least well-off segments of the population [46–51]. In India, for example, it has been demonstrated [52] that although family history and prevalence of glycemic abnormalities in high-income groups were double those of low-income groups, the reverse was true for smoking, alcohol consumption, prevalence of comorbid cardiovascular risks, and occurrence of complications (macrovascular disease, cataracts, proteinuria, and neuropathy). Indeed, since lower and middle socioeconomic classes make up such a large proportion of the populations in South Asia, even though the prevalence is lower, the absolute numbers of people in these classes affected by diabetes and comorbid cardiovascular disease (CVD) risks are much higher than in their wealthier counterparts [53]. Some studies even show greater disease susceptibility in lower socioeconomic groups in India [54, 55], mimicking patterns in wealthier nations [56–59]. As this chapter progresses, it will become evident that the countries suffering the greatest burdens of disease are also those least equipped to manage the growing epidemics.

Major burdens

The burden of any disease, including diabetes, can be described by its health-related impacts, the morbidity and mortality caused, and the social and economic costs to individuals, families, communities, and national economies (Box 5.1).

Acute and chronic disease complications

The patterns of major health-related burdens of diabetes vary with the type of disease. Of the two most common forms, T1DM and T2DM, the latter accounts for 90–95% of all cases worldwide. Both T1DM and T2DM may be associated with acute and chronic metabolic consequences, but the frequency of events varies according to the underlying pathophysiology and level of glycemic and cardiovascular risk factor (i.e. blood pressure, cholesterol, and tobacco) control [60].

Box 5.1 Evaluation of burden.

- Health-related burdens
  - Disease events and/or ill-health
  - Morbidity (physical and psychosocial)
  - Mortality
- Social implications of disease
  - Disability
  - Alteration of social roles or family structure
  - Caregiver burdens
- Economic costs of disease
  - Health-seeking and utilization (frequency and costs)
  - Direct medical expenditure
  - Direct non-medical expenditure (ancillary expenses of health seeking and care)
  - Indirect costs (losses in productivity)

Acute fluctuations in serum glucose may rapidly spiral into emergency situations, with potentially fatal repercussions if untreated. Episodes of severe acute hyperglycemia (e.g. diabetic ketoacidosis [DKA] [61] and hyperosmolar non-ketotic coma) or, conversely, severe hypoglycemia, most often require immediate medical management. Longer term follow-up is then intended to promote better blood glucose regulation and avoidance of precipitants (e.g. infection, non-adherence to treatments, missing meals, alcohol abuse). Apart from atypical variants such as ketosis-prone T2DM in Africans [12, 14], most acute metabolic complications occur in people with T1DM, whereas ~10–12% occur in those with T2DM. When treated properly, the mortality from acute hyperglycemic episodes such as DKA is extremely low (e.g. DKA mortality in Taiwan, the United States, and Denmark were estimated to occur in 0.67–4.0 % of cases) [62, 63]. In contrast, in some African countries, mortality from DKA can be as high as 25–33% [64], although data on the incidence of these complications from LMICs are limited [65]. Individual person (e.g. age, additional comorbidities) and resource (e.g. hospital facilities, experience of staff) characteristics may also modify the outcomes. In under-resourced settings, for example, complex, cumulative, and interconnected barriers (poor accessibility, inadequate therapeutic instruments and medication, and insufficient numbers of trained staff) result in poor glycemic control and higher risk of mortality [66]. Hence early-life mortality in persons with T1DM in low-resource settings is commonplace (e.g. the post-diagnosis life expectancy in some regions of Africa is just 1 year) [67].

Both T1DM and T2DM are associated with damaging effects on tissues, with eventual progression to devastating complications. In a large proportion of people with diabetes, other cardiometabolic risk factors (hypertension, dyslipidemia, proinflammatory, and procoagulant states) often co-occur [28], which further increase the risk of diabetes-related complications [68]. Diabetes-related complications include the following:

- Macrovascular diseases such as coronary heart disease, cerebrovascular disease or "stroke," and peripheral vascular disease). Those with diabetes have a 2–4-fold higher risk of developing coronary disease than people without diabetes [69]. More significantly, however, the age- and sex-adjusted mortality risk in persons with diabetes is roughly equivalent to that of individuals without diabetes who have suffered a previous myocardial infarction [68, 70, 71]. T2DM and CVD have common precursors such as insulin resistance, visceral adiposity, and excess inflammation [72–76], and also a complex mix of mechanistic processes including oxidative stress, enhanced atherogenecity of cholesterol particles, abnormal vascular reactivity, augmented hemostatic activation, and renal dysfunction [77]. Hence simply controlling glucose, at least in the short term, has not been found to reduce CVD events and mortality in large randomized controlled trials [78–80]. The implications, therefore, are that individualized, comprehensive, multifactorial risk management (i.e. treating all risk factors together) has been advocated for people with T2DM [81, 82], adding to the burdens on patients, providers, and health systems.
- Microvascular diseases (retinopathy and nephropathy): together with hypertension, diabetes is a leading risk factor for nephropathy and end-stage renal disease requiring dialysis or transplant [83, 84]. Further, visual impairment, mainly due to cataract development, and retinopathy in diabetes are increasingly common, and diabetes is the leading cause of adult-onset blindness globally [85]. In the case of retinopathy and nephropathy, duration of disease, age, glycemic control, and blood pressure control have all been found to be prominent modifying factors of disease onset, progression, and outcomes.
- Neurovascular diseases (neuropathies): neuropathies are also common consequences of diabetes and can occur in one-third of people affected by this disease. Lower extremity sensory loss and compromised peripheral vascular circulation [86, 87] put these persons at risk of ulceration [88] and subsequent infection. The combination of neuropathy, infection, poor wound healing, and poor distal circulation increases the risk of lower extremity amputation 15–40-fold [84, 89].

As diabetes and chronic diseases grow in LMICs, these countries still face residual burdens of communicable infectious diseases [90, 91]. This challenge is not just one of parallel epidemics, as diabetes predisposes both to higher risk of infections [92] and possibly poorer outcomes for those who contract infections. Indeed, this has been documented in terms of higher risks of pneumonia, urinary tract infections [93], osteomyelitis, and even tuberculosis (TB) [94, 95]. Regarding outcomes, we can use TB as an example: data from observational studies increasingly show that TB disease severity (e.g. sputum smear grade [96, 97], hemoptysis, cavitation [96, 98–100], and drug resistance[100]), treatment failure, TB relapse, and death appear greater among those with TB and diabetes than those with just TB alone.

These complications and the consequences that stem from them (e.g. congestive heart failure, diabetic foot, and death) are associated with considerable morbidity, greater healthcare seeking, reduced quality of life, disability, premature mortality, and high economic costs [42, 43, 101].

Health utilization patterns

Health-seeking and health utilization behaviors are influenced by a number of individual-, provider- and system-level factors. In the case of diabetes, the individual's ill-health and morbidity and desire for preventive care drive more health seeking. In addition, expert guidelines recommend regular follow-up and providers may request that persons with diabetes return more frequently. Hence people with diabetes visit medical care providers more than those without diabetes [25, 102–105]. Increased health seeking and utilization in people with diabetes and associated complications result in greater medical costs being incurred compared with the general population without diabetes [106, 107]. Further discussion of healthcare costs from individual, societal, and national

perspectives will continue in the section "Economic costs of diabetes."

Various studies have shown that having diabetes doubles one's risk of hospitalization and associated costs, compared with not having diabetes, and this risk is amplified by the development of diabetes-related complications [106]. The presence of poor peripheral circulation increases the risk of hospitalization by 70%, and CVD increases this risk by 310% [84, 103]. Although studies from most regions of the world report late-stage macro- or microvascular complications as the leading cause of diabetes-related hospitalizations, lower income settings also confront high proportions of admissions from acute episodes of hyperglycemia [108]. Furthermore, individuals with diabetes utilize an average of 3–4 medications (including all antihypertensives, lipid-lowering and antidepressant medications, and aspirin, in addition to glucose-lowering drugs) [109], hence the cost implications are substantial. The use of oral antidiabetes drugs increases health expenditure by 40% compared with the general population, and regular insulin use incurs a further 2–4-fold greater expense [103, 110].

Healthcare infrastructure and financing have strong impacts on health seeking and utilization. In a number of LMICs such as India, most healthcare costs are borne by individuals and their families from household income [109, 111–113]. Surveys have shown that health expenditures due to diabetes and CVD are associated with financial difficulties as a result of illness [102, 114]. Financial limitations to accessing treatment are not confined to LMICs, as persons with low socioeconomic status living in HICs curtail purchases of diabetes medications due to costs [115, 116].

Disability

Aside from the medical or biological dysfunction caused by diabetes, ill-health affects how an individual interacts with and functions in society. This concept of "disability" signifies that psychosocial illness or physical deviations (from generally accepted norms of anatomical structure or physiological function) may impair one's ability to perform domestic and occupational activities and assume societal roles. As a result, diabetes may inhibit one's general utility and ability to integrate fully in society.

Diabetes can lead to disability in a variety of ways. Excluding the medical aspects of diabetes-related complications that directly restrict bodily function, diabetes may be considered a "hidden" disability, whereby the individual concerned is hampered from partaking in routine activities, but displays no physical manifestation of this illness. For example, children with T1DM may suffer discrimination at school or may not be permitted to engage in physical activities [117]. Adults in the workplace may suffer lower work performance by virtue of any number of symptoms (impaired fine motor skills and concentration, grogginess, urinary frequency) [118], or even a decline in cognitive functioning [119–121]. People with diabetes take more working days off and often report difficulties with completing work tasks [122, 123]. Those requiring insulin may be limited additionally by highly structured activities of daily living (the requirement for meticulous glucose monitoring, insulin administration, timed eating), recurrent hospitalizations, hyper- and hypoglycemic episodes, and regular preventive or therapeutic medical visits. In the DAWN2 study, ~40% of participants reported that their medication interfered with their ability to live a normal life, and 57% reported that they were not working because of their disease [124]. The physical manifestations of diabetes become more significant with the development of complications. Visual impairment, restricted mobility (due to shortness of breath, chest pain, or even amputation), and general ill-health (ranging from increased susceptibility to infection to uremia related to irreversible renal dysfunction) are all considerable impediments to productive work and engagement in socially valuable activities [118, 125].

Depending on the health status of the individual and severity of disease, disability can be temporary or permanent. There are limited country-specific data on the permanent disability resulting from diabetes, although diabetes is the leading cause worldwide of adult-onset blindness, non-traumatic amputations, and irreversible kidney failure [39].

Psychosocial burdens

Less tangible, but no less severe, are the psychological, interpersonal, and social burdens that people with diabetes and their caregivers may experience (Table 5.1). In a study assessing

Table 5.1 The psychosocial burdens of diabetes.

Type	Individual	Family
Physical	Diabetes may lead to temporary or permanent disability: impaired fine motor skills and concentration, grogginess, increased urinary frequency, visual impairment, restricted mobility, non-traumatic amputations, and irreversible kidney failure	–
Mental	Diabetes may lead to mental health problems: decline in cognitive functioning, depression, distress, anxiety, sense of hopelessness, and suicidal ideation	Caring for persons with diabetes may lead to mental health problems: emotional well-being, distress, frustration, and depression
Societal	Diabetes may lead to poor productivity, poor functioning, and societal problems: difficulties with daily life activities, loss of work days, low social integration, discrimination, and stigma	Caring for persons with diabetes may lead to absenteeism, loss of income by family members, affected family and peers relations, and discrimination

the psychosocial burden of diabetes in 8596 adults across 17 countries (the DAWN2 study), 44% reported experiencing high diabetes-related distress, 14% were identified with depressive symptoms, and 12% reported very poor or poor quality of life [124]. Further, diabetes has been found to be a significant risk factor for suicidal ideation [126], hopelessness, and poor quality of life in adults [127] and for suicidal ideation in adolescents with diabetes [128, 129]. Compared with their healthy counterparts, adults with diabetes exhibit higher odds for depression, anxiety and cognitive dysfunction [130, 131] and spend three times more on anxiety medications annually [132]. These mental health issues interfere with optimal self-management and may lead to other diabetes complications and increased risk for all-cause mortality [133, 134]. Family members caring for relatives with diabetes also experience high levels of distress and report that diabetes has a significant negative impact on their well-being [135].

The mental health burdens associated with diabetes may also affect productivity and functioning [136, 137]. Of those suffering from any form of work disability inducing absence and/or poor productivity, over half of them had minor and/or major signs and symptoms of depression [138]. Similarly, family members of persons with diabetes report that their work-related activities are negatively affected by their relative's disease, and some report working part time to help care for the relative with diabetes [135].

Strong social networks and good social support are associated with fewer psychosocial problems and better self-management among people with diabetes [139, 140]. However, some studies have shown that people with diabetes have low levels of social integration (e.g. low contact with family) and support (e.g. living without a partner) [141, 142]. In the DAWN2 study, 20% of surveyed participants reported that diabetes had negatively impacted their family and peer relations [124]. This suggests that diabetes is a shared ailment negatively impacting people's interpersonal relations.

Studies have shown that one in five people with diabetes and their families experience some form of discrimination [124, 135]. The reasons for discrimination are varied; one involves perceiving that persons with diabetes are using up societal resources [143]. As a result, stigma is common among people with diabetes and prevents them from disclosing their disease. For instance, adolescents with T2DM have reported hiding their diagnosis from their peers because they fear their reaction [144], and adults with diabetes have reported that disclosing their disease to their supervisors and colleagues would jeopardize their job [143] or, possibly, their education opportunities or marital prospects [145, 146]. Owing to the stigma attached to T1DM, some parents choose not to disclose the condition of their child to relatives [145]. Use of insulin adds to the stigma, as people with diabetes report feeling mistaken for intravenous drug users [143, 144]. Societal stigma and discrimination are significant barriers to self-management and to improving care and social support for individuals with diabetes.

The individual and societal dysfunction associated with disability is difficult to quantify. Several methods have been used in attempts to quantify diabetes-related disability, but most suffer from at least some imperfection owing to the necessity for making judgments about the value of activities and subjectivity of responses. This is especially difficult where there are cultural and ideological dissimilarities between the evaluator and the population being appraised.

Mortality

Diabetes is associated with a 1.4–6-fold higher risk of mortality, and this varies by age and sex [147]. Diabetes is also associated with premature mortality, shortening life expectancy by ~7–15 years [148, 149]. An estimated 48% of deaths due to diabetes occur under the age of 60 years [1].

The most common causes of death among people with diabetes are CVD, chronic kidney disease, and/or infections (e.g. pneumonias). In HICs, CVDs account for an overwhelming 65–75% of deaths in people with diabetes [150, 151]. In low-resource settings, infections and acute metabolic emergencies are still the prevailing causes of death in people with diabetes [14, 15, 152, 153]. End-stage renal disease also carries inexorably high mortality, due mainly to the inaccessibility (physical and financial) of treatment (dialysis and/or transplant) in most LMICs [14]. Globally, CVD and nephropathy are the most prominent fatal endpoints, and long-standing duration of disease increases the susceptibility to succumbing from these illnesses [43].

Ascertaining the global mortality attributable to diabetes is no easy task. Most mortality statistics rely on documented causes of death and do not acknowledge the underlying roles of glucose dysregulation in diseases leading to death. For example, it has been argued that evaluating actual diabetes-related mortality should take into account that diabetes contributes to 21% of coronary heart disease and 13% of stroke mortality worldwide [45]. The International Diabetes Federation takes these aspects into account and approximates that diabetes was responsible for 14.5% of total global mortality (5 million deaths) of adults aged 20–79 years in 2015 [1]. In addition, the mortality attributable to diabetes would be even higher if deaths related to IGT were also included. This diabetes precursor independently increases the risk of mortality, and has a prevalence of 15–40% in adults [6].

There are some important themes regarding diabetes mortality. First, over time, the absolute numbers of deaths due to diabetes have increased, and the proportion of all deaths attributable to diabetes has also increased in every region of the world (Table 5.2) [1, 147, 154]. Second, there is some regional variation in the global distribution of diabetes-related mortality. Although the proportion of deaths in LMICs is lower than in HICs, the absolute numbers of deaths (by virtue of the larger population size) outnumber those in HICs. The highest absolute numbers of deaths due to diabetes were in the most populous countries of the world, i.e. China, India, USA, and Russia [155]. Third, there is a noticeably greater proportion of deaths in younger age groups in LMICs [147], resulting in a greater loss of life-years and affecting the economically active subpopulations in these countries. Fourth, whereas some higher income countries are demonstrating reductions in the incidence of mortality [24], the diabetes mortality has

Table 5.2 Estimated percentage of deaths attributed to diabetes by region and year.

Region	WHO 2005 Male	WHO 2005 Female	WHO 2010 Combined	IDF 2013 Combined
Africa	2.2	2.5	6.0	~8.5
Eastern Mediterranean and Middle East	6.1	8.8	11.5	~13
Europe	6.6	5.1	11.0	~10.5
North America	8.7	8.3	15.7	~13.5
South and Central America	4.0–4.4	6.5–9.4	9.5	~12
South-East Asia	5.4	6.9	14.3	~14
Western Pacific	3.4	4.8	9.7	~16

WHO, World Health Organization; IDF, International Diabetes Federation.
Source: Adapted from Roglic et al. 2005 [154], Roglic and Unwin 2010 [147], and International Diabetes Federation 2014.

been increasing in LMIC regions, particularly Africa, the Western Pacific, and the Middle East.

Economic costs of diabetes

The prototypical chronic nature of diabetes requires empowered self- and clinician-guided management for the duration between diagnosis and death. Forestalling complications and premature mortality is the central theme underlying metabolic control and preventive management. Together, the care and serious consequences of diabetes are burdensome and costly. Quantifying the costs of diabetes from the perspectives of people with diabetes and also national resource use and losses is critical towards informing appropriate healthcare planning, resource allocation, and response strategies.

Approaches used to estimate economic costs of disease vary, not only by the perspective taken, but also by the methodology applied, data sources used, year of estimation, and purchasing power and clinical practice patterns in different settings. Needless to say, between-country comparisons are even more problematic when issues emerge regarding uncertainty of incidence and prevalence estimates, and standardization of measures and criteria. General principles and concepts of estimating cost [2, 84, 156, 157] are described in the following.

Types of costs

- *Direct costs ("inputs"):* These include costs of treatment and/or care of the disease, broadly encompassing all outpatient consultations, inpatient care, diagnostic investigations, therapeutic procedures, pharmacotherapy, paramedical care (e.g. home nursing, physiotherapy), and rehabilitation. There are also direct nonmedical costs (e.g. transportation to and from care providers).
- *Indirect costs ("lost output"):* These costs represent the present and future value of economic productivity lost by society on account of temporary or permanent disability, excess morbidity, and premature mortality due to disease. They are typically calculated by estimating foregone income (summing the cumulative impacts of absenteeism and presenteeism based on employment status and income, for both the individual and employer or society).
- *Intangible costs:* These costs are associated with psychosocial impacts (e.g. stress, depression, emotional problems) and altered quality of life due to an illness. They may include diminished family role, informal care, and income foregone by family members. They are typically difficult to estimate owing to a lack of standardized methods.

Cost appraisal methods

- *Cost-of-illness method:* This is the most widely used approach to describe the direct and indirect costs of disease to society, conducted by exploring costs in a group of selected persons either over a defined finite period (e.g. 1 year) or through the natural progression of the disease.
- *Human capital approach:* This is a method of estimating indirect costs of disease, with an emphasis on foregone earnings and employment. It is criticized as a tool owing to a tendency for overestimating future values, accepting wage disparities, and disregarding socially valuable activities such as housekeeping and volunteer work.
- *Friction cost approach:* This is a more conservative measure of indirect costs that considers lost productivity as finite where restoration of productivity (return to work or replacement of worker) occurs within a time-frame and therefore limits production losses. It requires detailed data.
- *"Top-down" approach:* This involves calculating costs from national databases/estimates and partitioning costs of different illnesses according to diagnoses. It requires accurate data entry, especially when indirect costs are being investigated. It avoids the risk of double counting.
- *"Bottom-up" approach:* This involves following the trail of illness-related costs of a defined subpopulation with the illness over a finite period.

Studies that have examined the costs of diabetes vary in their estimates of the excess costs generated through resource consumption. The major drivers of direct healthcare costs include health service utilization (outpatient health practitioner consultations and inpatient care), medication usage, diagnostic tests, self monitoring and therapeutic medical devices, and therapeutic procedures. In HIC settings, auxiliary services such as paramedical care (dieticians, physiotherapists, occupational therapists, and home nursing) and preventive checks (foot care, urine, and eye testing) may contribute to costs.

In 2015, US$1 in every $8 of healthcare expenditures globally was spent on diabetes [1]. The relative contributions of different cost drivers in various regions of the world are shown in Table 5.3.

Table 5.3 Regional and country estimates of costs of diabetes.

Region	Country	Year	Method	Annual total cost per individual	Annual total costs for country/region	Main drivers of cost	Limitations
Europe	France [164]	2010	Cost of illness, prevalence-based study: review of published studies, policy documents, and government reports	€6930 for persons with T1DM; €4890 for persons with T2DM	€17.7 bn	€4.2 bn for treatment of diabetes complications; €3.5 bn due to comorbidities; €3.6 bn due to health expenditure indirectly related to diabetes; €2.5 bn for diabetes treatment and prevention; €7.4 bn due to health expenditure unrelated to diabetes	Excluded indirect and intangible costs; study based on data from health insurance claims
	Germany [160]	2000–2007	Retrospective, bottom-up, cost of illness study: national insurance database (275,000–320,000 individuals)	€5197 in 2000 to €5726 in 2007 (direct); €2400 in 2000 and €2605 in 2007 (incremental)	€27.8 bn in 2000 and €42.0 bn in 2007 (direct); €12.9 bn in 2000 and €19.1 bn in 2007 (incremental)	Direct: 37% for inpatient care, 19% for outpatient medications, 18.5% for other services, 15% for nursing care, and 13% for physician outpatient services Incremental: 31% for inpatient care, 23% for other services, 21% for outpatient medications, 13% for physician outpatient services, and 12% for nursing care 46% for diagnosis and laboratory, 28% for pharmaceuticals, and 56% for physician visits	Retrospective analysis; only included insured persons; excluded indirect and intangible costs; only included the state of Hesse
	Greece [175]	2007	Retrospective study employing patient records, national formulary, and physician survey (102 patients)	€1297: €981 (controlled); €1566 (not controlled)	n/r		Excluded indirect and intangible costs; excluded T1DM; excluded costs of hospitalizations and comorbidities; small patient sample selected from 51 physician practices
	Italy [200]	2012	Top-down and bottom-up approaches; expert interviews and review of published studies and national sources	€2756–2991	€9 bn	Hospital admissions (57%), medications (30%), and outpatient care (13%)	Excluded indirect costs; cost estimates obtained from five different studies employing different methodologies; included only one national study
	Lithuania [201]	2011	Prevalence-based, top-down approach: data from national health insurance database (762 persons)	€955; from €672 (no complications) to €1588 (with complications)	n/r	Inpatient: €1720 for psychiatrics, €1632 for hemodialysis, €1040 for nursing and palliative care, €1004 for vascular surgery Outpatient; €286 for outpatient day care, €43 for GP visits, €38 for rehab specialist	Excluded T1DM; excluded indirect and intangible costs
	The Netherlands [202]	2012	Cost–utility analysis and friction cost approach; prospective pre–post study using patient questionnaires ($n = 407$)	€3489	n/r	Direct: €941 for primary care, €338 for outpatient hospital care, €701 for inpatient hospital care, and €518 for medication Indirect: €174 for travel costs and €216 for loss of productivity	12-month prospective design subject to recall bias; excluded annual direct and indirect costs; only included 4 diabetes management programs in The Netherlands

	Spain [165]	2009	Bottom-up, top-down, cost of illness, and human capital approaches: review of published studies and national data sources (n = 3,007,182)	€1660 (direct); €916 (indirect)	€5.1 bn (direct); €2.8 bn (indirect)	Direct: €757 m for macrovascular complications, €579 m for microvascular complications Indirect: only loss of productivity included	Excluded intangible costs; used human capital approach for estimating indirect costs; excluded non-healthcare direct costs and informal care costs faced by people with diabetes and society as a whole
	UK [203]	2010–2011	Cost of illness, top-down approach: aggregated data sets from national health system, public health, hospital databases, and literature review	n/r	£23.7 bn; £9.8 bn (direct); £13.9 bn (indirect)	Direct: £7.7 bn due to complications, £2 bn for diagnosis Indirect: £4.8 bn for due to mortality, £945 m due to sickness days, £2.9 bn due to presenteeism	Excluded foot care and primary care monitoring costs; obtained data from various sources employing different methodologies; excluded intangible costs
Africa	Africa (46 member states in the WHO African Region) [183]	2000	Cost of illness, prevalence-based study: WHO publications, online resources, and health system sources	INT$3633	INT$25.5 bn; $8.1 bn (direct); $17.4 bn (indirect)	Direct: 32% for insulin treatment, 9% due to diabetes testing Indirect: 38% due to permanent disability, 4% due to premature deaths	Costs of diabetes complications were not included; the use of gross national income per capita might overestimate the economic burden of diabetes; it assumed that people with diabetes received five diagnostic tests; intangible costs were not included
	Algeria [204]	1998, 2010 and 2013	Cost of illness, prevalence-based study: literature review, online resources, and consultations with experts	Treatment costs US$503 DM spending US$313	US$513 m (direct)	US$28,422 for renal transplantation, US$3901 for ambulatory peritoneal dialysis, US$3742 for hemodialysis, and US$2451 for cardiovascular complications	Excluded indirect and intangible costs; cost estimates obtained from different studies employing different methodologies, estimates based on insufficient national data or limited reliability
	Morocco [161]	n /r	Cost of illness, prevalence-based study and human capital approach; review of published studies, Ministry of Health and international federations/organizations documents	US$259–830 (direct) US$1113 (indirect)	US$0.47–1.5 bn (direct); US$2 bn (indirect)	Direct: medications US$90,685,180–$217,363,962; hospitalization US$1,547,594–$326,190,375; testing US$32,619,037–$69,897,937; outpatient visits US$181,921,500–$454,803,750 Indirect: permanent disability US$1,486,940,942; temporary disability US$19,832,628; life years lost US$517,757,550	The cost of disability in young people (0–14 years) and those retired (above 60 years) was ignored; estimates are based on assumptions around the number of people using insulin, oral drugs, glucose meters and those needing outpatient care or inpatient hospitalization; scarcity of reliable data
	Sudan [185]	2001	Cost of illness, bottom-up approach: parent interviews of 147 T1DM children	US$283 per child	n/a	Direct costs: insulin (36%), glucose testing, physician visits Indirect costs: poor school performance, 65% of family expenses were used for care of one T1DM child	Subject to recall bias; sample may not be representative of wider population (private clinics); subjects had ≤5 years' duration of diabetes

(*continued*)

Table 5.3 (*Continued*)

Region	Country	Year	Method	Annual total cost per individual	Annual total costs for country/region	Main drivers of cost	Limitations
	Republic of Seychelles [205]	2004–2005	High-risk strategy to estimate direct medication costs; population-based survey (1255 aged 25–64 years)	US$45.6 in 2004 and US$84.6 in 2005	n/r	Diabetes US$ 21.5 in 2004 and US$ 3.8 in 2005; hypertension US$30.4 in 2004 and US$11.2 in 2005; hypercholesterolemia US$32.7 in 2004 and US$30.6 in 2005; medical visits US$8.2 and laboratory exams US$14.4	Excluded hospitalization, indirect and intangible costs; costs for a treatment strategy provided are likely to correspond to minimal figures; only the public sector was included
Asia	China[a] [206]	2007–2011	Cost of illness, prevalence-based study: national household survey from insurance evaluation (5344 people with DM)	¥8,914; ¥8,582 (direct); ¥331 (indirect)	n/r	¥8289 due to direct medical costs, ¥5519 due to medication costs, ¥1091 due to non-medical costs, ¥3769 out of pocket spending	Costs estimated from an analysis including 5 chronic diseases
	China [207]	2007	Cost of illness study: interviews with 1913 people with DM	¥10,164 (direct)	Direct: ¥6056 (complications); ¥3583 (no complications)	Outpatient: ¥242 for treatment, ¥28 for diagnosis, ¥0.5 for medical supplies Inpatient: ¥10,102 for treatment, ¥3218 for diagnosis, ¥430 for medical supplies, ¥86 for nursing	Excludes T1DM; estimates are based on patient self-report; excluded indirect and intangible costs; cross-sectional study including secondary and tertiary care hospitals from 4 cities
	Indonesia [208]	2005–2010	Review of published studies, national guidelines, policies, and Ministry of Health and insurance data	US$40–800	US$22.4 m	US$7691 m for renal-replacement therapy, US$4900–6500 for hemodialysis, $75 for hypertension and retinopathy complications	Excluded indirect and intangible costs; paucity of data representative at the national level; lack of a clear reference date; lack of data from primary care; lack of data from certain regions of the country
	Iran [209]	2004–2005	Cost of illness, prevalence-based study and human capital approach: interviews with people with DM ($n = 710$)	US$192; US$152 (direct); US$40 (indirect)	US$112 m (direct); US$10 m (indirect); US$50 m (complications)	Direct: 29% due to medications and devices and 29% due to hospitalization Indirect: only lost work days included Complications: 71% due to hospitalizations	Estimates are based on patient self-report; indirect costs were estimated in workers only; study was conducted in Tehran, which is more urbanized than other provinces of Iran; intangible costs were excluded
	India [187]	1999–2012	Bottom-up approach: systematic review of published studies (19 studies including 13,490 persons)	US$6–314 (direct); US$48 (indirect)	US$114–816 (direct); US$91–$393 (indirect)	Direct: 54–62% for medications Indirect: 61% for patient income loss and 39% for carer income loss	Excludes intangible and loss of productivity costs; heterogeneity of study designs and diversity of methods in included studies; provides a fragmented picture

	Pakistan [210]	2004–2005	Bottom-up approach: retrospective study employing case note review of hospital documents (214 patients)	n/r	PKR356 (transtibial or transfemoral amputation); PKR389 (minor amputation)	The cost of medication and of home visits for ulcers grades 2 and 3 constitute ~22–79% of the total cost	Included only one tertiary hospital; excluded indirect and intangible costs; small sample size; study findings are not generalizable
	Pakistan [211]	2006	Cost of illness: questionnaires; human capital approach; $n = 345$ (age 20–60 years) at 6 OPD clinics	PKR11,580 (= US$197)	Direct costs projection = PKR71 bn (= US$1.21 bn) annually	Direct: medication (46%), laboratory investigations (32%); age, complications, and duration of disease	Inclusion restricted to 20–60 years age group; did not include costs of self-monitoring; calculation of lost productivity limited to those employed
	Turkey [212]	2009	Cost of illness, prevalence-based study: literature review, expert interviews, hospital health records, and national databases, (4 million people)	₺.622–2.966 (direct)	₺11.4-12.9 bn (direct)	28% due to cardiovascular complications, 27% due to renal complications, 15% for non-diabetes drugs, 13% for other complications, 12% for diabetes drugs, 5% for complication screening	Excluded indirect and intangible costs; diabetes complications costs were derived from a single center in Turkey; the cost of undiagnosed people was excluded; incidence and prevalence rates were not exclusively derived from Turkey-specific studies
	Thailand [213]	2008	Cost of illness, prevalence-based study and human capital approach: hospital service utilization records, medical records and patient interviews (475 people with diabetes)	US$881.47	US$418,696; 23% direct medical cost, 40% direct non-medical cost, and 37% indirect cost	Direct medical (provider): 11% due to hospital care/inpatient service, 3% drug and outpatient visits Direct non-medical (patient): 28% due to informal care (the care provided by the family members, friends, relatives) Indirect: 19 % due to permanent disability, 17% due to mortality cost	Only one primary care hospital and affiliated health centers were included; persons not requiring treatment were omitted from the cost estimation, which may have inflated the cost per case; indirect cost calculation did not take into account reduced earnings or productive capacity due to disability; ignored intangible costs
Americas	Argentina [159]	2004	Review of published studies and national/provincial official sources	US$1628	n/r	Direct: Hospitalization is the main component of the total direct cost per person of diabetes care Intangible: 1,328,802 DALYs lost; 85% ascribed to disabilities	No annual total cost for country is reported; indirect medical costs are not reported; data were obtained using different methodologies, many of which have changed over time
	Brazil [174]	2007	Bottom-up and human capital approaches: healthcare system, Ministry of Health, and public health system data (1000 people in 2007)	US$2108, 63.3% (direct); 36.7% (indirect)	US$2,108,287; US$1,329,075 (direct); US$773,212 (indirect)	Direct: 48.2% due to medication; US$ 2062 per person for microvascular complications; US$2517 per person for macrovascular complications Indirect: loss of productivity of US$437 per person/year	Data on hospitalization costs was not included; only 8 Brazilian cities were included which are not representative of the whole country; the majority of included persons were women or workers

(*continued*)

Table 5.3 (*Continued*)

Region	Country	Year	Method	Annual total cost per individual	Annual total costs for country/region	Main drivers of cost	Limitations
	Canada [214]	2011	Cost of illness, prevalence-based study: utilizing economic burden of illness documents, medical billing system, and published studies	CAN$2300	CAN$ 2.5 bn; CAN$769.4 million (direct); CAN$1.7 bn (indirect)	Direct: CAN $350.1 m in hospital care, CAN$246.4 m in medication spending, and CAN$172.9 m in physician care costs Indirect: CAN$1.0 bn due to premature death and CAN$671.7 m due to long- and short-term disability	Does not take into account the indirect costs of complications, direct costs focus on the primary management of diabetes only, does not include costs associated with mental health
	Colombia [215]	2007	Cost of illness, incidence-based and human capital study; review of literature, national price lists, national statistics, and Ministry of Health data	US$847: $288 (direct); $559 (indirect)	US$2.7 m; US$921 m (direct); US$1.8 m (indirect)	Direct: 47% for drugs, 24% for cardiac and coronary disease, 15% for stroke, and 9% for amputation Indirect: 52% for cardiac disease, 10% for retinopathy and stroke	Excluded intangible costs and T1DM; the costs of hypoglycemia, diabetic neuropathies, ketoacidosis, infections, and other complications were not considered; cost estimates were based on international guidelines; quality of care variables were excluded
	Mexico [216]	2010	Cost of illness, prevalence-based study and human capital approach: national surveys, instrument developed, and expert panel consensus	n/r	US$778 m; US$343 m (direct); US$435 m (indirect)	Direct: US$133 m for medications, US$110 m for complications, US$60 m for diagnostics/consultations, and US$40 m for hospitalizations Indirect: US$409 m for permanent disability, US$196 m for premature mortality, US$64 m for temporary disability	Excludes T1DM, costs per person and intangible costs; estimates are based on expert reports and probabilistic models
	Mexico [217]	1992–2011	Cost of illness, prevalence-based study: review of published studies	n/r	US$205 bn	Direct: outpatient US$718 m, inpatient US$223 m Complications: retinopathy US$10 m, CVD US$13 m, nephropathy US$82 m, neuropathy US$3 m, peripheral vascular disease US$2 m Indirect: US$177 m	Estimates were obtained from studies conducted in different years using different methodologies; costs are based on probabilistic simulations
	USA [218]	2007	Cost of illness, prevalence-based study: cost of diabetes model utilizing published studies, government statistics, and analysis of national survey and medical claims databases	US$443 for prediabetes; US$2864 for undiagnosed diabetes; US$9677 for T2DM; US$14,856 for T1DM; US$3514 for gestational diabetes	US$218 bn; US$174.4 bn for diagnosed diabetes; US$18 bn for undiagnosed diabetes; US$25 bn for pre-diabetes; US$636 m for gestational diabetes	Direct: US$153 bn in medical costs Indirect: US$65 bn for productivity loss (higher levels of absenteeism, presenteeism, disability, and early mortality)	Estimates do not include intangible costs; calculation of lost productivity limited to those employed; does not estimate productivity loss associated with prediabetes or gestational diabetes

	USA [158]	2012	Cost of illness, prevalence-based study: cost of diabetes model utilizing national surveys and claims database (22.3 million people in 2012)	US$13,700 (US$7900 directly for diabetes care)	US$245 bn; US$176 bn (direct); US$69 bn (indirect)	Direct: 43% in hospital inpatient care, 18% in prescription medications to treat the complications of diabetes, 12% in antidiabetes agents and diabetes supplies, 9% in physician office visits, and 8% in nursing/residential facility stays	Estimates do not include: intangible costs, research, programs and administrative costs, over-the-counter medications, dental and optometry costs, caregiver loss of productivity, and undiagnosed diabetes
	Latin America and Caribbean [102]	2000	Cost of illness, prevalence-based study: cost estimates for groups of countries and human capital approach	US$703 (range: US$442–1219)	US$65.2 bn; US$10.7 bn (direct); US$54.5 bn (indirect)	Direct: drug costs (44%), consultations (24%), complications (23%—especially nephropathy) Indirect: disability and productive life years lost (93%), mortality (7%)	General lack of data forced the use of estimates in heterogeneous countries; diabetes-related deaths undercounted on death certificates; high indirect cost may reflect poor access to medical care
Australia	Australia: DiabCost Study	2003	Cost of illness, bottom-up approach: persons with T2DM; self-reported surveys	A$9625 (no complications); A$15,580 (with complications)	A$3 bn	n/r	Data were self-reported; costs not associated with DM could not be separated out
	Australia – AusDiab Study [132]	2004–2005	Bottom-up approach: data from national insurance, medical, hospital, and pharmaceutical databases; patient (558) questionnaires and examinations	A$3806 (direct); A$5379 (government subsides); A$2003 (non-healthcare)	A$10.6 bn; A$4.4 bn (direct); A$6.2 bn (government subsidies); A$1.3 bn (non-healthcare)	Direct: 35% for hospitalization, 32% for medication, 28% for ambulatory service, and 5% for consumables Non-healthcare: 48.7% for supported accommodation, 35.4% for home service and day center, 13.9% for transport, and 1.9% for purchase of special food	Excluded indirect and intangible costs; heart attack and stroke events were collected via patient self-report; the sample is skewed towards more people being diagnosed with diabetes

[a]Data obtained from article abstract.
T1DM, type 1 diabetes mellitus; T2DM, type 2 diabetes mellitus; DM, diabetes mellitus; BP, blood pressure; bn, billion; m, million; DALY, disability-adjusted life-year; OPD, outpatient department; GP, general practitioner or primary care doctor; €, euro (European Union); £, British pound sterling; US$, American dollar; CAN$, Canadian dollar; A$, Australian dollar; PKR, Pakistani rupee; , Turkish lira; ¥, Chinese yuan.

Broadly, diabetes results in ~2–5.6-fold greater healthcare expenditure than for the general population, depending on the context and the cost appraisal methodology employed [132, 158–161]. Themes that surface from these studies affirm the high costs of complications and associated hospitalization in HICs, but also point to high costs (relative to their purchasing power) of purchasing medications in LMICs [106, 162, 163]. In addition, it is important to note that the complex interconnections between the underlying pathophysiology of T2DM and associated cardiometabolic comorbidities may alter the scope of costs [106]. Hence, depending on the viewpoint and chosen values, resource use attributable to diabetes alone may in fact underestimate the broader range of costs associated with diabetes-related illnesses as a group. Indeed, from the data in Table 5.3, the supplemental costs of drugs for comorbid CVD risk management were also pronounced [102, 158, 164, 165]. Undiagnosed diabetes may not be described as a contributor to morbidity, mortality, and resource use, suggesting that we may be underestimating the true burden of this disease [41]. This is particularly relevant in regions of the world where there are few or no representative data regarding disease prevalence and causes of death (e.g. most LMICs) [166]. Finally, the value placed on the opportunity cost of diabetes-related ill-health and disability has not been widely quantified or even qualitatively described.

Individual-level cost drivers

Demographic and clinical characteristics can have profound influences on costs. Annual per capita cost increases for managing diabetes are higher for men than women in some countries, and among older age groups compared with their younger counterparts [103, 160]. The types of diabetes have different costs. T1DM accounts for a smaller proportion (~5%) of people with diabetes, but almost double the per capita costs compared with people with T2DM [167]. It has been postulated that more consultations and faster progression to retinopathy and nephropathy are the main drivers of cost and mortality risk in those with T1DM [43, 104]. In T2DM, the coexistence of hypertension and dyslipidemia has a relatively more significant role in mediating outcomes and associated costs [106, 168].

Promoting healthy behaviors, mainly physical activity, healthy eating, and weight loss, can help people with diabetes self-manage their illness and delay the onset of diabetes-related complications [169, 170], and are considered cost-effective from a health systems perspective [171]. Based on this, lifestyle programs have been included in expert guidelines for diabetes prevention and care [172]. However, lifestyle programs and changes adopted by people with diabetes also have a cost attached to them, compared with doing nothing. For instance, engaging in a 3-mile daily walk over 2 years can cost the person up to US$400 when one considers the cost of the individual's time, items needed to exercise (e.g. exercise apparel, footwear), transportation, and health center admissions [173]. Higher physical activity intensity translates into higher costs [173]. Dietary modifications are also costly, equivalent to about 20% of the direct ambulatory care costs incurred by people with diabetes [109]. As an example, in Brazil, people with diabetes spend approximately US$286 on artificial sweeteners and dietary products based on their diagnosis of diabetes [174]. Therefore, adhering to lifestyle changes can contribute to the financial burden that people with diabetes face.

Clinical status also matters with regard to resource utilization. Uncontrolled diabetes is associated with higher healthcare costs; people with uncontrolled diabetes have ~30% higher annual pharmaceutical costs, 70% higher costs for laboratory/diagnostic tests, and 85% higher consultation costs than those with good control [175]. A rudimentary but practical finding is that for every 1% increase in HbA_{1c} over 7%, there is a corresponding 10% increase in costs [168]. As mentioned previously, the presence of diabetes-related complications greatly increases both the magnitude and duration of resource consumption. Complications contribute up to 60% of all direct costs and 80–90% of indirect losses due to absenteeism and lost productivity [176]. Globally, healthcare costs are three times higher for people with macrovascular complications than for those without complications [166]. In particular, CVD and nephropathy are associated with the highest healthcare costs in most regions of the world. Coronary and cerebrovascular events, and heart failure have been found to increase hospital costs significantly, from INT$76 to $1800 (International dollars) in Asia, from INT$156 to $3000 in Eastern Europe, and from INT$296 to $4000 in more Established Market Economy countries [106]. Similarly, early renal dysfunction is the basis for 65% more costs, and the onset of end-stage renal disease signifies a 771% increase in costs [177–179]. Both the presence and the number of complications are associated with increased costs—the costs among persons with both micro- and macrovascular complications are 25–50% higher than for people with only one micro- or microvascular complication [113, 162, 174].

Country-level cost patterns

Globally, health expenditures related to diabetes totaled an estimated US$673–1197 billion in 2015 [1]. There are large differences in healthcare expenditures by region and country income level. By 2030, it is estimated that the world's richest countries will be responsible for more than 90% of the global expenditure on diabetes [180, 181]. The imbalance between resource expenditure and needs is further exemplified by estimates that only 20% of global expenditure occurs in the regions where 80% of people with diabetes live [155], demonstrating that Julian Tudor Hart's [182] "inverse care law" is very relevant to global diabetes burden (it states that "the availability of good medical care tends to vary inversely with the need for it in the population served").

Overall, direct costs were the main drivers of total diabetes-related costs across regions, although indirect costs (costs associated with loss of productivity, temporary or permanent disability, and premature mortality) were the main drivers for some regions of the world. For instance, in Africa, Latin America, and the Caribbean, indirect costs represent 70–80% of total diabetes costs [102, 183]. The main drivers of direct costs in HICs are the costs of hospitalization and patient care, whereas for LMICs, the

costs of medications and drugs predominate. In countries such as Mexico, India, Pakistan, and Sudan, medication spending accounts for 32–60% of total diabetes expenditures [162]. There are sizeable between-country disparities in per capita expenditures on diabetes [184]. These differences in expenditure are partially related to differences in pricing and prescription but are also linked to the high costs of new diagnostic and therapeutic options (e.g. treating a patient with maximal daily doses of metformin is approximately one-twentieth of the cost of using newer medication classes).

Industrialized countries are also advantaged in the organization of healthcare infrastructure, in addition to the financing of the healthcare system (e.g. nationalized insurance and social security schemes in Western Europe cover 80–90% of population costs), which ensure high accessibility to care for citizens [103, 110]. Owing to the inadequate public spending on health in LMICs and the lack of health insurance and other health financing mechanisms, sizeable proportions of household income are spent on healthcare costs. For instance, the healthcare expenses that families bear from their own pockets in LMICs ranges from 40 to 60% [14, 15, 102, 185]. In LMICs, the lowest income groups bear the greatest burdens, paying a larger proportion of their household incomes towards diabetes care [185, 186]. In a study of 35 LMICs, people with diabetes showed a greater risk of incurring catastrophic medical expenses than their counterparts without diabetes (18% vs. 14%), and the risk among persons from LMICs was more pronounced (21% vs. 15%) [163]. Poor access to medications augments the economic burden that low-income persons with diabetes and their families bear, as drug costs represent over half of the total household spending on diabetes [187]. Year-on-year increases in this proportion are greater in impoverished groups and worsen with duration of diabetes, presence of complications, hospitalization, surgical therapy, and glycemic control requiring insulin [113, 186, 188].

Additional considerations with regard to national economic impact concern the distribution of diabetes burden *within* populations. In LMICs, diabetes and its complications disproportionately affect the economically productive age range (15–59 years), whereas in HICs, the disease affects the older (≥65 years), disadvantaged, and minority subpopulations [189]. The implications emanating from these trends are that economic development in transitioning countries may be subdued owing to loss of unrealized productivity, whereas direct health costs for the aging and uninsured populations in HICs will continue to escalate [2].

Furthermore, LMICs contain large and growing populations of people with prediabetes, and also groups of people unaware that they have an asymptomatic metabolic disorder. Prediabetes is independently associated with the development of complications and increased specialist consultations, requiring supplementary expenses per person [190].

Augmented expenditures associated with complications further perpetuate destitution and socioeconomic disadvantage (i.e. opportunity costs of healthcare expenses are often endured by foregoing investments in education of children, etc.). Meanwhile, socioeconomic hardship amplifies vulnerability to disease as healthy foods and behaviors are costly. Studies on diabetes showed that later age at diagnosis of diabetes and occurrence of disabling complications were associated with lack of awareness, being unemployed, and being less educated (e.g. a 7-year difference in age of diagnosis was demonstrated between illiterates and those with college education) [44, 191, 192]. Similar observations substantiate a bidirectional link between poor health and poverty (Figure 5.1).

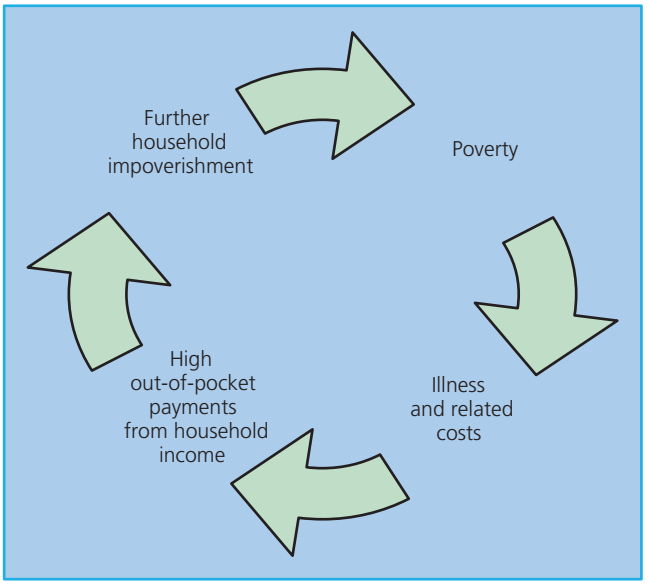

Figure 5.1 Diagram illustrating the cyclical relationship between poverty and ill-health: poverty predisposes one to illness, and costs of illness in a system of fee-for-service care have the potential to impoverish households, further perpetuating poverty.

Changing trends in costs

The global burdens associated with diabetes have been growing rapidly and are projected to escalate even further in the future. The hypothesized explanations for these trends of increasing burdens include, but are not limited to, the rising prevalence of diabetes and prediabetes worldwide, aging and longevity accompanied by costly comorbidities, lowered diagnostic thresholds, more attentive detection of cases, availability of newer, more costly treatment methods on the basis of industry research and development, and changes in clinical management, especially growth in the use of self monitoring and medical devices, new therapeutic drugs, and increasing demand for paramedical services. While it is evident that these latter reasons are more relevant in HICs, the continued epidemiological transitions will no doubt affect LMICs also. It is unfortunate that scarcity of resources and inadequate access in LMIC settings will result in greater disability and mortality, perpetuating the obstacles to socioeconomic development.

Gaps and future directions

Diabetes imposes serious health, social, and economic burdens worldwide. However, we still need more widespread and reliable data regarding burdens, access, and expenditures [193], especially in LMICs where the greatest burdens of diabetes occur. Few longitudinal studies are available in LMICs, thus limiting our understanding of incidence, risk factors, pathophysiology, variations in phenotypes, and natural history in these settings. In addition, studies are needed that include both long-understood and emerging complications of diabetes, such as cognitive function, in the models to create better estimates of diabetes-attributable mortality, morbidity, and cost. Assessing burdens using reliable, consistent methods will aid our comprehension of the complex mix of programmed, predisposing, and modifiable factors associated with diabetes and lays a foundation for policy development and advocacy.

Despite varied estimates of expenditure, the pattern is consistent: people with diabetes experience greater symptoms, morbidity, comorbidities, and mortality than those without diabetes, they suffer diminished functional capacity and psychosocial illness, and they incur greater costs for healthcare, self-care, and losses in earning potential and societal role. Also, although reductions in quality of life and other psychosocial measures of mental wellness are less numerically evident, they are no less distressing. Needless to say, intervening before diabetes onset may hold great benefit in reducing global burdens. However, although there is evidence from large trials demonstrating that prevention can forestall conversion from prediabetes to diabetes [194–197], widespread translation of these findings is hampered by multiple levels of barriers (political, social, cultural, behavioral, and economic factors). Preparation for the increasing diabetes burden requires progress in the wider collection of reliable data, collected in a standardized manner across various countries (especially assuaging the scarcity from LMICs regarding diabetes-related mortality, complications, disability, and costs), and a greater emphasis on cost-effectiveness studies that may inform better resource allocation [198]. On the shoulders of compelling evidence, greater investment and political will are required to overcome low accessibility and awareness, and also to translate the evidence into the practical, real-life implementation of proven and effective prevention strategies [199].

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2 Normal Physiology

6 Islet Function and Insulin Secretion

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Key points

- Regulation of fuel homeostasis in mammals is dependent on numerous small endocrine organs known as islets of Langerhans, which are located in the pancreas.
- Islets contain β cells, which are the only source of the polypeptide hormone insulin.
- Islet β cells are equipped to detect changes in circulating nutrients.
- Elevated levels of nutrients initiate an insulin secretory response from β cells that results in the storage of circulating nutrients in liver, muscle, and adipose tissue.
- A wide range of other signals, including hormones, neurotransmitters, and neuropeptides, can modify the insulin secretory response to circulating nutrients.
- Complex interactions between islet cells, the autonomic nervous system, and gastrointestinal incretin hormones allow precise integration between metabolic fuel intake, usage, and storage.

Introduction

The German anatomy student Paul Langerhans first described in 1869 the "islands of clear cells" distributed throughout the pancreas [1] but he did not realize the physiological significance of these cell clusters, which are today known as islets of Langerhans. We now know that islets are the endocrine compartment of the pancreas, comprising ~2–3% of the total pancreatic volume. Islets are approximately spherical (Figure 6.1a), with an average diameter of 100–200 μm, and a healthy human pancreas may contain up to a million individual islets, each having its own complex anatomy, blood supply, and innervation.

Islet structure and function

Islet anatomy

A typical mammalian islet comprises ~1000 endocrine cells including the insulin-expressing β cells (~60% of adult human islet cells), glucagon-expressing α cells (20–30%), somatostatin-expressing δ cells (~10%), and cells expressing pancreatic polypeptide (<5%), ghrelin, and peptide YY (<1%). The anatomical arrangement of islet cells varies between species. In rodents, the majority β-cell population forms a central core surrounded by a mantle of α and δ cells (Figure 6.1a), but human islets show less well-defined organization with α and δ cells also being located throughout the islet (Figure 6.1b) [2].

Islets are highly vascularized, and receive up to 15% of the pancreatic blood supply despite accounting for only 2–3% of the total pancreatic mass. Each islet is served by an arteriolar blood supply that penetrates the mantle to form a capillary bed in the islet core. Earlier studies using vascular casts of rodent islets suggested that the major route of blood flow through an islet was from the inner β cells to the outer α and δ cells [3], but more recent studies using optical imaging of fluorescent markers to follow islet blood flow *in vivo* [4] revealed more complex patterns of both inner-to-outer and top-to-bottom blood flow through the rodent islet.

Islets are well supplied by autonomic nerve fibers and terminals containing the classic neurotransmitters acetylcholine and norepinephrine, along with a variety of biologically active neuropeptides [5]. Vasoactive intestinal polypeptide (VIP) and pituitary adenylate cyclase-activating polypeptide (PACAP) are localized with acetylcholine to parasympathetic nerves, where they may be involved in mediating prandial insulin secretion and the α-cell response to hypoglycemia [6]. Other neuropeptides, such as galanin and neuropeptide Y (NPY), are found with norepinephrine in sympathetic nerves, where they may have a role in the sympathetic inhibition of insulin secretion, although there are marked inter-species differences in the expression of these neuropeptides [5].

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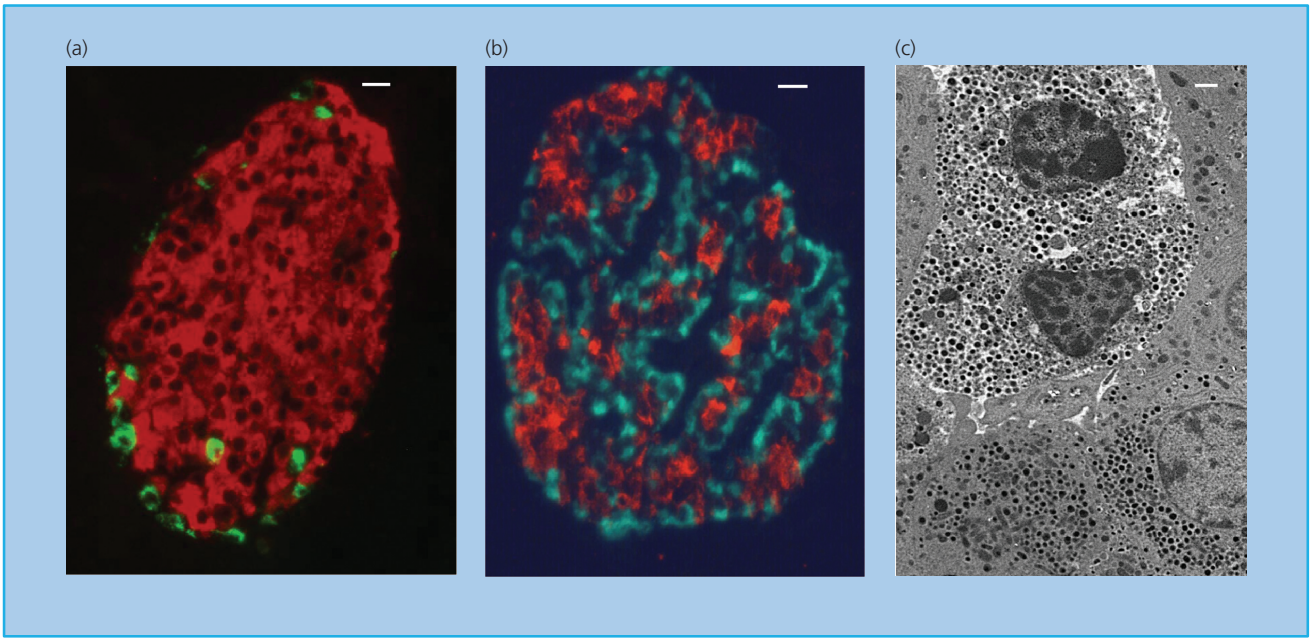

Figure 6.1 Anatomy of the islet of Langerhans. (a) Mouse islet. The image shows a section through a mouse pancreas in which insulin and glucagon are identified by red and green immunofluorescence, respectively, demonstrating the typical β-cell core surrounded by a thin mantle of α cells. In mouse islets, β cells comprise ~80% of the endocrine cell mass. Scale bar is 10 μm. Source: image courtesy of C. Li, King's College London. (b) Human islet. The image shows a section through a human pancreas in which insulin and glucagon are identified by red and green immunofluorescence respectively, demonstrating the less organized structure of the human islet when compared with mouse islets. In human islets, β cells comprise ~50–60% of the endocrine cell mass. Scale bar is 10 μm. Source: image courtesy of V. Foot, King's College London. (c) Transmission electron micrograph of human islet cells. The image shows a transmission electron micrograph of several cells within a human islet. The two cells at the top with the electron-dense secretory granules surrounded by a clear halo are β cells. The cells in the lower part of the micrograph are α cells. Scale bar is 2 μm. Source: authors' unpublished data.

Intra-islet interactions

The anatomical organization of the islet has a profound influence on the ability of the β cells to recognize and respond to physiological signals [7–9]. There are a number of mechanisms through which islet cells can communicate, although the relative importance of the different mechanisms is still uncertain [10]. Islet cells are functionally coupled through a network of gap junctions, and gene deletion studies in mice have highlighted the importance of gap-junctional coupling via connexin 36 in the regulation of insulin secretory responses [11, 12]. Cell–cell contact through cell surface adhesion molecules in localized microdomains offers an alternative communication mechanism [13], and interactions mediated by E-cadherin [13–15] or ephrins [16] have been implicated in the regulation of β-cell function. Components of the intra-islet extracellular matrix, which is predominantly synthesized by islet endothelial cells, influence β-cell proliferation, survival, and function via interactions with integrins on the β-cell surface [17]. A further important level of control is exerted via numerous intra-islet paracrine and autocrine effects in which a biologically active substance released by one islet cell can influence the functional status of a neighboring cell (paracrine), or of itself (autocrine) [18]. Figure 6.2 shows some of the molecules that have been implicated in this type of intra-islet cell–cell communication. Thus, islet cells can interact with each other via the classic islet hormones—insulin, glucagon, and somatostatin [19–22]; via other products secreted by the endocrine cells, including neurotransmitters, peptides such as kisspeptin [23], GLP-1 [24], and urocortin3 (Ucn3) [25], and adenine nucleotides and divalent cations that are co-released with insulin [26–29]; and via other less well-known mechanisms, including the generation of gaseous signals such as nitric oxide and carbon monoxide [30–32]. The wide range of intra-islet interactions presumably reflects the requirement for fine tuning and coordinating secretory responses of many individual islet cells to generate the rate and pattern of hormone secretion appropriate to the prevailing physiological conditions.

Insulin biosynthesis and storage

The ability to release insulin rapidly in response to metabolic demand, coupled with the relatively slow process of producing polypeptide hormones, means that β cells are highly specialized for the production and storage of insulin, to the extent that insulin comprises ~10% (~10 pg/cell) of the total β-cell protein.

Biosynthesis of insulin

In humans, the gene encoding preproinsulin, the precursor of insulin, is located on the short arm of chromosome 11 [33]. It is 1355 base pairs in length and its coding region consists of three exons: the first encodes the signal peptide at the N-terminus of preproinsulin, the second the B chain and part of the C

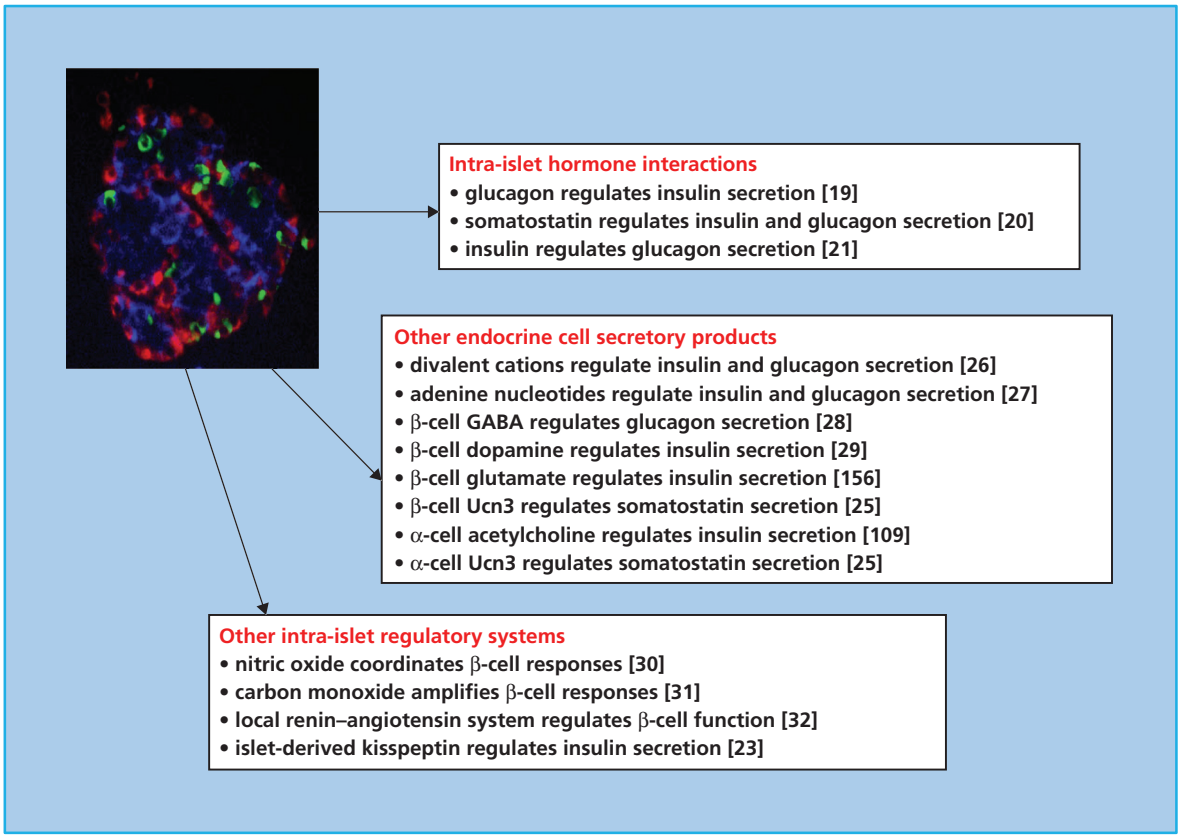

Figure 6.2 Intra-islet autocrine–paracrine interactions. The heterogeneous nature and complex anatomy of the islet permit numerous interactions between islet cells that are mediated by the release of biologically active molecules.

(connecting) peptide, and the third the rest of the C-peptide and the A chain (Figure 6.3). Transcription and splicing to remove the sequences encoded by the introns yields a messenger RNA of 600 nucleotides, translation of which gives rise to preproinsulin, an 11.5-kDa polypeptide. The cellular processes and approximate time-scales involved in insulin biosynthesis, processing, and storage are summarized in Figure 6.4.

Preproinsulin is rapidly (<1 min) discharged into the cisternal space of the rough endoplasmic reticulum, where proteolytic enzymes immediately cleave the signal peptide, generating proinsulin. Proinsulin is a 9-kDa peptide, containing the A and B chains of insulin (21 and 30 amino acid residues, respectively) joined by the C-peptide (30–35 amino acids). The structural conformations of proinsulin and insulin are very similar, and a major function of the C-peptide is to align the disulfide bridges that link the A and B chains so that the molecule is correctly folded for cleavage (Figure 6.5). Proinsulin is transported in microvesicles to the Golgi apparatus, where it is packaged into membrane-bound vesicles known as secretory granules. The conversion of proinsulin to insulin is initiated in the Golgi complex and continues within the maturing secretory granule through the sequential action of two endopeptidases (prohormone convertases 2 and 3) and carboxypeptidase H [34], which remove the C-peptide chain, liberating two cleavage dipeptides and finally yielding insulin (Figure 6.5). Insulin and C-peptide are stored together in the secretory granules and are ultimately released in equimolar amounts by a process of regulated exocytosis. Under normal conditions, >95% of the secreted product is insulin (and C-peptide) and <5% is released as proinsulin. However, the secretion of incompletely processed insulin precursors (proinsulin and its "split" products; Figure 6.5) is increased in some people with type 2 diabetes.

The β cell responds to increases in the circulating concentrations of nutrients by increasing insulin production in addition to increasing insulin secretion, thus maintaining insulin stores [34]. Acute (<2 h) increases in the extracellular concentration of glucose and other nutrients result in a rapid and dramatic increase in the transcription of preproinsulin mRNA and in the rate of proinsulin synthesis [35]. There is a sigmoidal relationship between glucose concentrations and biosynthetic activity, with a threshold glucose level of 2–4 mmol/L. This is slightly lower than the threshold for the stimulation of insulin secretion (~5 mmol/L), which ensures an adequate reserve of insulin within the β cell.

Storage and release of insulin

The insulin secretory granule has a typical appearance in electron micrographs, with a wide space between the crystalline electron-opaque core and its limiting membrane (Figure 6.1c).

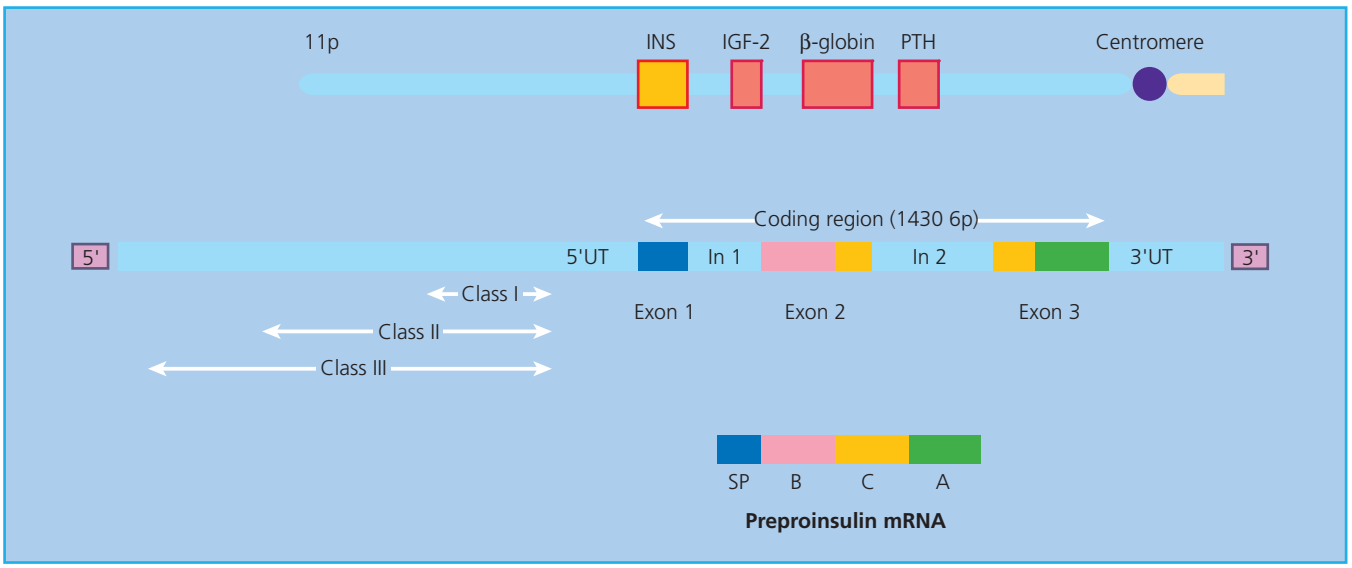

Figure 6.3 Structure of the human insulin gene. The coding region of the human insulin (INS) gene comprises three exons, which encode the signal peptide (SP), B chain, C-peptide, and A chain. The exons are separated by two introns (In1 and In2). Beyond the 5′ untranslated region (5′UT), upstream of the coding sequence, lies a hypervariable region in which three alleles (classes I, II and III) can be distinguished by their size.

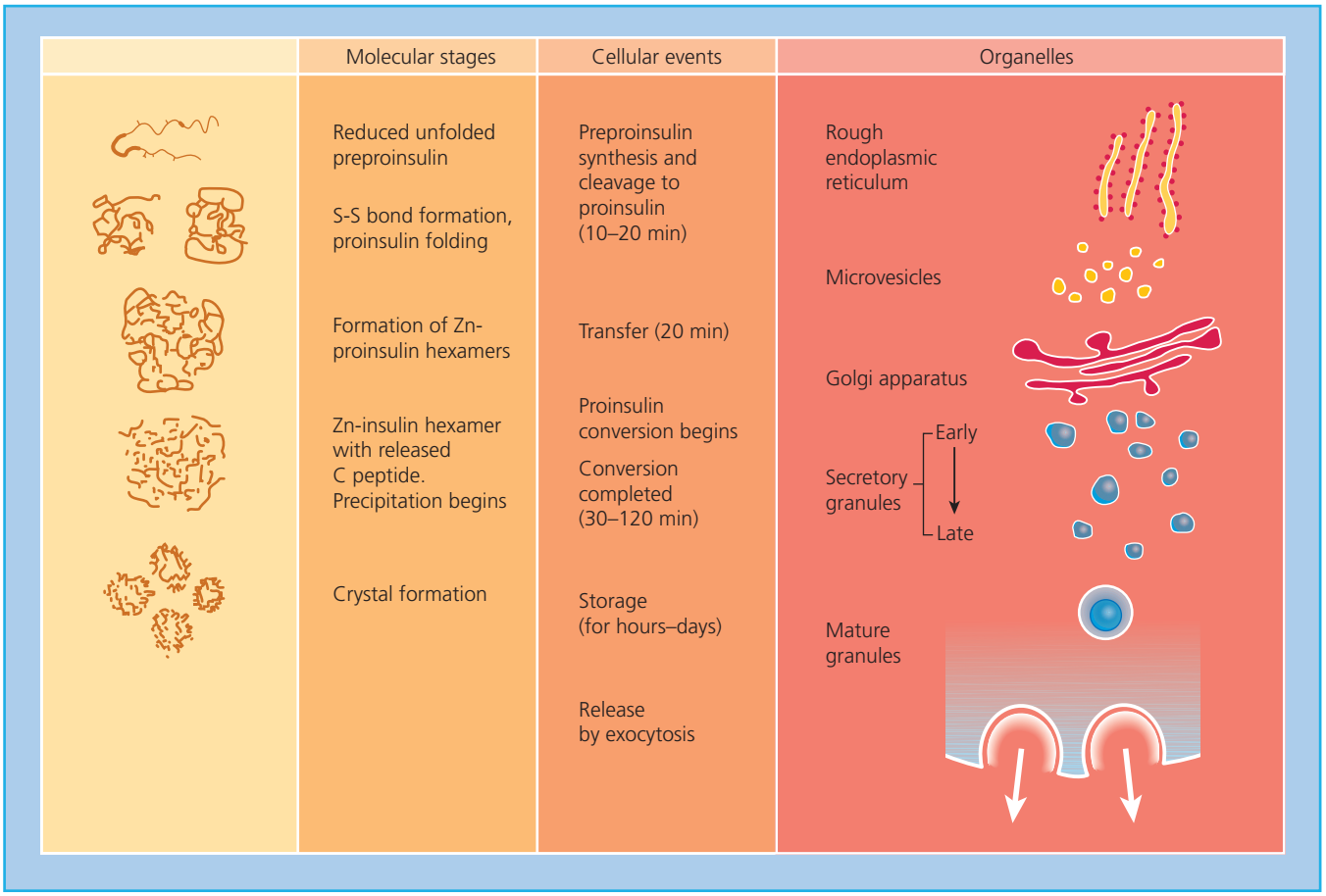

Figure 6.4 The intracellular pathways of (pro)insulin biosynthesis, processing, and storage. The molecular folding of the proinsulin molecule, its conversion to insulin, and the subsequent arrangement of the insulin hexamers into a regular pattern are shown at the left. The time course of the various processes and the organelles involved are also shown.

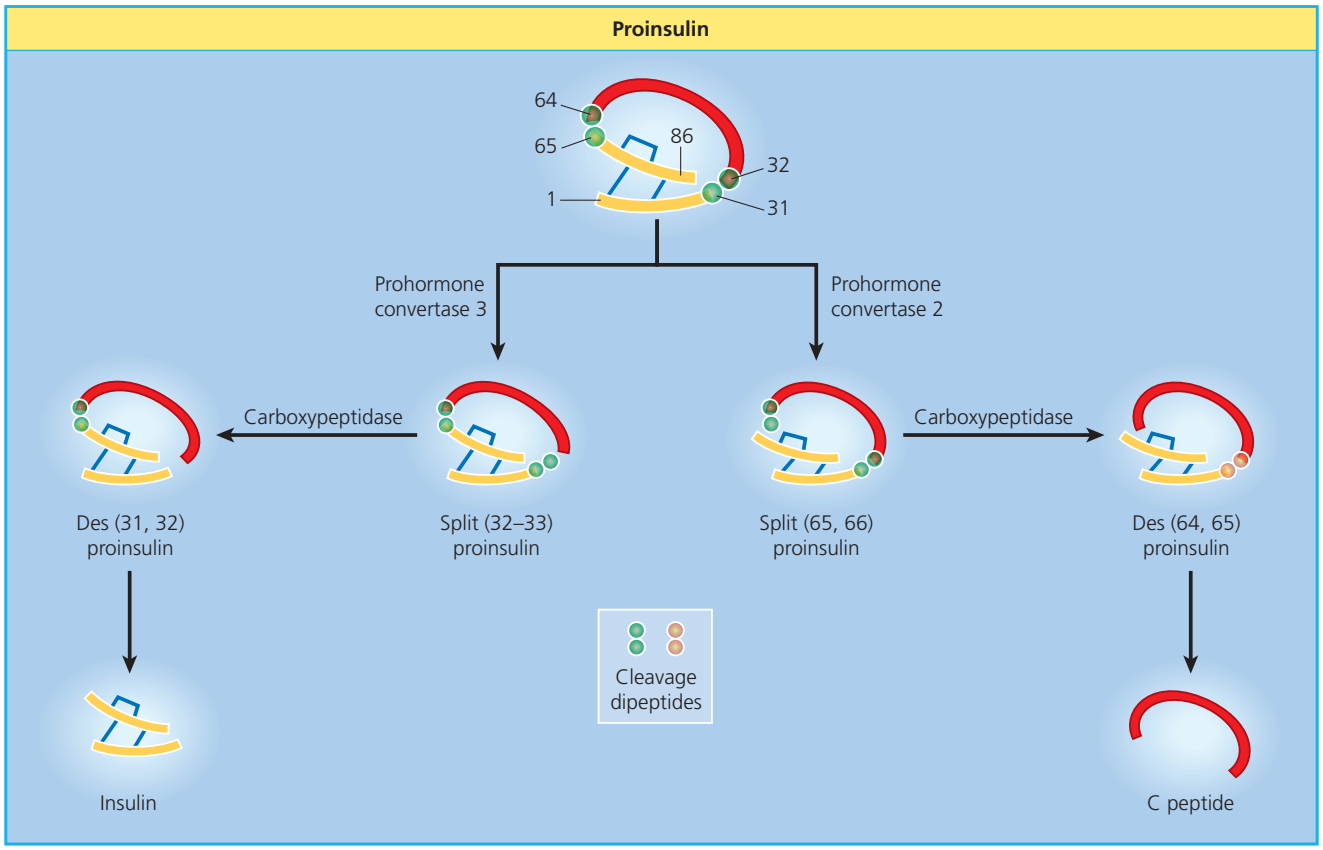

Figure 6.5 Insulin biosynthesis and processing. Proinsulin is cleaved on the C-terminal side of two dipeptides, namely Arg^{31}–Arg^{32} (by prohormone convertase 3) and Lys^{64}–Arg^{65} (prohormone convertase 2). The cleavage dipeptides are liberated, so yielding the "split" proinsulin products and ultimately insulin and C-peptide.

The major protein constituents of the granules are insulin and C-peptide, which account for ~80% of granule protein [36], with numerous minor components including peptidases, peptide hormones, and a variety of (potentially) biologically active peptides of uncertain function [36, 37]. Insulin secretory granules also contain high concentrations of divalent cations, such as zinc (~20 mmol/L), which is important in the crystallization and stabilization of insulin within the granule [38]. Zinc is transported into the insulin secretory granules by the islet specific zinc transporter ZnT8, where it binds to insulin to form a crystalline lattice of insoluble hexamers. Polymorphisms in the SLC30A8 gene encoding ZnT8, in which a single nucleotide polymorphism (SNP) generates a ZnT8 variant with lower Zn^{2+} transporting activity, are associated with increased risk of type 2 diabetes [39]. However, deletion of SLC30A8 in a number of transgenic mouse models produces only modest effects on insulin storage and secretion, and on whole-body glucose homeostasis, so the mechanistic link between SLC30A8 polymorphisms and type 2 diabetes risk remains unclear [39]. The intragranular function(s) of calcium (~120 mmol/L) and magnesium (~70 mmol/L) are uncertain, but they are co-released with insulin on exocytosis of the secretory granule contents so they may have extracellular signaling roles via the cell surface calcium-sensing receptor [26]. Similarly, the adenine nucleotides found in insulin secretory granules (~10 mmol/L) may have a signaling role when they are released into the extracellular space [27].

The generation of physiologically appropriate insulin secretory responses requires complex mechanisms for moving secretory granules from their storage sites within the cell to the specialized sites for exocytosis on the inner surface of the plasma membrane, and the role of cytoskeletal elements, notably microtubules and microfilaments, in the intracellular translocation of insulin storage granules has been studied extensively [40, 41]. Microtubules are formed by the polymerization of tubulin subunits and normally form a network radiating outwards from the perinuclear region [42]. The microtubular network is in a process of continual remodeling and the dynamic turnover of tubulin, rather than the total number of microtubules, is important for the mechanism of secretion. The microtubule framework may provide the pathway for the secretory granules but microtubules do not provide the motive force so other contractile proteins are likely to be involved. Actin is the constituent protein of microfilaments and exists in cells as a globular form of 43 kDa and as a filamentous form (F-actin), which associates to form microfilaments. F-actin remodeling in β cells is regulated by agents that alter rates of insulin secretion, and the pharmacological disruption of microfilament formation inhibits insulin secretion [43]. Myosin light and heavy chains are expressed at high concentrations in

β cells, suggesting that actin and myosin may interact to propel granules along the microtubular network, and a myosin- and Rab-interacting protein (MyRIP) has been implicated in cyclic adenosine monophosphate (cAMP)-dependent insulin secretion through interaction with the motor protein MyoVa [44]. It is likely that other molecular motors, including kinesin and dynein [45–47], are also involved in the movement of secretory granules, and perhaps other organelles, in β cells.

Insulin is released from secretory granules by exocytosis, a process in which the granule membrane and plasma membrane fuse together, releasing the granule contents into the interstitial space. Much of our knowledge of the molecular mechanisms of exocytosis is derived from studies of neurotransmitter release from nerve cells, and similar mechanisms operate in β cells, although some proteins implicated in synaptic vesicle exocytosis are not required for release of β-cell secretory granules [48]. The docking of the granules at the inner surface of the plasma membrane is via the formation of a multimeric complex of proteins known as the SNARE (soluble *N*-ethylmaleimide-sensitive factor attachment protein receptor) complex, which consists of proteins associated with secretory granules and the plasma membrane, and soluble fusion proteins [43, 49, 50]. The docked granules will fuse with the membrane and release their contents only in the presence of elevated levels of intracellular calcium, which is sensed by synaptotagmins, a class of calcium-binding granule proteins [49, 51]. Secretory granules are distributed throughout the β-cell cytoplasm (Figure 6.1c), and it is likely that the transport of granules from distant sites to the plasma membrane is regulated independently from the final secretory process, with a reservoir of pre-docked granules available at the inner surface of the plasma membrane. Fusion of this "readily releasable" pool of granules may account for the rapid first-phase release of insulin in response to glucose stimulation and direct electrophysiological measurements have demonstrated that the β-cell exocytotic response consists of a short-lived first phase with a very rapid rate of granule exocytosis from the readily releasable pool, followed by a sustained second phase with a slower rate of exocytosis, from a reserve pool [52]. A key role for the regulatory protein Munc18c in the β-cell secretory granule fusion complex has recently been identified in experiments where its knockdown in human β cells led to significant reductions in exocytosis of granules of both the readily releasable and reserve pools [53].

Regulation of insulin secretion

To ensure that circulating levels of insulin are appropriate for the prevailing metabolic status, β cells are equipped with mechanisms to detect changes in circulating nutrients, in hormone levels, and in the activity of the autonomic nervous system. Moreover, β cells have fail-safe mechanisms for coordinating this afferent information and responding with an appropriate secretion of insulin. The major physiological determinant of insulin secretion in humans is the circulating concentration of glucose and other nutrients, including amino acids and fatty acids. These nutrients possess the ability to initiate an insulin secretory response, so when nutrients are being absorbed from the gastrointestinal system the β cell detects the changes in circulating nutrients and releases insulin to enable the uptake and metabolism or storage of the nutrients by the target tissues. The consequent decrease in circulating nutrients is detected by the β cells, which switch off insulin secretion to prevent hypoglycemia. The responses of β cells to nutrient initiators of insulin secretion can be modified by a variety of hormones and neurotransmitters which act to amplify, or occasionally inhibit, the nutrient-induced responses (Table 6.1). Under normoglycemic conditions, these agents have little or no effect on insulin secretion, a mechanism that prevents inappropriate secretion of insulin, which would result in potentially harmful hypoglycemia. These agents are often referred to as potentiators of insulin secretion to distinguish them from nutrients that initiate the secretory response. The overall insulin output depends on the relative input from initiators and potentiators at the level of individual β cells, on the synchronization of secretory activity between β cells in individual islets, and on the coordination of secretion between the hundreds of thousands of islets in a human pancreas. This section considers the mechanisms employed by β cells to recognize and respond to nutrient initiators and non-nutrient potentiators of insulin secretion.

Table 6.1 Non-nutrient regulators of insulin secretion.

Stimulators	Inhibitors
Islet products	
Glucagon	SST-14
Adenine nucleotides	Ghrelin
Divalent cations	PYY
Neurotransmitters	
Acetylcholine	Norepinephrine
VIP	Dopamine
PACAP	NPY
GRP	Galanin
Gastrointestinal hormones	
CCK	SST-28
GIP	Ghrelin
GLP-1	
Adipokines	
Adiponectin	Leptin
	Resistin

CCK, cholecystokinin; GIP, glucose-dependent insulinotropic peptide; GLP-1, glucagon-like peptide-1; GRP, gastrin-releasing polypeptide; NPY, neuropeptide Y; PACAP, pituitary adenylate cyclase activating polypeptide; PYY: peptide tyrosine tyrosine; SST; somatostatin; VIP, vasoactive intestinal polypeptide.

Nutrient-induced insulin secretion

Nutrient metabolism

Islet β cells respond to small changes in extracellular glucose concentrations within a narrow physiological range and the

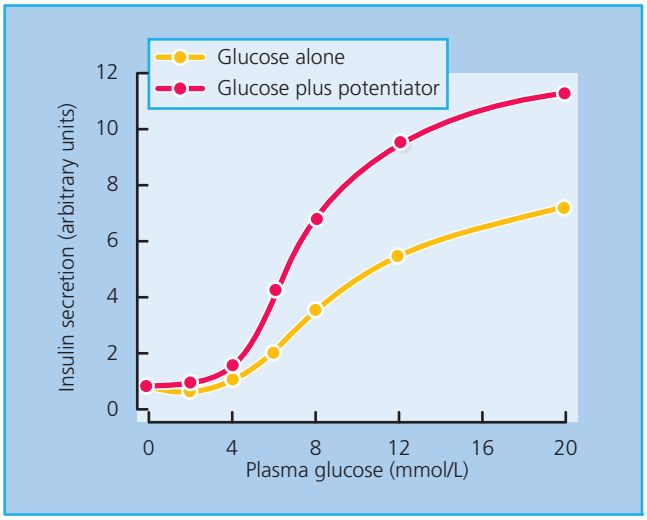

Figure 6.6 Glucose-induced insulin secretion from islets of Langerhans. No stimulation is seen below a threshold value of ~5 mmol/L glucose. Potentiators amplify insulin secretion at stimulatory concentrations of glucose, but are ineffective at subthreshold glucose levels.

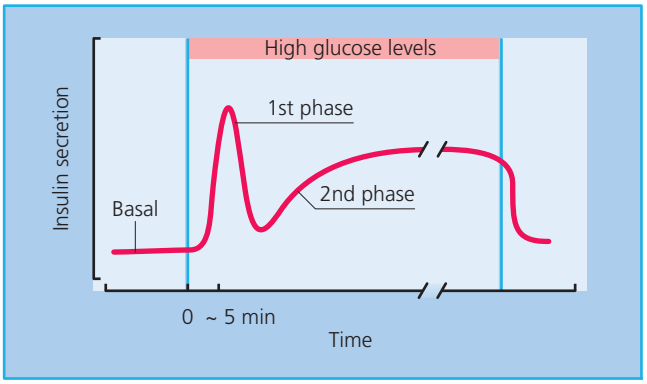

Figure 6.7 Glucose-induced insulin release *in vitro*. The image shows the pattern of glucose-induced insulin secretion from perfused pancreas, in response to an increase in the glucose concentration. An acute first phase, lasting a few minutes, is followed by a sustained second phase of secretion that persists for the duration of the high-glucose stimulus.

mechanisms through which β cells couple changes in nutrient metabolism to regulated exocytosis of insulin are becoming increasingly well understood. Glucose is transported into β cells via high-capacity glucose transporters (GLUT; GLUT-2 in rodents, GLUT-1, -2 and -3 in humans [54, 55]), enabling rapid equilibration of extracellular and intracellular glucose concentrations. Once inside the β cell, glucose is phosphorylated by glucokinase, which acts as the "glucose sensor," coupling insulin secretion to the prevailing glucose level [56]. The dose–response curve of glucose-induced insulin secretion from isolated islets is sigmoidal (Figure 6.6) and is determined primarily by the activity of glucokinase. Concentrations of glucose below 5 mmol/L do not affect rates of insulin release, and the rate of secretion increases progressively at extracellular glucose levels between 5 and ~15 mmol/L, with half-maximal stimulation at ~8 mmol/L. The time course of the insulin secretory response to elevated glucose is characterized by a rapidly rising but transient first phase, followed by a maintained and prolonged second phase, as shown in Figure 6.7. This profile of insulin secretion is obtained whether insulin levels are measured following a glucose load *in vivo*, or whether the secretory output from the perfused pancreas or isolated islets is assessed, suggesting that the characteristic biphasic secretion pattern is an intrinsic property of the islets.

ATP-sensitive potassium channels and membrane depolarization

In the absence of extracellular glucose, the β-cell membrane potential is maintained close to the potassium equilibrium potential by the efflux of potassium ions through inwardly rectifying potassium channels. These channels were called ATP-sensitive potassium (K_{ATP}) channels because application of ATP to the cytosolic surface of β-cell membrane patches resulted in rapid, reversible inhibition of resting membrane permeability to potassium ions [57]. This property of the K_{ATP} channel is pivotal in linking glucose metabolism to insulin secretion. Thus, it is now well established that ATP generation following glucose metabolism, in conjunction with concomitant lowering of ADP levels, leads to closure of β-cell K_{ATP} channels. Channel closure and the subsequent reduction in potassium efflux promote depolarization of the β-cell membrane and influx of calcium ions through voltage-dependent L-type calcium channels. The resultant increase in cytosolic Ca^{2+} triggers the exocytosis of insulin secretory granules, thus initiating the insulin secretory response (Figure 6.8).

At around the time that the K_{ATP} channels were established as the link between the metabolic and electrophysiological effects of glucose, they were also identified as the cellular target for sulfonylureas. The capacity of sulfonylureas to close K_{ATP} channels explains their effectiveness in type 2 diabetes where the β cells no longer respond adequately to glucose, as the usual pathway for coupling glucose metabolism to insulin secretion is bypassed. The β-cell K_{ATP} channel is a hetero-octamer formed from four potassium channel subunits (termed Kir6.2) and four sulfonylurea receptor subunits (SUR1) [58]. The Kir6.2 subunits form the pore through which potassium ions flow and these are surrounded by the SUR1 subunits, which have a regulatory role (Figure 6.8). ATP and sulfonylureas induce channel closure by binding to Kir6.2 and SUR1 subunits, respectively, while ADP activates the channels by binding to a nucleotide-binding domain on the SUR1 subunit. Diazoxide, an inhibitor of insulin secretion, also binds to the SUR1 subunit to open the channels. The central role of K_{ATP} channels in β-cell glucose recognition makes them obvious candidates for β-cell dysfunction in type 2 diabetes. Early studies in people with type 2 diabetes, maturity-onset diabetes of the young (MODY), or gestational diabetes, failed to detect any Kir6.2 gene mutations that compromised channel function [59, 60]. Since then, larger scale studies of variants in genes encoding Kir6.2 and SUR1 have demonstrated polymorphisms associated with increased risk

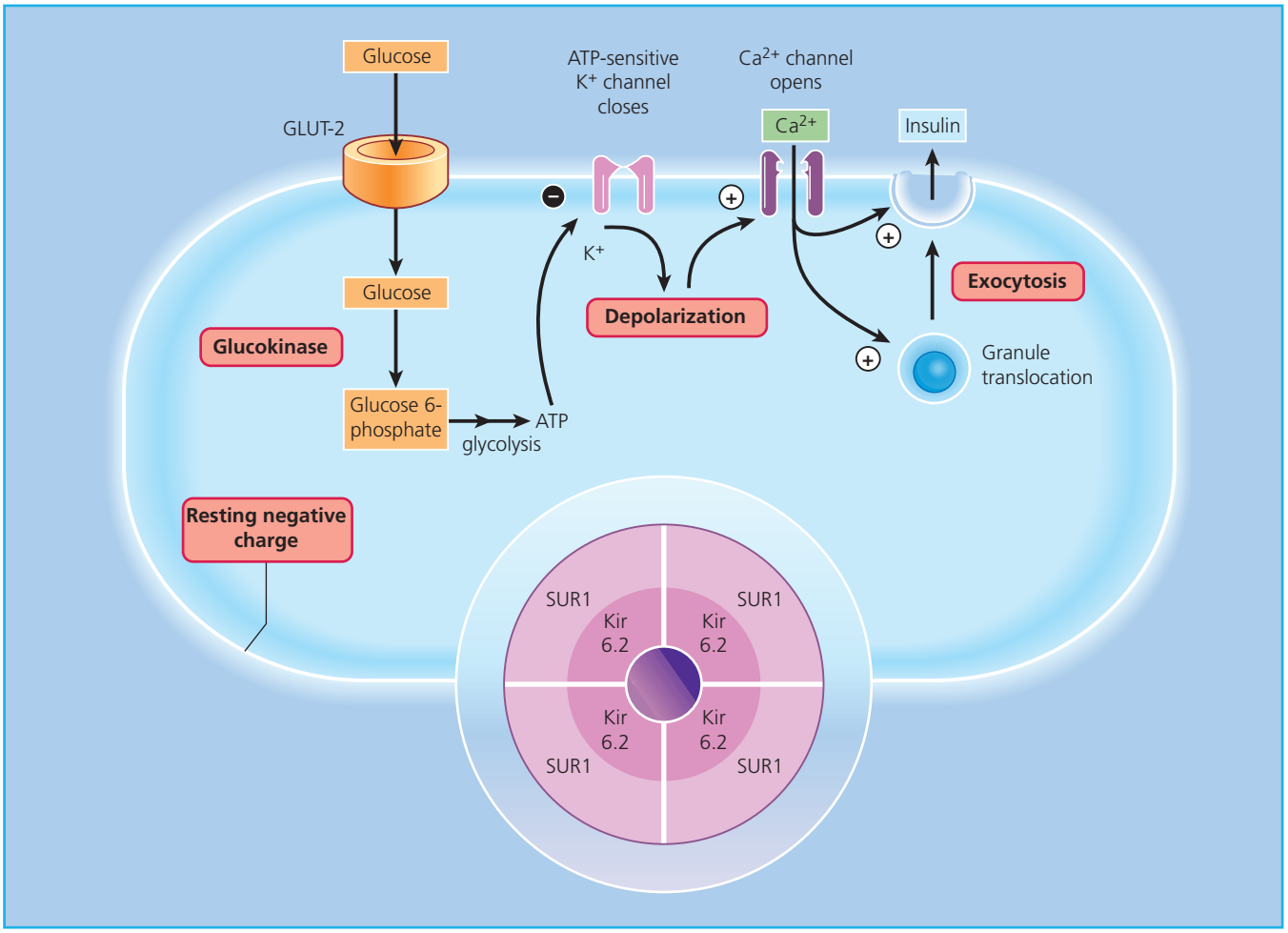

Figure 6.8 Intracellular mechanisms through which glucose stimulates insulin secretion. Glucose is metabolized within the β cell to generate ATP, which closes ATP-sensitive potassium channels in the cell membrane. This prevents potassium ions from leaving the cell, causing membrane depolarization, which in turn opens voltage-gated calcium channels in the membrane and allows calcium ions to enter the cell. The increase in cytosolic calcium initiates granule exocytosis. Sulfonylureas act downstream of glucose metabolism, by binding to the SUR1 component of the K_{ATP} channel (inset). GLUT, glucose transporter.

of type 2 diabetes [61]. Similarly, activating mutations in the Kir6.2 gene are causal for cases of permanent neonatal diabetes (PNDM) [62], which has enabled individuals with insulin-dependent PNDM to achieve glycemic control with sulfonylurea treatment alone. In contrast, loss of β-cell functional K_{ATP} channel activity has been implicated in the pathogenesis of congenital hyperinsulinism [63], a condition characterized by hypersecretion of insulin. Numerous mutations in both the Kir6.2 and SUR1 subunits have been identified in people with congenital hyperinsulinism and these are thought to be responsible for the severe impairment in glucose homeostasis in these individuals [64, 65].

Calcium and other intracellular effectors

Intracellular calcium is a principal effector of the nutrient-induced insulin secretory response, linking depolarization with exocytosis of insulin secretory granules (Figure 6.8). A large electrochemical concentration gradient (~10,000-fold) of calcium is maintained across the β-cell plasma membrane by a combination of membrane-associated calcium extruding systems and active calcium sequestration within intracellular organelles. The major route through which calcium is elevated in β cells is by influx of extracellular calcium through voltage-dependent L-type calcium channels that open in response to β-cell depolarization, and it has been estimated that each β cell contains about 500 L-type channels [66].

Studies with permeabilized β cells have demonstrated that elevations in intracellular calcium are alone sufficient to initiate insulin secretion [67], and conditions that elevate intracellular calcium usually stimulate insulin release. An increase in cytosolic calcium is essential for the initiation of insulin secretion by glucose and other nutrients: preventing calcium influx by removal of extracellular calcium or by pharmacological blockade of voltage-dependent calcium channels abolishes nutrient-induced insulin secretion. Glucose and other nutrients also induce a calcium-dependent activation of β-cell phospholipase C (PLC) [68], leading to the generation of inositol 1,4,5-triphosphate (IP_3)

and diacylglycerol (DAG), both of which serve second-messenger functions in β cells [69]. The generation of IP_3 leads to the rapid mobilization of intracellular calcium, but the significance of this in secretory responses to nutrients is uncertain, and it is likely to have little more than a modulatory role, amplifying the elevations in cytosolic calcium concentration induced by the influx of extracellular calcium.

The elevations in intracellular calcium are transduced into the regulated secretion of insulin by intracellular calcium-sensing systems within β cells. Important among these are the calcium-dependent protein kinases, which include myosin light-chain kinases, the calcium/phospholipid-dependent kinases, and the calcium/calmodulin-dependent kinases (CaMKs). CaMKs are protein kinases that are activated in the presence of calcium and the calcium-binding protein calmodulin, and a number of studies have implicated CaMK II in insulin secretory responses [69]. It has been proposed that CaMK II activation is responsible for the initiation of insulin secretion in response to glucose and other nutrients, and for enhancing nutrient-induced secretion in response to receptor agonists that elevate intracellular calcium [69]. Cytosolic PLA_2 ($cPLA_2$) is another β-cell calcium-sensitive enzyme. It is activated by concentrations of calcium that are achieved in stimulated β cells, and it generates arachidonic acid (AA) by the hydrolysis of membrane phosphatidylcholine. AA is capable of stimulating insulin secretion in a glucose- and calcium-independent manner, and it is further metabolized in islets by the cyclooxygenase (COX) pathways to produce prostaglandins and thromboxanes, and by the lipoxygenase (LOX) pathways to generate hydroperoxyeicosatetraenoic acids (HPETES), hydroxyeicosatetraenoic acids (HETES), and leukotrienes.

The precise roles of AA derivatives in islet function remain uncertain because experimental investigations have relied on COX and LOX inhibitors of poor specificity, and although prostaglandin E_2 is largely inhibitory in rodent islets [70] it has stimulatory effects on insulin secretion from human islets [71]. Calcium sensors are also important at the later stages of the secretory pathway, where the calcium-sensitive synaptotagmin proteins are involved in the formation of the exocytotic SNARE complex, as described above, to confer calcium sensitivity on the initiation and rate of exocytotic release of insulin secretory granules [49].

The elevations in intracellular calcium induced by nutrients activate other effector systems in β cells, including PLC and $cPLA_2$, as discussed above, and calcium-sensitive adenylate cyclase isoforms, which generate cAMP from ATP. Although these signaling systems are of undoubted importance in the regulation of β cells by non-nutrients, their role in nutrient-induced insulin secretion is still uncertain. Thus, DAG generated by glucose-induced PLC activation has the potential to activate some protein kinase C (PKC) isoforms. PKC was first identified as a calcium- and phospholipid-sensitive, DAG-activated protein kinase, but some isoforms of PKC require neither calcium nor DAG for activation. The isoforms are classified into three groups: calcium- and DAG-sensitive (conventional), calcium-independent, DAG-sensitive (novel), and calcium- and DAG-independent (atypical) groups, and β cells contain conventional, atypical, and novel PKC isoforms [69, 72]. The early literature on the role of PKC in nutrient-induced insulin secretion is confusing, but several studies have shown that glucose-induced insulin secretion is maintained under conditions where DAG-sensitive PKC isoforms are depleted, suggesting that conventional and novel PKC isoforms are not required for insulin secretion in response to glucose [69, 73].

The role of cAMP in the insulin secretory response to nutrients is similarly unclear. cAMP has the potential to influence insulin secretion by the activation of cAMP-dependent protein kinase A (PKA), or via the cAMP-regulated guanine nucleotide exchange factors known as exchange proteins activated by cAMP (EPACs) [74]. However, elevations in β-cell cyclic AMP do not stimulate insulin secretion at substimulatory glucose concentrations, and the secretagogue effects of glucose can be maintained in the presence of competitive antagonists of cAMP binding to PKA or EPACs [75]. These observations suggest that cAMP does not act as a primary trigger of nutrient-stimulated β-cell secretory function, but observations linking glucose-induced oscillations in β-cell cAMP to oscillations in insulin secretion [76] suggest that a role for this messenger system in nutrient-induced insulin secretion cannot be ruled out.

K_{ATP} channel-independent pathways

Since the early reports linking K_{ATP} channel closure to the exocytotic release of insulin, it has become apparent that β cells also possess a K_{ATP} channel-independent stimulus–secretion coupling pathway: this is termed the amplifying pathway to distinguish it from the triggering pathway that is activated by K_{ATP} channel closure [77]. Studies in which β-cell calcium is elevated by depolarization and K_{ATP} channels are maintained in the open state by diazoxide have indicated that glucose, at concentrations as low as 1–6 mmol/L, is still capable of stimulating insulin secretion [78]. The triggering and amplifying pathways are both physiologically relevant for the first and second phases of glucose-induced insulin secretion [79], but the mechanisms by which glucose stimulates insulin secretion in a K_{ATP} channel-independent manner have not been established [79, 80]. However, it is clear that glucose must be metabolized and there is convincing evidence that changes in adenine nucleotides are involved [81], and it has been established that activation of PKA and PKC is not required. It has been suggested that the K_{ATP}-independent amplifying pathway is impaired in type 2 diabetes and that identification of novel therapeutic strategies targeted at this pathway may be beneficial in restoring β-cell function in people with type 2 diabetes [77].

Amino acids

Several amino acids stimulate insulin secretion *in vivo* and *in vitro*. Most require glucose, but some, such as leucine, lysine, and arginine, can stimulate insulin secretion in the absence of glucose, and therefore qualify as initiators of secretion. Leucine enters islets by a sodium-independent transport system and stimulates a

biphasic increase in insulin release. The effects of leucine on β-cell membrane potential, ion fluxes, and insulin secretion are similar to, but smaller than, those of glucose [82]. Thus, metabolism of leucine within β cells decreases the potassium permeability, causing depolarization and activation of L-type calcium channels through which calcium enters the β cells and initiates insulin secretion. Leucine is also able to activate the amplifying pathway of insulin secretion in a K_{ATP} channel-independent manner, as described above for glucose. The charged amino acids lysine and arginine cross the β-cell plasma membrane via a transport system specific for cationic amino acids. It is generally believed that the accumulation of these positively charged molecules directly depolarizes the β-cell membrane, leading to calcium influx.

Regulation of insulin secretion by non-nutrients

The complex mechanisms that have evolved to enable changes in extracellular nutrients to initiate an exocytotic secretory response are confined to islet β cells, and perhaps to a subset of hypothalamic neurons [83]. However, the mechanisms that β cells use to recognize and respond to non-nutrient potentiators of secretion are ubiquitous in mammalian cells, and so are covered only briefly in this section, followed by a review of the physiologically relevant non-nutrient regulators of β-cell function.

Most, if not all, non-nutrient modulators of insulin secretion influence the β cell by binding to and activating specific receptors on the extracellular surface. Because of its central role in coordinating whole-body fuel homeostasis, the β cell expresses receptors for a wide range of biologically active peptides, glycoproteins, and neurotransmitters (Table 6.1), and quantitative reverse transcriptase polymerase chain reaction (RT-PCR) analysis has indicated that human islets express 293 different types of G-protein-coupled receptors [84]. However, receptor occupancy generally results in the activation of a limited number of intracellular effector systems, which were introduced in the section Nutrient-induced insulin secretion (Figures 6.9 and 6.10).

Islet hormones

There is convincing evidence for complex intra-islet interactions via molecules released from islet endocrine cells (Figure 6.2). The physiological relevance of some of these interactions is still uncertain, but some of the intra-islet factors that are thought to influence insulin secretion are discussed briefly in this section.

It is now clear that β cells express insulin receptors and the associated intracellular signaling elements, suggesting the existence of autocrine and/or paracrine feedback regulation of β-cell function [22, 85]. Earlier suggestions that secreted insulin regulates insulin secretion [86] have not been confirmed [22, 87], and the physiological rationale of a positive feedback loop for insulin to promote further insulin release is questionable [88]. The main autocrine function of insulin on β cells is to regulate β-cell gene expression [85, 89] and β-cell mass through effects on proliferation and apoptosis [22, 90].

Glucagon is a 29 amino acid peptide secreted by islet α cells. The precursor, proglucagon, undergoes differential post-translational processing in the gut to produce entirely different peptides with different receptors and biological activities. These include glucagon-like peptide 1 (GLP-1) (7–36) amide, an "incretin" hormone that is discussed below, and GLP-2, which promotes growth of the intestinal mucosa. Although glucagon is the major proglucagon product in islet α cells, a subpopulation of human α cells also synthesize and secrete GLP-1, presumably to exert local effects within islets [24]. Glucagon secretion is regulated by nutrients, islet and gastrointestinal hormones, and the autonomic nervous system, with hypoglycemia and sympathetic nervous input being important stimulators of glucagon secretion [91]. Glucagon enhances insulin secretion through the stimulatory G-protein (G_s)-coupled activation of adenylate cyclase and the consequent increase in intracellular cAMP (Figure 6.9).

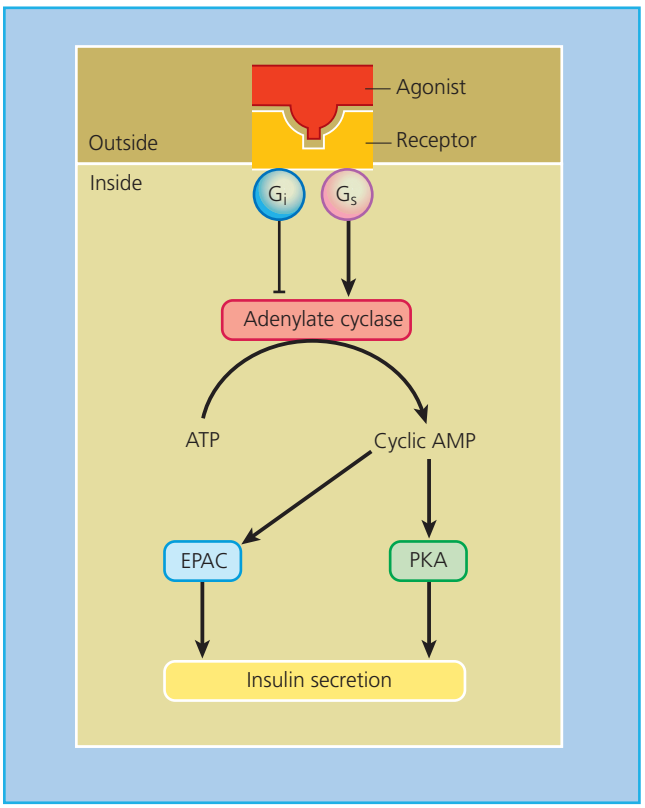

Figure 6.9 Adenylate cyclase and the regulation of insulin secretion. Some receptor agonists (e.g. glucagon, glucagon-like peptide 1, pituitary adenylate cyclase activating polypeptide) bind to cell-surface receptors that are coupled to adenylate cyclase (AC) via the heterotrimeric GTP-binding protein Gs. Adenylate cyclase hydrolyzes ATP to generate adenosine 5′ cyclic monophosphate (cAMP), which activates protein kinase A (PKA) and exchange proteins activated by cAMP (EPACs). Both of these pathways potentiate glucose-stimulated insulin secretion. Glucose also activates adenylate cyclase, but increases in intracellular cyclic AMP levels in response to glucose are generally smaller than those obtained with receptor agonists. Some inhibitory agonists (e.g. norepinephrine, somatostatin) bind to receptors that are coupled to adenylate cyclase via the inhibitory GTP-binding protein G_i, resulting in reduced adenylate cyclase activity and a decrease in intracellular cAMP.

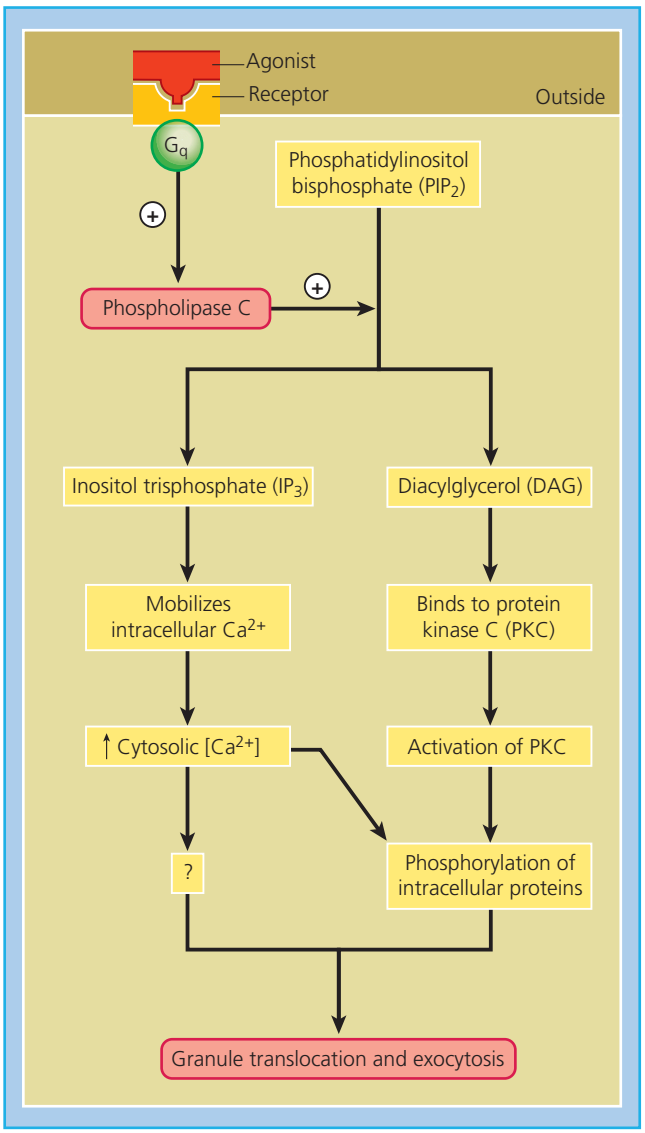

Figure 6.10 Phospholipase C and the regulation of insulin secretion. Some receptor agonists (e.g. acetylcholine, cholecystokinin) bind to cell-surface receptors that are coupled to phospholipase C (PLC) via the heterotrimeric GTP-binding protein G_q. Phospholipase C hydrolyzes phosphatidylinositol bisphosphate (PIP_2), an integral component of the membrane, to generate inositol 1,4,5-trisphosphate (IP_3) and diacylglycerol (DAG). IP_3 mobilizes calcium from the endoplasmic reticulum and DAG activates protein kinase C (PKC), both of which enhance insulin secretion. Nutrients also activate PLC in a calcium-dependent manner but the importance of IP_3 and DAG in nutrient-induced insulin secretion is uncertain.

Somatostatin (SST) is expressed by islet δ cells and in numerous other sites, including the central nervous system and D cells of the gastrointestinal tract, where it acts predominantly as an inhibitor of endocrine and exocrine secretion [92]. The precursor, prosomatostatin, is processed by alternative pathways: in islets and the CNS SST-14 is generated, and SST-28, the major circulating form of SST in humans, is produced in the gastrointestinal tract [93]. SST secretion is regulated by a variety of nutrients and endocrine and neural factors [20, 92, 94, 95]. Islets express five different somatostatin receptor (SSTR) subtypes, and SST-14 released from islet δ cells has a tonic inhibitory effect on insulin and glucagon secretion [20], via activation of SSTR5 and SSTR2, respectively [96, 97]. SST receptors are coupled via an inhibitory G-protein(Gi) to the inhibition of adenylate cyclase and decreased formation of cAMP [98] (Figure 6.9), and to ion channels that cause hyperpolarization of the β-cell membrane and reductions in intracellular calcium [99].

Pancreatic polypeptide (PP) is a 36 amino acid peptide produced by PP cells that are found in the mantle of islets, predominantly those located in the head of the pancreas. PP secretion is mainly regulated via cholinergic parasympathetic stimulation [92], but the physiological function of PP as a circulating hormone, or as an intra-islet signal, is uncertain [100]. Peptide YY, which is structurally related to PP, is also expressed in islets and is mainly expressed by subpopulations of PP and δ cells [101]. PYY inhibits insulin secretion via the NPY family of receptors, the most abundant of which is Y1 in both mouse and human islets [84, 101]. It has recently been reported that ablation of PYY-expressing cells *in vivo* causes β-cell destruction and induction of diabetes, suggesting a role for islet PYY in maintaining β-cell mass [102].

Ghrelin is a 23 amino acid peptide first identified in the gastrointestinal system, but now known also to be expressed in islet ε cells that are localized to the islet mantle in rodents, and which appear to be developmentally distinct from the classic islet endocrine cells [103, 104]. The physiological function of ε-cell-derived ghrelin has not been established, but most experimental evidence suggests an inhibitory role in the regulation of insulin secretion [105], analogous to that of δ-cell SST [20].

Neural control of insulin secretion

The association of nerve fibers with islets was shown over 100 years ago by silver staining techniques [106], and since that time it has become well established that islets are innervated by cholinergic, adrenergic, and peptidergic autonomic nerves. Parasympathetic (cholinergic) fibers originating in the dorsal motor nucleus of the vagus and sympathetic (adrenergic) fibers from the greater and middle splanchnic nerves penetrate the pancreas and terminate close to the islet cells. The autonomic innervation of the islets is important in regulating insulin secretion, with enhanced insulin output following activation of parasympathetic nerves and decreased insulin secretion in response to increased sympathetic activity. The autonomic nervous regulation of islet hormone secretion is thought to be involved in the cephalic phase of insulin secretion during feeding, in synchronizing islets to generate oscillations of hormone secretion, and in regulating islet secretory responses to metabolic stress [5].

Neurotransmitters: acetylcholine and norepinephrine

The numerous parasympathetic nerve fibers that innervate islets are postganglionic and originate from the intra-pancreatic ganglia, which are controlled by preganglionic fibers originating in the dorsal vagal nucleus [5]. Acetylcholine is the major postganglionic parasympathetic neurotransmitter, and it stimulates the

release of insulin and glucagon in a variety of mammalian species [5, 84, 107]. Acetylcholine is also synthesized in and secreted from α cells in human islets where it primes the β cells to respond optimally to increases in glucose [108]. Acetylcholine acts predominantly via M3 receptors in β cells [107, 109] to activate PLC (Figure 6.10), generating IP_3 and DAG, which act to amplify the effects of glucose by elevating cytosolic calcium and activating PKC [67]. Activation of β-cell muscarinic receptors can also lead to the activation of PLA_2, with the subsequent generation of AA and lysophosphatidylcholine, which can further enhance nutrient-induced insulin secretion. Acetylcholine also depolarizes the plasma membrane by affecting Na^+ conductivity, and this additional depolarization induces sustained increases in cytosolic calcium [107].

Islets also receive an extensive sympathetic innervation from postganglionic nerves whose cell bodies are located in the celiac or paravertebral ganglia, while the preganglionic nerves originate from the hypothalamus [5]. The major sympathetic neurotransmitter norepinephrine (noradrenaline) can exert positive and negative influences on hormone secretion. Thus, norepinephrine can exert direct stimulatory effects on the β cell via β_2-adrenoreceptors [110], or inhibitory effects via α_2-adrenoreceptors [111], and the net effect of norepinephrine may depend on the relative levels of expression of these receptor subtypes. Differences between species in the expression levels of adrenoreceptor subtypes probably account for the differential effects of β-adrenergic agonists on human islets, where they are stimulatory, and rodent islets, where they are ineffective [112]. The stimulatory effects mediated by β_2-receptors occur by activation of adenylate cyclase and an increase in intracellular cAMP (Figure 6.9), while the inhibitory effect of α_2-receptor activation involves reductions in cAMP and of cytosolic calcium [98, 111], and an unidentified inhibitory action at a more distal point in the stimulus–secretion coupling mechanism [113]. Increased expression of α_2A adrenoreceptors and decreased insulin secretion are a consequence of an SNP in the human α_2A receptor gene [114], and an α_2A receptor antagonist has been used to improve the insulin secretion deficiency in individuals with type 2 diabetes [115]. In contrast to the inhibitory effects of norepinephrine on insulin release, it has direct stimulatory effects on glucagon secretion from α cells mediated by both β_2- and α_2-receptor subtypes [5]. Circulating catecholamines secreted by the adrenal medulla (mainly epinephrine) also have the potential to influence islet hormone secretion through interactions with the adrenoreceptors expressed on the α and β cells.

Neuropeptides

Parasympathetic nerve fibers in islets contain a number of biologically active neuropeptides, including VIP, PACAP, and gastrin-releasing polypeptide (GRP), all of which are released by vagal activation and they all stimulate the release of insulin and glucagon.

VIP (28 amino acids) and PACAP (27 or 38 amino acids) are abundantly expressed neuropeptides that are widely distributed in parasympathetic nerves that supply the islets and gastrointestinal tract [6]. VIP and PACAP have similar structures, and VIP1 and VIP2 receptors also have an affinity for PACAP. The stimulatory effects of VIP and PACAP on insulin secretion *in vitro* and *in vivo* are through β-cell VIP2 and PAC1 receptors, respectively, and are thought to involve increases in intracellular cAMP (Figure 6.9) and cytosolic calcium [6, 116, 117]. GRP is a 27 amino acid peptide that also stimulates the secretion of insulin, glucagon, SST, and PP [5]. These effects of GRP are mediated through specific receptors, and involve the activation of PLC and the generation of IP_3 and DAG (Figure 6.10).

Sympathetic nerves contain different neuropeptides to parasympathetic nerves, and these include NPY and galanin, both of which have inhibitory actions within islets. NPY (36 amino acids) and galanin (29 amino acids) are expressed in fibers innervating both the endocrine and exocrine pancreas [5, 118]. Both neuropeptides inhibit basal and glucose-stimulated insulin secretion [98, 118, 119], although differences between species have been reported. Both NPY and galanin act through specific G_i-coupled receptors to inhibit adenylate cyclase [84, 120, 121], and galanin may have additional inhibitory effects at an undefined late stage of exocytosis [98].

Regulation of insulin secretion by gut- and adipose-derived factors

Incretins

It has been known for over 50 years that insulin secretion from islets is greater following oral rather than intravenous administration of glucose [122], and it is now known that this enhanced insulin secretory output is a consequence of the release of gastrointestinal-derived "incretin" hormones [123]. The main incretins that have been implicated in an elevated insulin response to absorbed nutrients after food intake are glucagon-like peptide 1 (GLP-1), glucose-dependent insulinotropic peptide (GIP) and cholecystokinin (CCK), all of which are hormones secreted by specialized endocrine cells in the gastrointestinal tract in response to the absorption of nutrients [123, 124]. These hormones are carried to the islets in the blood and they interact with specific receptors on the β-cell surface to stimulate insulin secretion.

Glucagon-like peptide 1

After food intake, L cells of the distal gastrointestinal tract secrete GLP-1 in response to elevated levels of nutrients derived from carbohydrates, lipids, and proteins in the intestinal lumen [123, 124]. GLP-1 is generated by prohormone convertase 1–3 cleavage of proglucagon in the L cells and it is highly conserved in mammals, with identical amino acid sequences in humans and mice [93, 123]. GLP-1 is degraded by dipeptidyl protease 4 (DPP-4), which cleaves two amino acids from its N-terminus. Full-length GLP-1 (1–37) does not show biological activity, but the truncated peptides GLP-1 (7–36) amide and GLP-1 (7–37) are potent stimulators of insulin secretion *in vitro* and *in vivo* [123]. Observations that infusion of the peptide into individuals with type 2 diabetes before food intake improved insulin output and reduced the

postprandial increase in circulating glucose led to studies to determine whether GLP-1 or related peptides may be useful as therapies for type 2 diabetes. Reports of other beneficial effects of GLP-1, including its capacity to inhibit glucagon secretion, delay gastric emptying, and decrease food intake, indicated its positive effects on normalizing postprandial glycemia, but its half-life of less than 2 min precludes its use as a diabetes therapy. Nonetheless, exenatide, a synthetic version of a GLP-1 analogue present in the saliva of the Gila monster lizard, has been developed for clinical use for type 2 diabetes [125]. It has ~50% amino acid homology with GLP-1, thus allowing it to exert the same effects on islets as native GLP-1, but its resistance to degradation by DPP-4 increases its half-life to around 2 h *in vivo*, which ensures effective regulation of blood glucose levels. Another GLP-1 analog, liraglutide, has a greatly extended half-life (>12 h) as a result of incorporation of the fatty acid palmitate into the GLP-1 sequence, allowing it to bind to plasma albumin and reducing its exposure to DPP-4. Selective DPP-4 inhibitors such as sitagliptin are used clinically to normalize blood glucose levels in type 2 diabetes by extending the half-life of endogenous GLP-1. GLP-1, exenatide, and liraglutide act at islet GLP-1 receptors [84, 123] that are linked, via G_s, to adenylate cyclase activation, which ultimately increases insulin secretion (Figure 6.9). Although cAMP has been implicated in the majority of effects of GLP-1 in islets, including its stimulation of insulin secretion via activation of the β-cell TCF7L2/Wnt pathway [123] and upregulation of two β-cell microRNAs [126], GLP-1 may also close β-cell K_{ATP} channels in a cAMP-independent manner, reported in studies done in rats [127]. It has been proposed that improved glucose homeostasis following bariatric gastric bypass surgery results, at least in part, from more rapid delivery of food to the L cells through a shorter gastrointestinal tract, which results in enhanced postprandial secretion of GLP-1 [128]. See chapter 32 for additional discussion of GLP-1 physiology and therapeutic usage. See chapter 32 for additional discussion of GLP-1 physiology and therapeutic usage.

Glucose-dependent insulinotropic peptide

GIP, a 42 amino acid peptide, is released from K cells in the duodenum and jejunum in response to the absorption of glucose, other actively transported sugars, amino acids, and long-chain fatty acids [124]. It was originally called "gastric inhibitory polypeptide" because of its inhibitory effects on acid secretion in the stomach, but its main physiological effect is now known to be stimulation of insulin secretion in a glucose-dependent manner [123]. GIP receptors, like those activated by GLP-1, are coupled to G_s, with essentially the same downstream cascades leading to stimulation of insulin secretion (Figure 6.9). Although GLP-1 and GIP both enhance insulin output following their release in response to food intake, it seems unlikely that GIP-related peptides will be developed as therapies for type 2 diabetes because GIP stimulates glucagon secretion and inhibits GLP-1 release, and its infusion in individuals with type 2 diabetes is reported to worsen postprandial hyperglycemia [129].

Cholecystokinin

CCK is another gastrointestinal hormone that is released from I cells in response to elevated fat and protein levels [124]. It was originally isolated from porcine intestine as a 33 amino acid peptide and the truncated CCK-8 form stimulates insulin secretion *in vitro* and *in vivo* [130]. CCK-8 acts at specific G_q-coupled receptors on β cells to activate PLC (Figure 6.10), and its potentiation of insulin secretion is completely dependent on PKC activation [131]. However, the physiological role of CCK as an incretin has not been established because high concentrations are required for its effects on insulin secretion, and it is possible that its major function is in digestion in the duodenum.

Bile acids

Bile acids act as endocrine factors to enable signaling between the gut and other tissues involved in metabolic homeostasis, including islet cells. They signal via the nuclear receptor farnesoid-X receptor (FXR) and the G-protein-coupled receptor TGR5, both of which are expressed in islets [84, 132]. TGR5 activation is reported to stimulate insulin secretion from mouse and human islets *in vitro* [133], but *in vivo* studies using transgenic mice suggest that FXR mediates most, if not all, of the effects of bile acids to enhance insulin secretion [132]. The composition and plasma concentrations of bile acids are altered by gastric bypass surgery, perhaps as a consequence of changes in the gut microbiome, and these changes have been linked to improved β-cell function and metabolic control [134].

Decretins

Starvation studies in humans and other mammals suggest the existence of gut-derived factors that are released postprandially to suppress insulin secretion and thus prevent postprandial hyperinsulinemic hypoglycemia [135], these factors being referred to as "decretins" [136, 137] or "anti-incretins" [138]. Studies in baboons first identified gut-derived SST-28 as a putative decretin by demonstrating that immunoneutralization of SST-28 caused elevations in postprandial plasma insulin concentrations [136]. In *Drosophila* the neuropeptide limostatin (Lst) acts as a decretin by suppressing the activity of insulin-producing cells and reducing the secretion of *Drosophila* insulin-like peptides [137]. The mammalian homolog of Lst is neuromedin U (NMU), a neuropeptide that is expressed in foregut enteroendocrine cells, and which acts as a decretin by suppressing glucose-induced insulin secretion from human islets through a specific β-cell receptor, NMUR1 [137]. Foregut-derived dopamine (DA) has also been proposed as a physiological decretin that is released postprandially to inhibit glucose- and GLP-1-stimulated insulin secretion [139]. Decretins such as SST, NMU, and DA may be important in the pathophysiology of type 2 diabetes because it has been suggested that the rapid resolution of metabolic dysfunction following gastric bypass surgery is due, at least in part, to a reduction in overactive decretin signaling, with resultant improvements in β-cell secretory function [138].

Adipokines

Obesity is a risk factor for diabetes, and hormones (adipokines) released from fat depots have been implicated in insulin resistance associated with obesity and type 2 diabetes [140]. Some adipokines, such as leptin, resistin, and adiponectin, are also reported to influence islet function. Thus, β cells express Ob-Rb leptin receptors, which, when activated by leptin, lead to inhibition of insulin secretion [141], and specific deletion of β-cell Ob-Rb receptors is associated with enhanced insulin secretion [142]. The inhibitory effects of leptin on glucose-stimulated insulin secretion have been attributed to activation of β-cell K_{ATP} channels [143] or of c-Jun N-terminal kinases (JNKs) [144]. Leptin may also further impair β-cell function through reductions in β-cell mass [142, 144]. Resistin, another adipocyte polypeptide, also inhibits glucose-stimulated insulin release [145] and stimulates apoptosis of rat β cells [146], suggesting that it has similar functions to leptin. However, resistin is not considered to be a true adipokine because, although it is secreted at high levels from mouse adipocytes, it is not produced by human adipocytes, and high plasma resistin levels do not correlate with reduced insulin sensitivity [147]. However, it is possible that resistin has paracrine effects on β-cell function in humans as it has been identified in human islets [148]. Unlike leptin and resistin, adiponectin has protective effects by improving insulin sensitivity, and decreased plasma adiponectin levels may contribute to the development of type 2 diabetes [149]. Human and rat β cells express AdipoR1 and AdipoR2 adiponectin receptors [150, 151], and adiponectin is reported to stimulate insulin secretion [150, 151], protect against β-cell apoptosis [152] and stimulate β-cell regeneration [153]. The signaling cascades that couple adiponectin receptors to downstream effects in β cells have not been fully defined, but adiponectin is reported to activate the kinases Erk and Akt in islets [154], and it also stimulates expression of genes that regulate lipid transport and metabolism [155].

Conclusions

Islets of Langerhans are complex micro-organs containing several different types of endocrine cells, with extensive vasculature and autonomic nerve supply. Interactions between the islet cells, the autonomic nervous system, and hormones secreted by the gastrointestinal system and adipose tissue permit the appropriate release of islet hormones to regulate metabolic fuel usage and storage.

The insulin-secreting β cells within islets respond to changes in circulating nutrients by linking changes in nutrient metabolism to β-cell depolarization and the calcium-dependent exocytotic release of stored insulin. Islet β cells can also respond to a wide range of hormones and neurotransmitters through conventional cell-surface receptors that are linked to a variety of intracellular effector systems regulating the release of insulin. The ability to detect nutrient, hormonal, and neural signals allows β cells to integrate information about the prevailing metabolic status, and to secrete insulin as required for glucose homeostasis.

This detailed understanding of islet cell biology has informed the development of new treatments for type 2 diabetes, as exemplified by the introduction of GLP-1 agonists and DPP-4 inhibitors in the past decade. Recent studies have suggested associations between type 2 diabetes and polymorphisms in genes associated with β-cell development or function, and so current understanding of normal β-cell function may assist in identifying the β-cell pathologies in type 2 diabetes.

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7 Glucagon in Islet and Metabolic Regulation

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Key points

- Glucagon is predominantly made in islet α-cells and regulates systemic glycemia primarily through actions in the liver.
- Beyond endocrine actions in glucose counter-regulation and metabolism of protein rich meals, glucagon may have roles in the paracrine regulation of islet function and energy balance.
- Excess glucagon contributes to dysglycemia in people with diabetes and has a central role in diabetic ketoacidosis.
- Compounds that stimulate and block the glucagon receptor are under investigation for the treatment of metabolic disorders.

Introduction

Glucagon is a gluco-regulatory peptide made almost exclusively in the α-cells of the pancreatic islet and has a notable history in basic research, clinical physiology, and therapeutics. Discovered initially as a contaminant in pancreatic extractions of insulin [1], the demonstration of specific actions to raise blood glucose led to a physiological model in which glucagon was attributed a central role for providing fuel under circumstances of need [2]. The fundamental aspects of glucagon signaling at the cellular level formed much of the basis for the discovery of cyclic AMP (cAMP) and G-proteins [3]. Glucagon was one of the first hormones that could be measured in the circulation and tissues of humans and experimental animals. Early work demonstrated dramatic increases in circulating levels with hypoglycemia and extreme physical exertion [2], and smaller but consistent elevations during starvation [4]. Especially important was the observation that glucagon levels were elevated in people with diabetes, dramatically so during diabetic ketoacidosis [5, 6]. These findings raised the possibility that both islet hormones, insulin and glucagon, had a role in the pathogenesis of diabetes [7], a hypothesis that was supported by human experiments using somatostatin to inhibit α-cell secretion [8]. Notably, interest in glucagon as a central factor in diabetic pathophysiology waned for several decades as the focus of metabolic research and treatment of diabetes centered on insulin resistance and defects in β-cell function. However, in recent years glucagon has regained its status as a topic of interest in diabetes investigation, and renewed attention to glucagon physiology has been bolstered by the advent of new drugs that suppress glucagon as part of their glucose-lowering activity.

This chapter reviews basic concepts in α-cell biology and glucagon physiology with an emphasis on how these processes are altered in disease states, particularly diabetes. Relatively new findings that implicate glucagon in intra-islet signaling and energy balance are discussed, and descriptions of new uses for glucagon activity in drug development are presented. The role of glucagon in hypoglycemic counter-regulation is addressed in detail elsewhere in this book (Chapter 35) and will not be considered in depth here. The pharmacology of available diabetes drugs that affect glucagon secretion, such as dipeptidyl peptidase inhibitors and GLP-1 receptor analogs, are also covered elsewhere (Chapters 31 and 32). There are several recent reviews that cover the molecular and systemic physiology of glucose in more detail than in this chapter [9–12].

α-Cell anatomy and development

The function of glucagon and other α-cell products is based in great part on the anatomy of the pancreatic islet. New research implicates the α-cell in the paracrine regulation of the endocrine pancreas, and islet structure has an important bearing on this function. Recent studies demonstrating key differences in islet architecture between rodents and humans have provided new insights into pancreatic endocrine function. These differences include heterogeneity of islet size and organization within species

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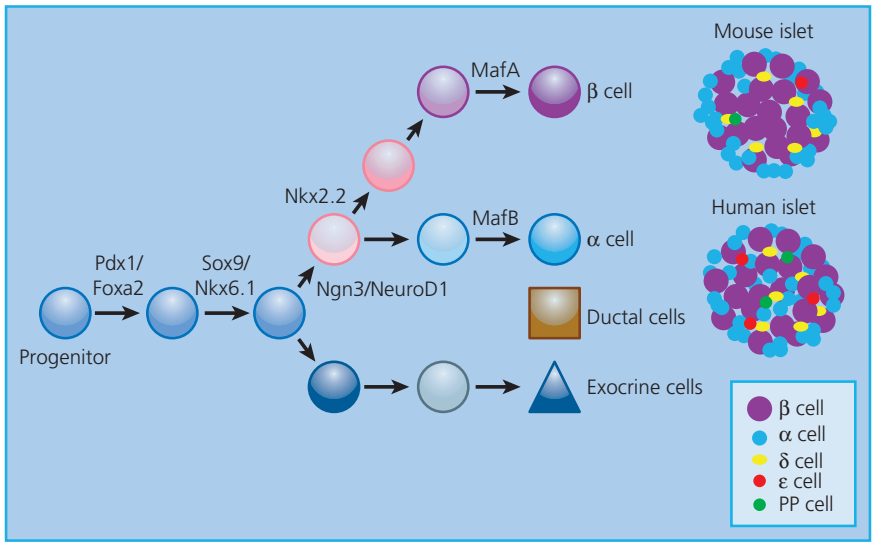

Figure 7.1 Islet development and anatomy. A simplified model of pancreatic islet–cell differentiation in the developing pancreas and the role of islet transcription factors during islet–cell development. Transcriptional factors such as neurogenin 3 (Ngn3) and pancreatic duodenal homeobox 1 (Pdx1) are critical for the endocrine cell fate determination, and aristaless-related homeobox (Arx) and forkhead box A2 (Foxa2) are important for the initial or terminal differentiation stages of α-cell differentiation, respectively. In mice and rats, the organization of the islet includes a mantle of α and δ cells on the periphery of the islet, surrounding a core of β cells. In humans, the major endocrine cell types are spread more diffusely throughout the islet and most β cells have contact with either α or δ cells.

[13, 14]. It is well established that in mice and rats the organization of the islet includes a mantle of α- and δ-cells on the periphery of the islet, surrounding a core of β cells (Figure 7.1). Estimates of the relative cell composition in rodent islets are ~75–80% β and 20–15% α cells, and most β cells have contact with other β cells [15–17]. In humans, the major endocrine cell types are spread more diffusely throughout the islet, most β cells have contact with either α or δ cells, and the proportion of β cells per islet is 40–60% [13–15] (Figure 7.1). Based on recent analyses of large numbers of human pancreata, the frequency of contacts between α and β cells appears to be much greater than previously estimated, as is the location of islet endocrine cells in close proximity to the microvasculature [13]. It is notable that in humans, smaller islets have a cellular architecture that resembles that of rodents, i.e. a mantle of α cells surrounding a β-cell core with a higher percentage of β cells than larger islets; these smaller islets also have greater relative insulin secretion [13, 14]. These recent studies on the organization of islet anatomy, particularly in humans, have shifted the focus from interactions mediated through the microcirculation to control through direct cell-to-cell contacts.

Neural regulation of islet function is well established, although the nature and magnitude of effects are still under debate. In general, sympathetic nervous system activity is thought to be important in settings where there is enhanced demand for glucose, i.e. hypoglycemia and physical activity, and parasympathetic activity is important before and during meal ingestion [18–20]. Recent data suggest a difference between the density of autonomic innervation of rodent and human α and β cells, with rats and mice having a greater density of neural fibers in islets [21]. Although this has led to the hypothesis that neural regulation of islet secretion is more important in rodents, and paracrine control in humans, this has not been formally tested, and not all studies have demonstrated reduced innervation of human islet cells [22].

α-Cells are formed within the concert of pancreatic development in early embryonic life, directed by the sequential and interacting effects of specific transcription factors. Most of the current knowledge on endocrine pancreatic development comes from studies in mice, and although there are general similarities with human islet development, some key differences exist [23–25]. In both mice and humans, pancreatic duodenal homeobox 1 (Pdx1) directs the differentiation of pancreatic epithelial cells, that will become the exocrine and endocrine pancreas, from the foregut endoderm [26]. Subsequent expression of neurogenin 3 (Ngn3) initiates the primary differentiation of endocrine precursors and their initial association into discrete cellular aggregates. The transcription factor aristaless-related homeobox (Arx) is critical for determining a definitive α-cell fate for developing endocrine progenitors, and in its absence normal α cells do not develop [27]. Both mice and humans also have a secondary transition of endocrine development where the various hormone-producing cells start to express the gene profiles that mark mature endocrine cells [26, 27]. In mice, glucagon-producing cells are the first endocrine cell type that is detected, whereas insulin-containing cells are the earliest form in humans [23]. Once the secondary transition has occurred, the formation of islets in the distinct murine and human forms progresses throughout the remainder of the prenatal period [23, 24]. The molecular physiology of islet development has assumed particular importance as efforts progress to generate β cells for potential use in therapeutics. In fact, there is evidence that mature α cells can be reprogrammed to insulin-producing cells in states of severe β-cell loss [28], and that diabetes induces dedifferentiation of β cells into α cells [29]. The plasticity of islet cells is only beginning to be understood but holds promise for understanding the mechanisms of various forms of diabetes.

Proglucagon gene transcription, translation and peptide processing

Preproglucagon (*Gcg*), the gene that encodes glucagon, is expressed in pancreatic islet α cells, but also within the hindbrain, specifically the nucleus of the solitary tract (NTS), and within the

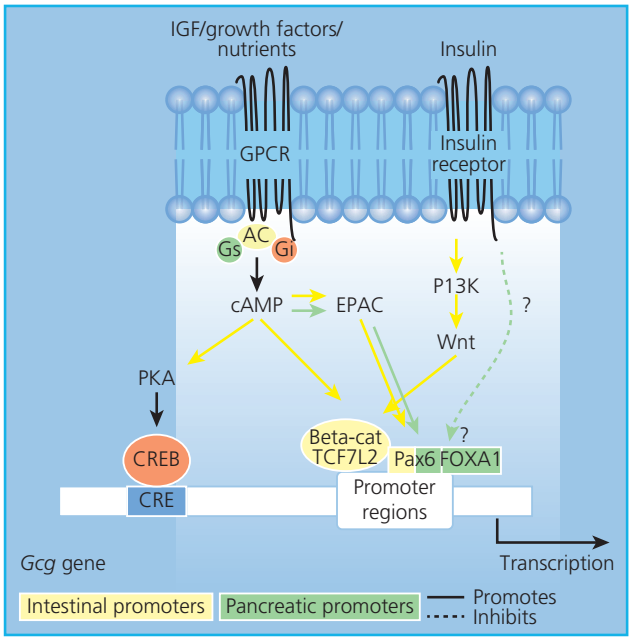

Figure 7.2 Regulation of *Gcg* gene expression. IGF (insulin-like growth factor), other growth factors, nutrients, and insulin are stimulatory factors for *Gcg* expression. IGF, growth factors, and nutrients activate a GPCR/cAMP signaling that has multiple downstream effects including activation of PKA and subsequently CREB (cAMP response element-binding protein). cAMP either directly or indirectly (via EPAC) activates other transcription factors (beta-cat/TCF7L2, Pax6/MafB, or Foxa1 depending on whether the activation occurs in the intestine or pancreas) that bind to promoter regions of the *Gcg* gene. Additionally, insulin signaling is also upstream of these transcription factors and can stimulate transcription in both the pancreas and intestine.

enteroendocrine L cell of the intestinal mucosa [30, 31]. Regulation of *Gcg* expression is complex (Figure 7.2), but involves elevations of cAMP, exposure to amino acids, and/or binding of several specific transcription factors [32–34]. Recent work also suggests that *Gcg* expression is differentially regulated in the pancreas and intestine (Figure 7.2). The most relevant example of this is related to nutritional state, with fasting increasing islet *Gcg* expression, while feeding promotes transcription in L cells [35]. As an extension of this level of regulation, insulin inhibits *Gcg* transcription in islet α cells [34, 36], but increases *Gcg* expression in intestinal endocrine cells [37, 38]. The latter effect is mediated in part by signaling related to transcription factor 7 like 2 (TCF7L2), a gene product linked to type 2 diabetes mellitus (T2DM) in genetic epidemiological studies [39], that seems to be specific for control of L-cell *Gcg* transcription [38]. It is also known that bowel resection or injury causes a large increase in intestinal *Gcg* expression [40]. Differential regulation of *Gcg* transcription in intestinal and islet endocrine cells is in keeping with their distinct patterns of prohormone processing and the predominant secretion of glucagon from the pancreas and GLP-1 and GLP-2 by the gut.

The differential synthesis and release of *Gcg* peptides from α cells compared with intestinal and neural cells expressing *Gcg* is due to tissue-specific post-translational modification by prohormone convertases (PCs). In the α cell, PC2 is the major convertase and it cleaves specific sites along proglucagon to release glucagon, but not the glucagon-related peptides [41]. In contrast, intestinal L cells have significantly more PC1/3 than PC2 activity, and process proglucagon into GLP-1, oxyntomodulin, and GLP-2 as the physiologically relevant products [42–44]. There is PC1/3 expression in α cells, albeit at lower levels than PC2, and increasing evidence for islet production of GLP-1. Although PC2 is expressed by some central nervous system (CNS) neurons, it is not co-localized with *Gcg*, and only trace amounts of glucagon have been detected in the CNS [42]. In addition to glucagon and the glucagon-like peptides, other proglucagon-derived peptides are measurable in tissue extracts and the circulation, and may have signaling properties. These include oxyntomodulin, glicentin, glicentin-related pancreatic polypeptide (GRPP), major proglucagon fragment (MPGF), and miniglucagon [12].

Regulation of α-cell secretion

Glucagon is the chief secretory product of α cells and concentrations of glucagon have been used as the principal measure of α-cell function *in vivo* and *in vitro*. There is no evidence that the other cell types that express *Gcg*, either enteroendocrine L cells or neurons in the hindbrain, contribute to plasma glucagon levels. Glucagon secreted from islets in the pancreas collects in the portal vein, where concentrations are higher than in other major vascular systems, and it is generally agreed that the liver is the primary target of glucagon signaling. Circulating glucagon is cleared by the liver and kidney, with roughly equal contributions by each organ, and 20–40% hepatic clearance of portal venous content [45–47]. Glucagon secretion is regulated by a complex interplay of nutrient, endocrine, paracrine, and neural factors (Figure 7.3). Although there is convincing evidence to support this diverse control of α-cell secretion, how this system is integrated, varies under different physiological states, and is altered by disease are still not well understood.

Similarly to β-cell secretion of insulin, α-cell release of glucagon is highly dependent on ambient glucose concentrations. Low glucose levels increase and high concentrations inhibit glucagon secretion, in part through changes in α-cell electrical activity involving K_{ATP} channels [48–50]. It remains a curiosity that α and β cells have similarities in key aspects of glucose transport, metabolism, and K_{ATP} channel activity, yet opposite secretory responses to changes in ambient glucose. Recent evidence suggests that differences in resting electrical characteristics and ion channel function downstream of K_{ATP} channel closure can explain much of the reciprocal pattern of glucagon and insulin secretion at relative hypo- and hyperglycemia [49, 51, 52] (Figure 7.3). Moreover, newer findings suggest that α cells, but not β cells, express sodium–glucose co-transporters (SGLTs)-1 and -2 [53], and that reduced flux through SGLT-2 increases glucagon secretion. It is not clear how SGLT function is integrated with other aspects of α-cell glucose metabolism, but observations that humans treated

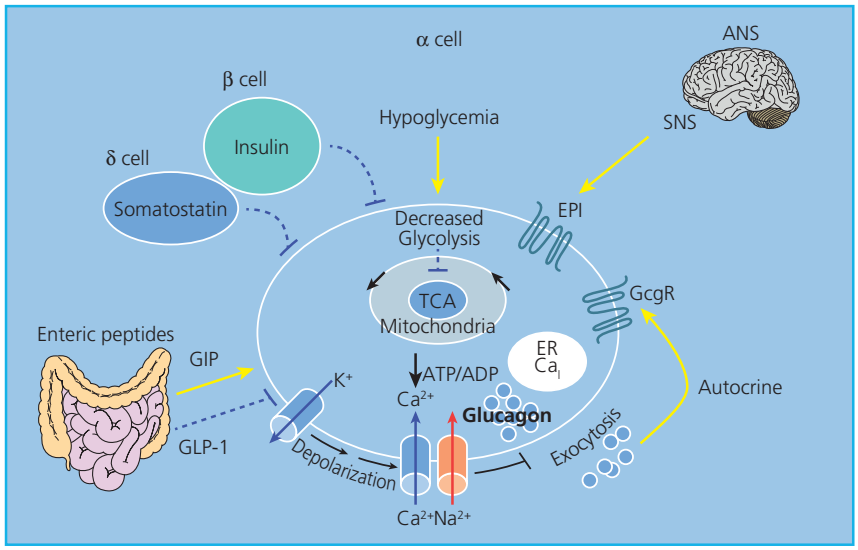

Figure 7.3 Regulation of glucagon secretion. Neural (SNS stimulates and PNS inhibits), paracrine (insulin and somatostatin inhibit), autocrine (glucagon stimulates its own secretion), endocrine (GIP stimulates and GLP-1 inhibits), and nutrient (low glucose stimulates) factors all regulate glucagon secretion. ADP, adenosine diphosphate; ANS, autonomic nervous system; ATP, adenosine triphosphate; EPI, epinephrine; SNS, sympathetic nervous system; TCA, tricarboxylic acid cycle.

with SGLT-2 inhibitors have increased plasma glucagon suggest that this is an active physiological mechanism [54, 55]. Beyond glucose, amino acids are another nutrient source that stimulates α cells. Protein meals or infusions of amino acids stimulate glucagon release, and arginine is commonly used to stimulate glucagon secretion in research studies.

Substantial differences exist between glucagon release from isolated α cells and intact islets [9, 56, 57], suggesting that other islet cells have important roles in α-cell regulation. Endocrine cells in islets are exposed to high concentrations of local products and both insulin and somatostatin are important inhibitors of glucagon release [9], acting either through the microvasculature or by local cell-to-cell contact. Insulin contributes measurably to the suppression of glucagon after meals [58] and during progressive hyperglycemia [59]. Other compounds released from β cells have been shown to inhibit glucagon release, including zinc [56], γ-aminobutyric acid [60], and glutamate [9], but the ultimate importance of these compounds is not clear. Exogenous somatostatin is a potent inhibitor of glucagon secretion [61], and a substantial body of experimental observations suggest that somatostatin secreted from islet δ cells is important in restraining α-cell secretion during exposure to circulating nutrients after meals. A final mechanism of intra-islet regulation of glucagon is autocrine, as recent work suggests that other α-cell products may regulate the α cells. Alpha cells from both primates and mice secrete glutamate and express ionotropic glutamate receptors (iGlutR) [62]. Glutamate stimulates glucagon release, and this seems to be important for the normal response to low plasma glucose since inhibition of iGlutR impairs hypoglycemic counter-regulation in mice [62].

The autonomic nervous system is critical for the regulation of glucagon secretion, particularly in the setting of hypoglycemic counter-regulation. Activation of both the parasympathetic and sympathetic limbs of the autonomic nervous system increase glucagon release [19]; adrenal epinephrine has a similar effect. Importantly, catecholaminergic signaling synergizes with low ambient glucose to stimulate glucagon release [52], and genetic disruption of autonomic neurons in the islet predisposes mice to hypoglycemia [63]. More recent studies suggest that the key regions in the CNS for sensing circulating blood glucose and initiating counter-regulation are located in the hypothalamus and hindbrain [64, 65].

Similarly to insulin, glucagon release is also affected by the actions of enteric peptides [9, 66]. Glucose-dependent insulinotropic polypeptide (GIP) stimulates glucagon release, possibly through direct actions on the GIP receptor expressed on α cells [67]. Of great importance, the other major *Gcg* peptide, GLP-1, inhibits glucagon secretion, although there is some question about the mechanism by which this occurs. GLP-1 increases the secretion of hormones from both β and δ cells, and so could act indirectly to reduce glucagon release [9, 66], and this is currently considered to be the primary means by which GLP-1 acts on the α cell. In addition, there is evidence that GLP-1 affects electrical activity and secretion of α cells even in the absence of changes in somatostatin or insulin [67].

Overall α-cell regulation is a complex, multilayered process with dense integration of control by nutrient substrates, neural, endocrine, paracrine, and autocrine inputs to secretion. Because glucagon has a key role across a range of physiological settings—fasting, exercise, hypoglycemia and following mixed nutrient meals—α cells are subject to a diversity of controlling factors. Although there appears to be some overlap in α-cell regulation, it seems likely that some of these also have specific roles. Further understanding of the regulation of glucagon secretion, and adaptation of therapeutic approaches to control this process, have great potential for the treatment of metabolic disease.

Glucagon actions: hepatic glucose and lipid metabolism

Glucagon action is mediated by the glucagon receptor (GCGR), a family class B G-protein coupled receptor that is highly conserved

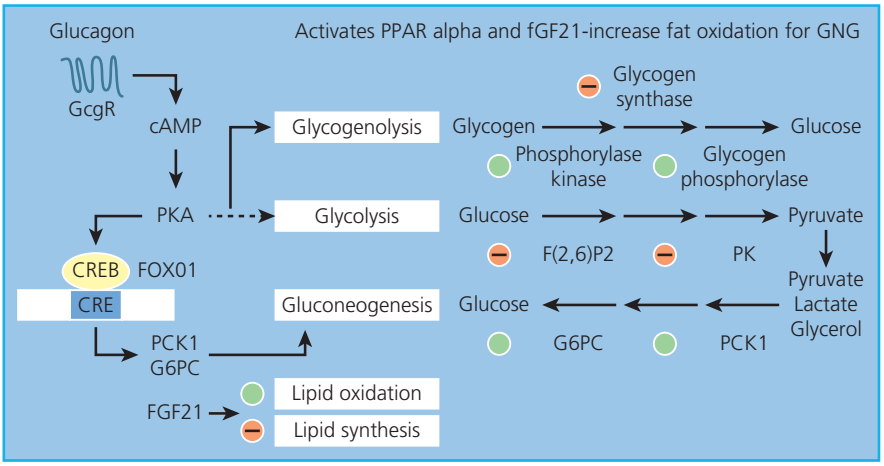

Figure 7.4 Glucagon GPCR signaling via PKA activates glycogenolysis (via inhibition of glycogen synthase; activation of phosphorylase kinase and glycogen phosphorylase) and inhibits glycolysis (via inhibition of fructose 2,6-bisphosphatase and pyruvate kinase) via regulation of major rate-limiting enzymes in these pathways. PKA also activates CREB, which increases transcription of Pck1 and G6PC, major enzymes regulating gluconeogenesis, and also FGF21, which activates several downstream genes that increase lipid oxidation and inhibit lipid synthesis.

across mammalian species [68]. Binding of glucagon to the GCGR activates adenylyl cyclase through the G_s subtype G-protein, generating cAMP and activating protein kinase A (PKA) as the major mode of intracellular signaling [69]. The richest source of glucagon binding is in the liver and kidney; lesser binding occurs in heart, adipose tissue, CNS, adrenal gland, and spleen [68]. Consistent with the relative receptor expression, the liver and kidney play the major role in glucagon clearance, accounting for ~70% of the removal from the circulation [46, 47, 68]. The half-life of glucagon in circulating plasma is relatively short, 2, 5 and 7 min in rats, dogs, and humans, respectively [68, 70].

The first known action of glucagon, to increase hepatic glucose production, was recognized nearly 100 years ago [3]. Subsequent work demonstrated effects of glucagon to counter hypoglycemia and led to the general principle that it has a role opposing that of insulin to maintain plasma glucose in times of stress, fasting, or exercise [3]. The endocrine mechanism of glucagon action is based on the effects of exogenous glucagon to increase hepatic glucose output in animals, humans, and a number of *in vitro* systems, and removal of circulating glucagon with a neutralizing antibody to reduce blood glucose [71, 72].

The cAMP/PKA signaling pathway is critical for the ability of glucagon to regulate hepatic glucose production [71, 73] (Figure 7.4). Subsequent activation of phosphorylase kinase and its downstream target glycogen phosphorylase activates glycogenolysis and inhibits glycogenesis [74, 75]. However, insulin also regulates these pathways. The result is that the balance between glycogen breakdown and synthesis results from the balance of insulin and glucagon effects on hepatocytes, the cAMP signal, and the level of glycogen stores [75]. Strategies that increase glycogen synthesis relative to glycogenolysis promote glucose tolerance [74, 76] and are potential therapeutic targets for hyperglycemia. GCGR signaling also regulates the flux between glucose-6-phosphate and fructose bisphosphate via action on fructose 2,6-bisphosphatase and consequent inhibition of pyruvate kinase activity [71] (Figure 7.4). The result of cAMP signaling is rapid inhibition of hepatic glucose metabolism and mobilization of stored glucose in order to deliver glucose to peripheral tissues.

Another critical aspect of glucagon-induced regulation of hepatic glucose production is via activation of the gluconeogenic pathway, an action mediated by PKA activation of CREB and Fox01. Glucagon upregulates phosphoenolpyruvate carboxykinase (*Pepck*) transcription (Figure 7.4), which varies with the metabolic state, increasing during fasting and decreasing in response to insulin [71]. PEPCK catalyzes a key step in gluconeogenesis by converting oxaloacetate, a product of the TCA cycle, into phosphoenolpyruvate. In animal models, gluconeogenesis is increased by overexpression of *Pepck* [77] and conversely decreased by deletion of *Pepck* [78, 79]. Other key genes involved in glucose production including peroxisome proliferator activated receptor-γ coactivator 1 (PGC-1), and glucose-6-phosphatase (G6P) are also activated by glucagon signaling. Overall, glucagon regulates several processes within the gluconeogenic pathway that enable sustained glucose production, an effect that is enhanced in the face of limited glycogen supply. Gluconeogenesis is an energy-demanding process, requiring 6 mol of high-energy phosphate bonds for each mole of glucose produced, and is tightly linked to TCA cycle activity and lipid oxidation for sources of ATP [79]. Indeed, glucagon contributes to hepatic fatty acid oxidation and ketogenesis at several metabolic steps [80, 81], and elimination of glucagon action increases the liver triglyceride content during fasting. These findings indicate that glucagon has broad effects on hepatic fuel metabolism, generating energy from lipids to support glucose production.

The lipid and glycemic effects of glucagon in the liver may also lead to pathological consequences if they are not counterbalanced by appropriate levels of insulin action. Increased glucagon during extended periods of fasting or uncontrolled T1DM stimulates fatty acid oxidation and contributes to ketogenesis [10]. The transcription factor Foxa2 has been suggested to play a central role in this process. Foxa2 controls the expression of genes involved in fatty acid oxidation and ketogenesis [82, 83] and is activated both by fasting and by glucagon. Notably, insulin has opposing effects on Foxa2 [84], presenting yet another example of coordinate and inverse regulation by insulin and glucagon

on glucose and lipid metabolism, with glucagon more active in the fasted state and insulin predominating during and after feeding.

Studies in humans using somatostatin to inhibit insulin and glucagon secretion, with selective replacement of one or both hormones, are consistent with the knowledge gained from preclinical animal studies. Glucagon is necessary to support normal fasting glucose levels [85, 86], and basal insulin replacement without glucagon results in hypoglycemia. However, regulation of hepatic glucose production by glucagon occurs in the context of hepatic insulin action [87]. At glucose levels of 4.5–5.5 mM plasma glucagon levels are relatively low and unchanging, whereas changes in glycemia within this range can affect insulin secretion. This suggests that the effect of glucagon to promote glycogenolysis and initiate gluconeogenesis during fasting occurs tonically, with the absolute level of fasting blood glucose determined by variations of hepatic insulin action. At a cellular level, this can be conceived as glucagon maintaining a threshold of cAMP, or other signaling mediators, that can be modulated by changes in hepatic insulin signaling.

Although glucagon-driven hepatic glucose productions includes both glycogenolysis and gluconeogenesis, these two processes follow different temporal patterns. As fasting progresses, the contribution of glyogenolysis to total hepatic glucose output wanes such that glycogenolysis contributes ~50% of liver glucose output in the postabsorptive state but less than 10% after 36 h of fasting [88, 89]. In acute experiments, where glucagon action can be selectively increased, glycogenolytic effects predominate [90]. This is because activation of gluconeogenesis by glucagon requires a supply of glucose precursors, primarily lactate, alanine, and glycerol. Increased delivery of these compounds to the liver is not directly regulated by glucagon, and requires a longer period of fasting to reduce plasma insulin and disinhibit lipolysis and proteolysis. With extended periods of starvation, gluconeogenesis becomes even more tightly controlled by precursor supply as preservation of protein stores becomes essential [91].

The hallmark of glucagon's function in homeostasis is to increase hepatic glucose production during hypoglycemic counter-regulation [92]. Glycogenolysis provides the most rapid source of glucose. However, the rise in catecholamines that also occurs with hypoglycemia provides a supply of glucose precursors for gluconeogenesis [93]. Hence there is an integrated, synergistic effect of catecholamines and hypoglycemia to stimulate glucagon release and glucagon action in order to return glucose levels to normal.

Glucagon also contributes to the maintenance of blood glucose during exercise, another metabolic stressor [94, 95]. Similarly to hypoglycemia, increasing catecholamines and glucagon in response to exercise, combined with the usually low circulating levels of insulin, enhance glucagon action and ensure an adequate glucose output to maintain the glucose supply to peripheral working muscles. With prolonged exercise, the impact of glucagon on promoting lipid oxidation becomes increasingly important to preserve limited glucose and provide energy [96].

Non-hepatic effects of glucagon

Although the liver is the principal target for circulating glucagon, recent work indicates that other tissues also respond to the hormone. The brain is one of these sites, and there is evidence that glucagon can affect feeding behavior. People given pharmacological doses of glucagon, or those with neuroendocrine tumors and neoplastic production of large amounts of glucagon, reduce their food intake significantly, and weight loss is a dominant feature of glucagonoma [97]. Moreover, glucagon excess contributes to negative energy balance by increasing energy expenditure [98]. Although the CNS centers that account for these effects have not been identified, it is now clear that pharmacological administration of glucagon increases resting energy expenditure and decreases food intake across multiple species [99–111].

Another recently discovered site of glucagon action is brown adipose tissue (BAT), a target organ that has been recognized as a mediator of energy expenditure. BAT is a highly metabolic tissue that generates heat when stimulated. In some studies, glucagon increases both core body temperature [112] and BAT mass and temperature [112–115], indicative of an increase in energy expenditure. BAT is highly activated during cold exposure as a way to maintain body temperature, and indeed, cold exposure increases both plasma and BAT glucagon levels [116], raising the possibility that glucagon contributes to thermogenesis. It has been suggested that the impact of glucagon on BAT is primarily a response to cold exposure as acclimatized animals have a greater response than those maintained at room temperature [112].

The GCGR is expressed by islet β cells and it has long been appreciated that supraphysiological amounts of glucagon stimulate insulin release *in vitro* and *in vivo* [117–119]. Similarly to other peptide secretagogues, glucagon amplifies glucose-stimulated insulin secretion primarily through mechanisms activated by increased cAMP, and does so in both rodent and human islets [118, 120]. In isolated human and rat islets studied in culture, antagonism of the GCGR impairs insulin secretion in response to increased media glucose, suggesting a tonic role for islet glucagon action to maintain normal stimulus–secretion coupling [71, 74, 75]. Consistent with glucagon effects to potentiate insulin secretion, dispersed β cells are more responsive to glucose when attached to an α cell [121]. Hence a body of evidence has been generated that supports islet glucagon in the potentiation of insulin secretion, most likely through paracrine and cell-to-cell interaction.

Other α-cell peptides

There is emerging evidence that glucagon is not the only important *Gcg* peptide with a role in intra-islet regulation. GLP-1 also seems to be produced by the α cell and contribute to the regulation of β-cell function. Early studies that focused on differential proglucagon processing were consistent with a general

theme in fashion at that time that α cells turned the majority of N-terminal proglucagon into glucagon, with the bulk of C-terminal prohormone left unprocessed as an inactive peptide containing both GLP-1 and GLP-2. More recent studies suggest that α-cell production of GLP-1 may also have a role in the regulation of islet function. Rodent islets studied in culture have demonstrable expression of PC1/3, and release fully processed, bioactive GLP-1 in culture [122, 123]. In cultured α-cell lines or isolated islets, high media glucose concentrations increase PC1/3 expression and cellular GLP-1 content [123–125]. Moreover, intact GLP-1 [7–36] amide is secreted from isolated rat islets [122, 125], and from isolated human islets and α cells [126]. Interruption of GLP-1 receptor (GLP-1R) signaling in isolated rodent islets or pancreata, using receptor antagonists or gene knockout techniques, reduces basal [122] and glucose-stimulated insulin secretion [127]. These findings have recently been corroborated in a mouse model with β-cell-specific deletion of the GLP-1R [128]. Finally, infusion of a GLP-1 receptor antagonist to fasting humans, with fixed, low circulating GLP-1 levels decreases glucose-stimulated insulin secretion [129, 130]. These findings can be taken as support for the action of local islet GLP-1. Overall, there has been an accumulation of evidence to support a role for local production of GLP-1 in the islet in the regulation of insulin secretion as a paracrine factor.

Beyond a role in normal islet function, α-cell GLP-1 also seems to be involved in response to stress and illness. In rats treated with the β-cell toxin streptozotocin, islet PC1/3 and ProG expression, and processing of the propeptide to GLP-1, were increased [131]. Moreover, increased GLP-1 signaling in the islet was implicated in the recovery from injury. Islet GLP-1 production and action are also mediated by the cytokine interleukin-6 (IL-6), which is released in response to exercise, obesity, and diabetes [132, 133]. Expression of the IL-6 receptor is relatively high on α cells, and IL-6 signaling increases ProG transcription and GLP-1 production in mice. There are as yet no data to support this pathway in humans, but a recent study has demonstrated elevated levels of IL-6 and GLP-1, which were significantly correlated, in humans with critical illness [134]. These data suggest that IL-6, released from adipose tissue and skeletal muscle, regulates insulin secretion in part through α-cell production of GLP-1. Overall, the findings from these and other studies suggest that a paracrine system of islet GLP-1 signaling plays a role in several adaptations to metabolic stress. Understanding the control of the relative production of α-cell GLP-1 and glucagon would seem to hold promise for therapeutic development.

More recently, the incretin GIP has been demonstrated to be produced and secreted from α cells [135]. This interesting finding builds on the coincident production of proGIP and ProG in K/L enteroendocrine cells and their coexpression has now also been demonstrated in the endocrine pancreas. In the α cell, proGIP is processed by proconvertase 2 into a truncated $GIP_{1–30}$ form that is distinct from the longer $GIP_{1–42}$ produced in the gut. However, $GIP_{1–30}$ is equipotent to full-length GIP as an insulin secretagogue. Also, like glucagon and GLP-1, $GIP_{1–30}$ appears to contribute to glucose competence since interference with its action attenuates glucose-stimulated insulin release. In keeping with this novel discovery in islets, mice with a deletion of ProG gene have increased circulating GIP levels, production and release of GIP from islets, and localization of GIP immunostaining to both α and β cells [136]. Expression of GIP in β cells seems to be ectopic as it is not seen in wild-type mice. These findings support the notion that a component of the incretin effect is mediated locally in the islet, by the classical incretins.

Abnormalities of glucagon secretion and action in diabetes

The potent effects of glucagon in promoting fasting hepatic glucose production can be amplified in the setting of diabetes, where insulin secretion is impaired and insufficient for normal opposition of glucagon effects [137–139]. The secretion of both of the principal islet hormones, insulin and glucagon, is abnormal in people with diabetes. Plasma glucagon levels tend to be substantially elevated in poorly controlled diabetes with severe insulin deficiency or ketoacidosis [10]. In T2DM, modest fasting hyperglucagonemia occurs even without metabolic decompensation, and clinical studies suggest that this increase is sufficient to contribute to the elevated hepatic glucose production in people with diabetes [139, 140]. In a classic study using somatostatin to inhibit α-cell secretion, individuals with T1DM had substantial improvements in hyperglycemia and ketogenesis when plasma glucagon was reduced [6]. Moreover, in individuals with T2DM, suppression of islet hormone secretion by somatostatin reduced basal hepatic glucose production significantly, and this effect was enhanced when insulin was given at basal levels [10]. Together, these findings exemplify the basis for concluding that glucagon action contributes to both pathogenic and physiological control of fasting glucose control.

Similarly to the diabetic β cell, the α cell in people with diabetes has abnormal sensitivity to glucose and is less suppressed during hyperglycemia. As a result, plasma glucagon levels after mixed nutrient meals are generally higher with T2DM [10, 141, 142]. In contrast, glucagon responses to hypoglycemia are also reduced [10, 143]. The mechanism for this is not clear, but the functional result suggests another form of α-cell glucose insensitivity. There is emerging evidence that α-cell dysfunction in diabetes has a genetic origin. Specifically, there is a common polymorphism in the KIR6.2 gene that predisposes people to T2DM and is related to blunted glucose-induced suppression of glucagon [144, 145].

In addition to the effects of hyperglucagonemia on fasting glucose levels, there is evidence that abnormal α-cell regulation also contributes to glucose intolerance. Following meals, glucagon levels remain abnormally elevated in persons with diabetes, rather than making the abrupt postprandial decline typical of those without diabetes [146]. In normal physiological regulation, the postprandial suppression of glucagon is a key factor in shifting hepatic metabolism from glucose production to glucose clearance [147],

and failure to make this shift disrupts normal glycemic control after meals. For example, people without diabetes have significantly greater glycemic excursions after a test meal when glucagon levels are maintained at fasting concentrations compared with when they are allowed to follow the normal postprandial decline [148]. Similar results can also be demonstrated in individuals with T2DM [149]. Thus, failure to suppress fasting levels of glucagon after a meal contributes to glucose intolerance, and this effect is magnified in the setting of diabetes where insulin secretion and action are reduced.

Pharmacology based on glucagon action

Exogenous glucagon has been used by persons with diabetes for the acute treatment of hypoglycemia for nearly 50 years. However, approaches to block glucagon action as a means of lowering blood glucose in people with diabetes goes back nearly as far. Mouse models with interruption of glucagon receptor function [150, 151] or absence of α-cell secretion [152, 153] have lower fasting glucose and significantly improved glucose tolerance than control mice and provide proof of principle that long-lasting blockade of glucagon signaling could be an effective means of reducing diabetic hyperglycemia. Despite these compelling findings, there is no approved drug that selectively blocks the effects of glucagon as a therapeutic strategy for diabetes. This is primarily due to several worrisome findings in preclinical models and safety concerns with compounds tested in humans. Animal models with genetic elimination of glucagon signaling develop α-cell hyperplasia and/or profound elevations of circulating proglucagon-related peptides [154]; this has also been reported in humans with GCGR mutations [155]. In addition to the expansion of endocrine cells, animals deficient in glucagon signaling also have increased total pancreatic weight, reflecting expansion of the exocrine compartment. Moreover, lack of glucagon action is associated with reductions in hepatic lipid oxidation [152, 156] and increased hepatic susceptibility to toxic injury [157]. Blockade of glucagon action in humans has been possible with several small-molecule GCGR antagonists. One of these compounds was demonstrated to block the actions of exogenous glucagon in persons without diabetes [158], but was not further developed and no information on the treatment of people with diabetes with fasting hyperglycemia or endogenous hyperglucagonemia was published. Other drugs have been reported to lower fasting [159] and postprandial [160] glucose in people with diabetes in a dose-responsive manner. As the pharmacological approach most analogous to genetic models of reduced GCGR signaling, antagonists have obvious potential as drugs to lower glucose and treat diabetes. However, the data from preclinical studies, and the failure of products tested in humans to progress from the trial stage, raise concerns that adverse effects such as α-cell hyperplasia, hepatic steatosis, or susceptibility to hepatic toxicity could occur in treated individuals (Figure 7.5). Moreover, the effects of these agents on glucose counter-regulation would need to be carefully assessed.

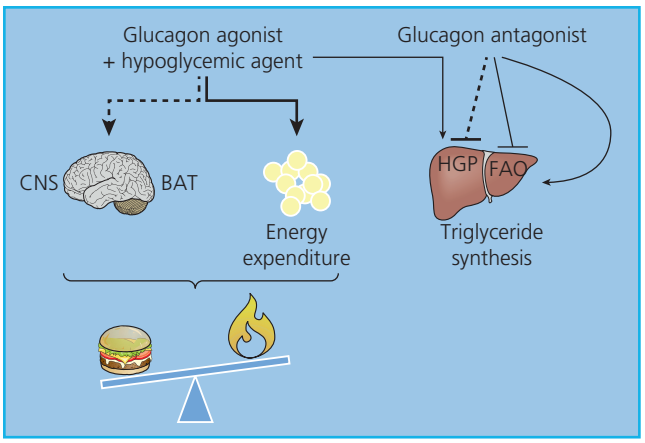

Figure 7.5 Pharmacological targeting of glucagon signaling. Approaches to block glucagon action to suppress the elevated hepatic glucose production (HGP) seen in T2DM has been explored for decades. However, the additional effect of inhibiting fatty acid oxidation (FAO) and increasing triglyceride synthesis may limit this therapeutic target. Newer hybrid peptides that favor glucagon's ability to suppress feeding and increase energy expenditure combined with hypoglycemic agents (such as GLP-1 agonists) have potent effects on weight loss in preclinical models. BAT, brown adipose tissue; CNS, central nervous system.

Importantly, drugs for diabetes are now available that work at least in part by inhibiting glucagon secretion. Glucagon-like peptide 1 (GLP-1) receptor agonists and DPP-4 inhibitors mimic the effect of endogenous GLP-1 to inhibit glucagon secretion and hepatic glucose production, and this contributes to their effect to improve glucose control in T2DM [161]. These compounds have achieved common usage in clinical practice. In fact, administration of pharmacological amounts of GLP-1 to hyperglycemic persons with T1DM with minimal β-cell function reduced blood glucose by ~4 mmol/L, and this was associated with a 40–50% decrease in plasma glucagon [162].

A novel and exciting recent approach to T2DM therapy is the development of hybrid peptides that activate more than one receptor to generate an effect [163]. Some of the first compounds developed using this strategy were targeted to the glucagon and GLP-1 receptors, for example peptides engineered to activate the cognate receptors of both peptides in different relative potencies [164, 165]. The rationale for this was that activating both glucagon and GLP-1, which bind to specific and distinct receptor populations in the brain to cause satiety [166, 167], might have synergistic results. Two different initial reports suggest that hybrid peptides with balanced GCGR and GLP-1R potency reduced body weight and fat, increased energy expenditure, and dramatically improved glucose tolerance in obese mice and rats [164, 168] (Figure 7.5). The effects on weight loss were significantly greater than those of a GLP-1R-agonist alone, and this additive response supports different activation of different neural pathways for glucagon and GLP-1 to cause weight loss. In humans, whereas GLP-1 infusion alone had no effect on energy expenditure, and glucagon infusion alone raised both blood glucose levels and energy expenditure, co-administration of both peptides increased

energy expenditure but did not raise glucose levels [169]. The potential for a GLP-1R/GCGR co-agonist to raise blood glucose has also been demonstrated with oxyntomodulin [170], a *Gcg* product that activates both receptors. Thus, the coupling of GLP-1 activity has promise to provide greater weight loss effects than either compound administered alone, with hyperglycemic actions of glucagon mitigated by GLP-1 signaling. Given the technology to engineer peptides with multireceptor effects, and the dramatic responses in preclinical models, this is likely to be an area of active diabetes drug development in the future.

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8 Mechanism of Insulin Action

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Key points

- The insulin receptor is a transmembrane protein. The α subunits of the insulin receptor are entirely extracellular and create the ligand binding sites. The β subunits contain a transmembrane-spanning segment that separates the extracellular regions from the intracellular tyrosine kinase.
- Insulin and insulin-like growth factor signaling integrates the storage and release of nutrients with animal growth during development and tissue maintenance throughout life. The human genome encodes a superfamily of structurally related insulin-like peptides—including insulin, insulin-like growth factor-1 (IGF1) and insulin-like growth factor-2 (IGF2), which activate five receptor tyrosine kinases assembled from two genes.
- Insulin resistance, the reduced responsiveness of tissues to normal insulin concentrations, is an important risk factor for the metabolic syndrome—hyperglycemia, hyperinsulinemia, dyslipidemia and hypertension—and its progression to cardiovascular disease, non-alcoholic fatty liver disease, and type 2 diabetes.
- Insulin receptor substrates (IRS) proteins are composed of tandem structurally similar pleckstrin homology (PH) and phosphotyrosine-binding (PTB) domains followed by a long, unstructured tail of tyrosine and serine phosphorylation sites that coordinate insulin and insulin-like growth factor signaling. These domains are strongly conserved in IRS from *Drosophila* (Chico), zebra fish, mouse, chimpanzee, and humans.
- During insulin and IGF1 stimulation, some tyrosine residues in the IRS tail are phosphorylated and bind to the SH2 domains of various signaling proteins, including the 85 kDa regulatory subunit (p85) of the phosphatidylinositol 3-kinase (PI3K) and the RAS GTP exchange factor Grb2•Sos.
- IRS1 expression can be regulated by transcriptional repressors, including AP2β (transcription factor AP-2-beta), or the p160 family of nuclear receptor coactivators p/CIP (p300/CBP/cointegrator-associated protein) and SRC1 (steroid receptor coactivator-1).
- IRS2 transcription is regulated by multiple factors, including CREB (cAMP response element binding protein) and its coactivator CRTC2 (CREB-regulated transcription coactivator 2), FOXO1/3, NFAT (nuclear factor of activated T cells), TFE3 (transcription factor E3), HIF2α (hypoxia-inducible factor-2α encoded by Epas1), and SREBP1 (sterol regulatory element binding protein 1).
- IRS1 and IRS2 can be polyubiquitinylated during chronic inflammatory states, nutrient excess, and hyperinsulinemia through various tissue specific mechanisms. Several pathways are known to promote the degradation of IRS1 or IRS2: (1) proinflammatory cytokine-mediated upregulation of SOCS1/3 (suppressors of cytokine signaling); (2) the cullin-RING E3 ubiquitin ligase 7 (CRL7); (3) CBLB (Cbl proto-oncogene B), a RING-type E3 ubiquitin ligase; and (4) MG53 (mitsugumin 53), a TRIM (tripartite motif-containing) family E3 ubiquitin ligase.
- IRS1 and IRS2 can be regulated through a complex mechanism involving phosphorylation of more than 50 serine/threonine residues (phospho-S/Ts) located in the long tail regions.
- Pancreatic β cells have a special place in nutrient homeostasis as the unique source of insulin secretion, and like other cells they also require insulin and insulin-like growth factor signaling for growth, function and survival. Since β cells are always exposed to insulin and IGF, insulin and insulin-like growth factor signaling appears to be regulated through multifactor transcriptional control of IRS2 through the action of FOXO1/3, NFAT, and the CREB•CRTC2.

Introduction

Insulin and insulin-like growth factor signaling integrates the storage and release of nutrients with animal growth during development and tissue maintenance throughout life. The human genome encodes a superfamily of structurally related insulin-like peptides, including insulin, insulin-like growth factor-1 (IGF1), and insulin-like growth factor-2 (IGF2), which activate five receptor tyrosine kinases assembled from two genes. Circulating glucose enters pancreatic islet β cells, where it promotes insulin gene expression and insulin secretion. By contrast, endocrine IGF1 is secreted largely from hepatocytes during growth hormone stimulation; IGF1 and IGF2 are also produced locally in tissues and cells, including the central nervous system (CNS) and many tumors [1, 2]. This chapter focuses upon mammalian insulin and insulin-like growth factor signaling mechanisms, which originate at the receptor kinases, pass through the insulin receptor

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substrates (IRS), and on to various effector systems largely through the class 1A phosphatidylinositol 3-kinase (PI3K).

The purification and genetic cloning of insulin signaling components and their analysis in cell-based assays have played a key role in the discovery of the insulin and insulin-like growth factor signaling network. Modern understanding of insulin signaling and its failure has been achieved largely with the use of genetically modified mice. Today, genetic or environmental causes are thought to underlie progressive insulin resistance that is associated with metabolic disease and type 2 diabetes. Although there are important physiological differences between humans and mice, the study of genetically modified mice continues to provide an integrative experimental model to guide the discovery of novel treatments for insulin resistance and its progression to diabetes [3].

Diabetes is a complex disorder that arises from various causes, including impaired glucose sensing or insulin secretion (MODY), autoimmune-mediated β-cell destruction (type 1 diabetes), or insufficient β-cell insulin secretory capacity to compensate for peripheral insulin resistance (type 2 diabetes) [4]. Type 2 diabetes is the most prevalent form of diabetes that usually manifests at middle age, but is becoming more common in children and adolescents in the developed world [5]. Physiological stress—the response to trauma, inflammation, or excess nutrients—activates pathways that promote chronic insulin resistance [6]. Insulin resistance, defined as the reduced responsiveness of tissues to normal insulin concentrations, is an important risk factor for the metabolic syndrome, the constellation of hyperglycemia, hyperinsulinemia, dyslipidemia, and hypertension, and its progression to cardiovascular disease, non-alcoholic fatty liver disease, and type 2 diabetes [7]. Variations in the human genome, which modulate individual responses to environmental and nutritional stress, appear to promote the metabolic disorders that progress to type 2 diabetes. GWAS (genome-wide association studies) reveals more than 60 genetic loci displaying modest or weak but significant effects upon the risk for type 2 diabetes [8–10]. In a few informative cases, mutations in downstream insulin and insulin-like growth factor signaling components such as the insulin receptor or AKT2 can explain severe forms of insulin resistance and hyperglycemia [11]. Mutations of *SH2B1* (SH2B Adaptor Protein 1), an adapter protein that interacts with insulin and other receptors, are associated with severe early-onset obesity and insulin resistance in people and mice [12]. Although numerous genetic and physiological factors interact to produce and aggravate insulin resistance, rodent and human studies implicate dysregulated signaling through the insulin receptor substrate proteins IRS1 and IRS2 as important nodes where chronic inflammation might act to disrupt the core insulin and insulin-like growth factor signaling mechanisms [13]. Regardless of the specific mechanisms, the full understanding of the integrated nature of insulin and insulin-like growth factor signaling including its systemic nuances can provide a flexible toolbox to resolve the pathophysiology of metabolic disease.

Insulin receptor

Introduction

The insulin receptor (InsR) tyrosine kinase was found through hard-won biochemical experiments using ^{32}P-labeled cells or partially purified insulin receptors incubated with insulin and [γ^{32}P]ATP [14]. The InsR cDNA was isolated and sequenced [15, 16], other mechanisms for signal transduction were proposed and many have found their place in the cascade as components of downstream effectors or feedback inhibition [17–20]. However, the discovery that rare cases of severe insulin resistance in humans are associated with InsR mutations that inactivate the tyrosine kinase without altering insulin binding supports definitively the central hypothesis of tyrosyl phosphorylation as the principal signal that drives insulin action [21].

Structure and function

The InsR is encoded by a 150-kb gene on human chromosome 19p13.3-p13.2 that contains 22 exons (Figure 8.1). Exon11 is alternatively spliced depending upon the tissue and developmental stage to produce two InsR isoforms: IRA lacks the residues encoded by exon11; IRB includes the 12 amino acid residues encoded by exon11 [22] (Figure 8.1). The homologous type 1 IGF receptor (IGF1R) is assembled without alternative splicing from its 19 exon gene located on human chromosome 15. The insulin and IGF1 receptor precursors are synthesized as a single polypeptide composed of a signal sequence followed by several well-defined extracellular modules including two leucine-rich motifs (L1 and L2) flanking a cysteine-rich (CR) region, three fibronectin-III motifs ($Fn_3$1, $Fn_3$2, and $Fn_3$3), and ending with the intracellular tyrosine kinase (Figure 8.1). $Fn_3$2 is

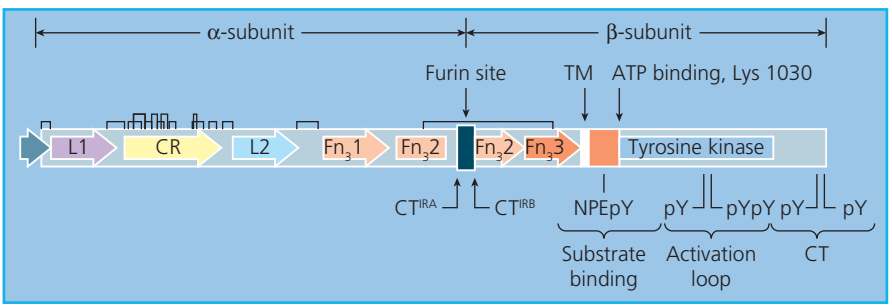

Figure 8.1 A linear diagram of the insulin receptor (IR) precursor protein showing the position of important modules in the α and β subunits including leucine-rich regions (L1 and L2), a cysteine-rich region (CR), disulfide bonds (⊔), the alternative IRA/IRB splice site that generates the short CT^{IRA} or long CT^{IRB}, a transmembrane region (TM), the furin cleavage site, the IRS binding motif (NPEpY), the kinase activation loop autophosphorylation sites, and C-terminal tyrosine phosphorylation sites (CT).

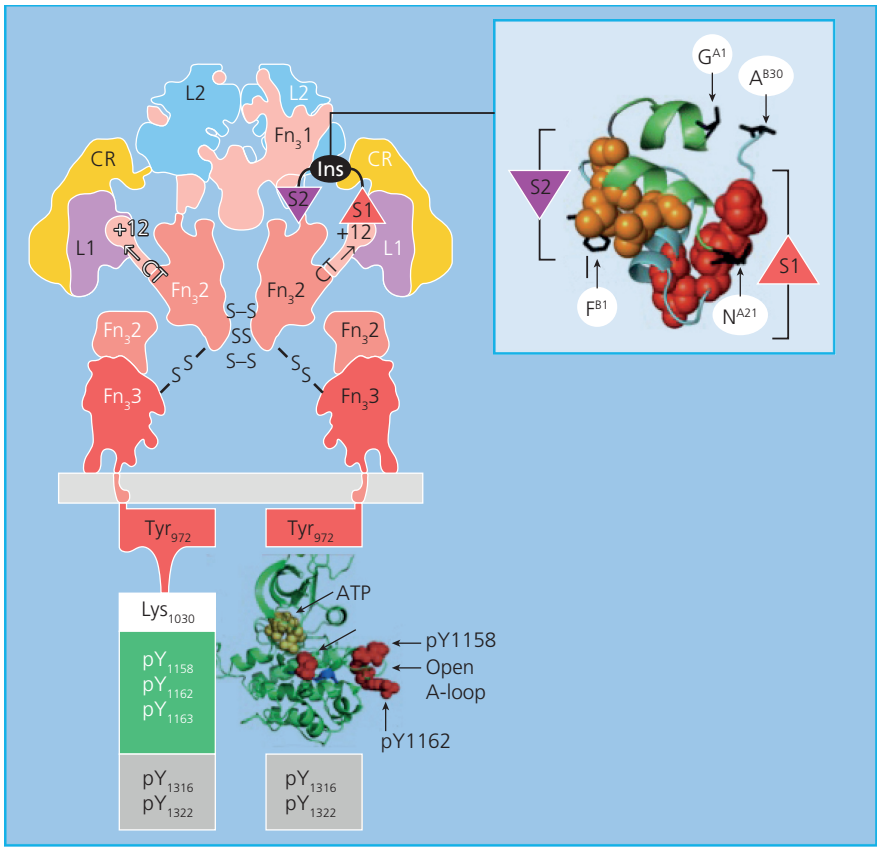

Figure 8.2 Diagram of the mature insulin receptor composed of two extracellular α-subunits and two transmembrane β-subunits. The juxtaposed α-subunit are labeled with either black or white (L1, CR, L2, $Fn_3$1, $Fn_3$2, $Fn_3$3) symbols to outline the two α-subunit. The holoreceptor is stabilized extracellularly by disulfide bonds between cysteine residues (S–S) in the α and β subunits, and also by non-covalent interactions. Two regions within the α subunit contribute to insulin binding including L1•CR (and the extra 12 amino acids encoded by exon-11 in the B form of the insulin receptor) that binds the S1 site of insulin; and the junction between $Fn_3$1 and $Fn_3$2 that binds the S2 site of insulin.
The β subunit contains the tyrosine kinase catalytic domain with an ATP binding site (Lys_{1030}) and a number of tyrosine phosphorylation sites, including those in the juxtamembrane region (pY_{972}), activation loop ($pY_{1158, 1162, 1163}$), and C-terminal regions (gray box). A structure of the catalytic domain is shown.
An inset shows the insulin structure with the position of some critical amino acids that compose the two binding surfaces (S1 and S2) that interact with the L1•CR•CT and $Fn_3$1•$Fn_3$2 regions of the insulin receptor, respectively. The A chain is shown in green and the B chain in blue, and some amino acids composing each binding site are shown as space-filling residues in red (S1) or orange (S2). The N- and C-terminal residues of each chain are labeled in black.

interrupted by a 120 amino acid insert containing a furin cleavage site that yields the α and β subunits upon cleavage. During translation, the pro-receptors for insulin and IGF1 can assemble as homodimers, which are linked by disulfide bonds to produce the InsR ($\alpha\beta^{IR}$•$\alpha\beta^{IR}$) or the IGF1R ($\alpha\beta^{IGF1R}$•$\alpha\beta^{IGF1R}$). However, when expressed together, the αβ dimer of each receptor can associate to form hybrid receptors ($\alpha\beta^{IR}$•$\alpha\beta^{IGF1R}$) [23]. Since the InsR occurs in two isoforms, a total of five receptors types can be produced from the two receptor genes.

The α subunits of the InsR or IGF1R are entirely extracellular and create the ligand binding sites. Each β subunit contains a transmembrane spanning segment that separates the extracellular $Fn_3$2–$Fn_3$3 regions from the intracellular tyrosine kinase (Figure 8.2) [15, 16]. The holoreceptor (αβ•αβ) has an approximate molecular mass of 350,000 by sodium dodecyl sulfate polyacrylamide gel electrophoresis (SDS-PAGE) and is larger than expected from the amino acid sequence owing to glycosylation of the α and β subunits [24, 25]. Upon reduction of the disulfide bonds, SDS-PAGE resolves the InsR and IGF1R into the α and β subunits that migrate near 135 and 95 kDa, respectively [26]. Hybrid receptors can be detected by specific immunoblotting strategies [23].

Insulin binds with high affinity (K_d < 0.5 nM) to the homodimeric IRB, which predominates in the classical insulin target tissues such as adult liver, muscle, and adipose. Liver and adipose are purely insulin responsive tissues as they express IRB without detectable IGF1R [1]. By comparison, IRA predominates in fetal tissues, the adult CNS, and hematopoietic cells [27]. Most cancers express IRA, IRB, and IGF1R, and the hybrid receptors [2]. IRA binds IGF2 with moderate affinity to promote embryogenesis and fetal development. IGF1 and IGF2 bind with high affinity (K_d < 1 nM) to the homodimeric IGF1R and to the hybrid receptors ($\alpha\beta^{IRA}$•$\alpha\beta^{IGF1R}$ and $\alpha\beta^{IRB}$•$\alpha\beta^{IGF1R}$). Insulin binds to IRA almost as well as to IRB, but insulin binds poorly to the hybrids [23]. Hence, under ordinary conditions, insulin never activates the IGF1R tyrosine kinase, whereas IGF1 and IGF2 can activate the InsR tyrosine kinase when it forms a hybrid with the IGF1R [28].

The insulin binding site

Insulin possesses two asymmetric receptor binding surfaces designated "S1" (the classical site) and "S2" (the novel site) (Figure 8.2) [22]. Natural insulin mutants together with alanine scanning mutagenesis show that "S1" is composed of residues from the A and B chains—including Gly^{A1}, Ile^{A2}, Val^{A3}, Glu^{A5}, Thr^{A8}, Tyr^{A19}, Asn^{A21}, Val^{B12}, Tyr^{B16}, Gly^{B23}, Phe^{B24}, and Phe^{B25} (Figure 8.2) [29]. By comparison, "S2" is composed of Ser^{A12}, Leu^{A13}, Glu^{A17}, His^{B10}, Glu^{B13}, and Leu^{B17}. Together, both sites are necessary to generate high-affinity insulin binding that activates the receptor tyrosine kinase.

Site-directed mutagenesis reveals the location of two insulin binding sites in the α subunit of the InsR [30]. Chimeric receptors between the α subunits of the insulin and IGF1 receptors reveal a

site in the first leucine-rich (L1) region of the InsR that creates a binding site together with the CR and C-terminal (CT) domains (L1•CR•CT site) [31]. Photoaffinity labeling of mutant insulin receptors reveals the other binding site near the $Fn_3 1 \rightarrow Fn_3 2$ interface [32]. Insulin binding apparently begins when "S2" on insulin binds at the $Fn_3 1 \bullet Fn_3 2$ interface followed by interaction of "S1" with the L1•CR•CT site (Figure 8.2) [33]. Although the α subunits are arranged symmetrically in the dimer, there is a sharp bend between the L2 and $Fn_3 1 \rightarrow Fn_3 2$ regions that juxtaposes the L1→CR→CT domain anti-parallel to $Fn_3 1 \rightarrow Fn_3 2$ (Figure 8.2) [34, 35]. When insulin binds to the L1→CR→CT site of one α subunit and to the $Fn_3 1 \rightarrow Fn_3 2$ region of the adjacent α subunit, a new "transient" cross-link activates the kinase [35]. Owing to space constraints, only one insulin molecule can bind with high affinity. Inclusion of exon-11 in IRB lengthens the C-terminus by 12 amino acids, which modifies the L1•CR•CT domain to exclude IGF1 and IGF2 while retaining insulin binding (Figure 8.2). These details have been investigated recently [36, 37].

Regulation of the InsR kinase

The tyrosine kinase activity of the InsR was found originally by hard-won biochemical experiments using ^{32}P-labeled hepatoma cells or partially purified insulin receptors incubated with insulin and [γ^{32}P]ATP [26]. The intracellular portion of the InsR β subunit is composed of three distinct regions that contain tyrosyl phosphorylation sites (numbered as in IRB): Y_{972} in the juxtamembrane region between the transmembrane helix and the cytoplasmic tyrosine kinase domain; Y_{1158}, Y_{1162}, and Y_{1163} in the activation loop (A loop) of the catalytic core; and Y_{1328} and Y_{1334} in the C-terminus [38, 39] (Figures 8.1 and 8.2). Most receptor tyrosine kinases are activated by ligand-induced dimerization, which brings two intracellular catalytic domains together to mediate tyrosine phosphorylation of the A loop and the other sites that recruit cellular substrates [40]. However, the homologous InsR and IGF1R reside in the plasma membrane as inactive covalent dimers that undergo an activating transition upon insulin or IGF binding [35].

Before insulin binding, the unphosphorylated Tyr_{1162}, the second of the three A loop tyrosine residues, is positioned near the catalytic site while the amino-terminal end of the A loop (D_{1150}FG motif) folds into the ATP-binding site, elevating the Michaelis constant (K_m) for ATP [35]. Apparently, this closed A loop is in equilibrium with an alternative conformation that can allow occasional access by ATP to mediate basal autophosphorylation [41]. Infrequent oscillation from the "closed" to the "open" conformation in the basal state might be coupled to complementary changes in the α subunits, which can be stabilized by insulin binding to promote ATP entry and drive additional autophosphorylation of Tyr_{1162} and Tyr_{1158} to lock the kinase in the active conformation [38]. Although autophosphorylation of Tyr_{1163} is relatively slow, it appears to stabilize the open conformation to allow unrestricted access by Mg-ATP and protein substrates [35]. The final autophosphorylation probably occurs through the interaction between the adjacent β subunits [35, 42].

This model of kinase regulation is supported by activation of the kinase upon substitution of Asp_{1161} in the middle of the A loop with alanine, which shifts the steady-state conformation of the unphosphorylated A loop towards the open configuration [41]. Moreover, replacement of Tyr_{1162} with phenylalanine increases basal autophosphorylation, consistent with its role in stabilizing the closed conformation or blocking ATP and protein substrates at the kinase active site [43, 44]. Whether other kinases can activate the InsR by direct phosphorylation of A loop tyrosine residues independently of insulin is an open question that deserves attention. For example, a hybrid receptor created through the interaction of the hepatocyte growth factor receptor (cMET) with the InsR promotes tyrosine phosphorylation and activation of the InsR [45].

Systemic deletion of the insulin or type 1 IGF receptor

InsR and IGF1R have many overlapping functions during development and adult life. In mice, the complete deletion of the InsR or the IGF1R has serious physiological consequences that cause death shortly after birth [46]. The IGF1/2→IGF1R signaling is the principle growth regulatory pathway in fetal mice, which is not influenced by growth hormone or augmented by the InsR until after birth [47]. IGF1R-deficient mice are born 50% smaller than normal littermates, and die after a few days owing to developmental defects [48]. By contrast, mice lacking the InsR have nearly normal size at birth, except for a reduced adipose tissue mass. Regardless, InsR-deficient mice also die a few days after birth owing to severe hyperglycemia, pancreatic β-cell failure and ketoacidosis [47]. Thus the *Insr* gene is necessary for postnatal fuel homeostasis but not for prenatal growth and metabolic control [49]. Mice retaining at least 20% of the normal InsR expression throughout the body can survive with severe postnatal growth retardation and hyperglycemia that resembles human leprechaunism [46]. This growth defect might arise, at least in part, from elevated hepatic IGF binding protein 1 (FOXO mediated) that reduces IGF1 bioavailability. Thus, small mice with severely reduced insulin or IGF-1 signaling have short life spans owing to developmental and metabolic defects. However, these mice can be rescued genetically by transgenic expression of the InsR in brain, liver, and pancreatic β cells [50].

Mouse knockout experiments are uninformative on the role of InsR during human gestation. Rodents are born at a developmental stage corresponding to about 26 weeks of human gestation, so the InsR-dependent phase of mouse embryonic growth is minimal [49]. Unlike mice, humans lacking InsR display intrauterine growth retardation, failure to thrive, and hypoglycemia [49]. Occasionally, InsR-deficient human neonates survive with extreme hyperinsulinemia that might activate homologous IGF1Rs [51]. Moreover, unlike mice, some IGF2 expression persists throughout human life [49].

Tissue-specific inactivation of the insulin receptor

Owing to metabolic interactions between various tissues and the lethal consequences of whole-body InsR knockout, it is difficult to

establish the tissue-specific behavior of insulin signaling in whole-body knockout mice. The best approach is to use Cre–loxP technology to delete the InsR in single tissues or organs [46, 49]. Even tissue-specific knockouts has limitations for our understanding of diabetes as the complete absence of insulin signaling is never involved in common metabolic disease. Regardless, conditional InsR knockout mouse models are remarkably informative regarding the role of insulin receptors in the liver, muscle, and adipocytes and in all other tissues investigated, including pancreatic β cells, endothelial cells, and brain (hypothalamus) [49, 52–54].

Liver

The liver is an important site of insulin action that plays a role in systemic glucose and lipid homeostasis. LIRKO (liver-specific InsR knockout) mice display moderately elevated fasting glucose and severe postprandial hyperglycemia and glucose intolerance [55]. This metabolic disorder is related, at least in part, to diminished hepatic glucose utilization and constitutive gluconeogenesis owing to dysregulated hepatic gene expression including decreased GCK (glucokinase, hexokinase 4) and elevated PCK1 (phosphoenolpyruvate carboxykinase 1), G6PC (glucose-6-phosphatase, catalytic subunit), and PK1 (pyruvate kinase) [3, 55]. Moreover, LIRKO mice exhibit marked hyperinsulinemia owing to a combination of decreased hepatic insulin clearance and increased insulin secretion associated with β-cell mass expansion. The chronic hyperinsulinemia might promote systemic insulin resistance, which could contribute to the postprandial hyperglycemia [56]. However, it is unlikely that the mechanisms of systemic insulin resistance are similar between LIRKO and more conventional models such as leptin-deficient *ob*/*ob* (obese) mice. Unlike *ob*/*ob* mice, LIRKO mice display reduced levels of circulating free fatty acids and triglycerides [55]. On an atherogenic diet, LIRKO mice develop dyslipidemia by 12 weeks of age including decreased circulating high-density lipoprotein (HDL) cholesterol and increased non-HDL cholesterol, which progresses to atherosclerosis [57]. Unexpectedly, glucose intolerance of the LIRKO mice resolves with age, which might be associated with hepatic failure and mitochondrial dysfunction. Thus, insulin signaling is essential for normal hepatic function beyond the expected regulation of glucose metabolism.

Muscle

One of the most informative and unexpected discoveries was obtained with skeletal muscle-specific InsR knockout (MIRKO) mice [58]. Whereas muscle insulin resistance promotes some aspects of metabolic disease including mild obesity and elevated circulating free fatty acids and triglycerides, elevated glucose and hyperinsulinemia never develop [3, 58]. This result might arise partly from insulin-independent glucose influx owing to the activation of AMPK (AMP-activated protein kinase), and the redistribution of glucose to liver and adipose [49]. Residual IGF1R signaling might compensate for the deletion of the InsR in muscle as genetic inactivation of insulin and insulin-like growth factor signaling in muscle with a dominant-negative IGF1R transgene causes a systemic insulin-resistant state, including β-cell dysfunction [59].

Adipose

Insulin has important effects on adipocytes to promote adipogenesis, stimulate glucose influx and lipid synthesis, and inhibit lipolysis [60]. White adipose tissue displays several important physiological functions, including the storage of postprandial glucose as triglyceride and the secretion of signaling factors that regulate appetite and energy homeostasis (leptin, adiponectin). Genetic insulin resistance of adipose tissue caused by the deletion of the InsR (FIRKO mice) reduces fat mass by 50% while consuming the same amount of food. Although adipose insulin signaling is eliminated, FIRKO mice display increased systemic insulin sensitivity and normal glucose tolerance that persists during aging. Hence it appears that insulin signaling in adipose tissue is not needed to maintain glucose tolerance in mice [61]. FIRKO mice also have a longer lifespan, suggesting that leanness and insulin sensitivity are associated with longevity even in the absence of reduced calorie intake [62]. These beneficial effects might arise from reduced adipocyte-related inflammation.

IRS-proteins coordinate insulin and insulin-like growth factor signaling

Structure and function

IRS proteins are composed of tandem structurally similar pleckstrin homology (PH) and phosphotyrosine-binding (PTB) domains followed by a long, unstructured tail of tyrosine and serine phosphorylation sites that coordinate insulin and insulin-like growth factor signaling (Figure 8.3). These domains are strongly conserved in IRS from *Drosophila* (Chico), zebra fish, mouse, chimpanzee, and humans. During insulin and IGF1 stimulation, some tyrosine residues in the IRS tail are phosphorylated and bind to the SH2 domains of various signaling proteins, including the 85 kDa regulatory subunit (p85) of the PI3K and the RAS GTP exchange factor Grb2•Sos (Figure 8.3). The interaction between IRS1 and PI3K was the first insulin signaling cascade to be reconstituted *in vivo* and *in vitro* [63]. Two highly conserved and closely spaced YMPM motifs that bind p85 are conserved in IRS1 and IRS2 from zebra fish, mouse, chimpanzee, and humans (Figure 8.3); however, different sites are used in Chico (Y_{411}IPM and Y_{641}LEM) to bind the 60 kDa regulatory subunit (dp60) in *Drosophila* [64].

Specific insulin-stimulated tyrosine phosphorylation of IRS is accomplished through at least two mechanisms. First, IRS proteins bind through their PTB domain to the InsR juxtamembrane autophosphorylation motif at $NPEY_{972}$ (Figures 8.1 and 8.2) [65, 66]. In vivo phosphorylation of $NPEY_{972}$ is very sensitive to insulin and can be detected before that of other regions [67]. The $NPEpY_{972}$ motif fills an L-shaped cleft on the PTB domain, while the N-terminal residues of the bound peptide form an additional strand in the β sandwich [66]. Regardless, the $NPEpY_{972}$ motif

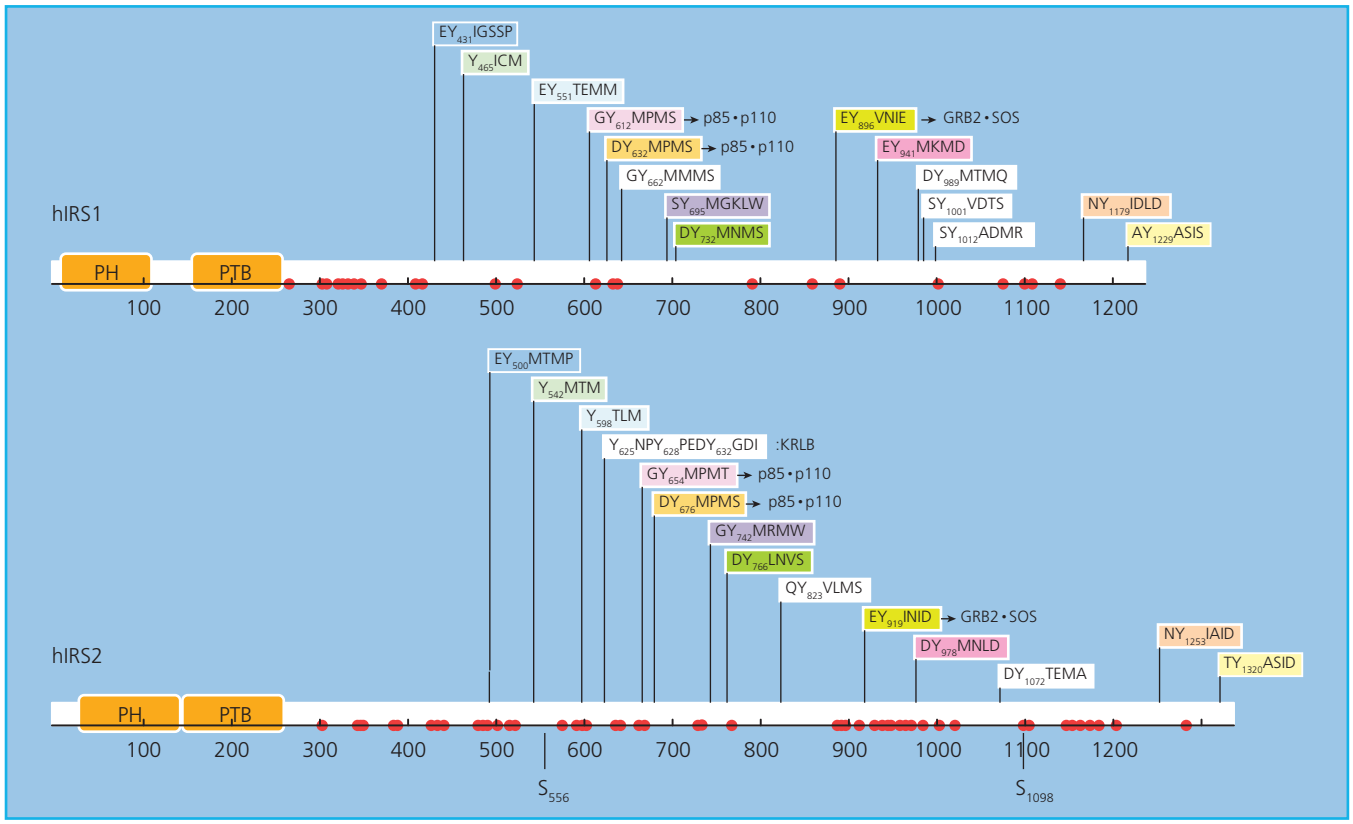

Figure 8.3 Alignments of IRS1 and IRS2 tyrosine phosphorylation sites relative to the N-terminal pleckstrin homology (PH) and phosphotyrosine-binding (PTB) domains. Conserved tyrosine phosphorylation sites—including their number in the human protein and the surrounding amino acid sequences—are color coded; white boxes indicates unique sites in IRS1 or IRS2. The relative position of serine/threonine phosphorylation sites in IRS1 or IRS2 revealed by MS/MS are indicated with red circles (•).

is a low-affinity binding site for the PTB domain of IRS1 ($K_d \approx$ 87 μM), owing to a destabilizing effect of E_{971} that is essential for its autophosphorylation by the InsR [35, 68]. By comparison, the PTB domain of another substrate SHC binds to $NPEpY_{972}$ with a much higher affinity ($K_d \approx 4$ μM). How competition between IRS and SHC might modulate insulin and insulin-like growth factor signaling is unclear.

Phosphorylation selectivity is also achieved by recognition by the catalytic domain of specific tyrosine phosphorylation motifs in the IRS tail including several YMXM motifs, and the YVNI, YIDL, and a YASI motif [69–72]. These motifs are targeted by the InsR catalytic domain as antiparallel β strands relative to the C-terminal end of the open A loop. This orientation positions the hydrophobic side-chain in the Y + 1 and Y + 3 positions into two hydrophobic pockets on the activated kinase. Tyrosine residues lying N-terminal to polar side-chains at the Y + 1 and Y + 3 positions fit poorly in this site, excluding them from phosphorylation [72]. Based upon these recognition features, there are many potential tyrosine phosphorylation motifs conserved in IRS1 and IRS2 (Figure 8.3).

IRS also contains a PH domain immediately upstream of the PTB domain, which helps recruit the IRS to the InsR (Figure 8.3) [73]. The PH domain is structurally similar but functionally distinct from the PTB domain [74]. Although the PH domain promotes the interaction between IRS and the InsR, its mechanism of action remains poorly understood as it does not bind phosphotyrosine. PH domains are generally thought to bind phospholipids, but the PH domains in the IRSs are poor examples of this binding specificity [75, 76]. However, the IRS1/IRS2 PH domain binds to negative patches in various proteins, which might also be important for InsR recruitment [77]. Regardless, the PH domain in the IRS protein plays an important and specific role as it can be interchanged among the IRS proteins without noticeable loss of bioactivity. By contrast, heterologous PH domains reduce IRS1 function when substituted for the IRS1 PH domain, confirming a specific functional role that still needs to be resolved [78].

IRS2 utilizes an additional mechanism to interact with the insulin receptor that involves a region, originally called the kinase regulatory-loop binding (KRLB) domain because trisphosphorylation of the A loop was required to observe the interaction, between amino acid residues 591 and 786 in IRS2 (Figure 8.3) [79, 80]. Structure analysis reveals the functional part of the KRLB-domain (residues 620–634 in murine IRS2) that fits into the "open" catalytic site of the InsR (Figure 8.3) [81]. With the A loop out of the catalytic site by autophosphorylation or other means, Tyr_{621} of IRS2 inserts into the receptor ATP binding pocket while Tyr_{628} aligns for phosphorylation. This interaction might attenuate signaling by blocking ATP access to the catalytic site, or it might

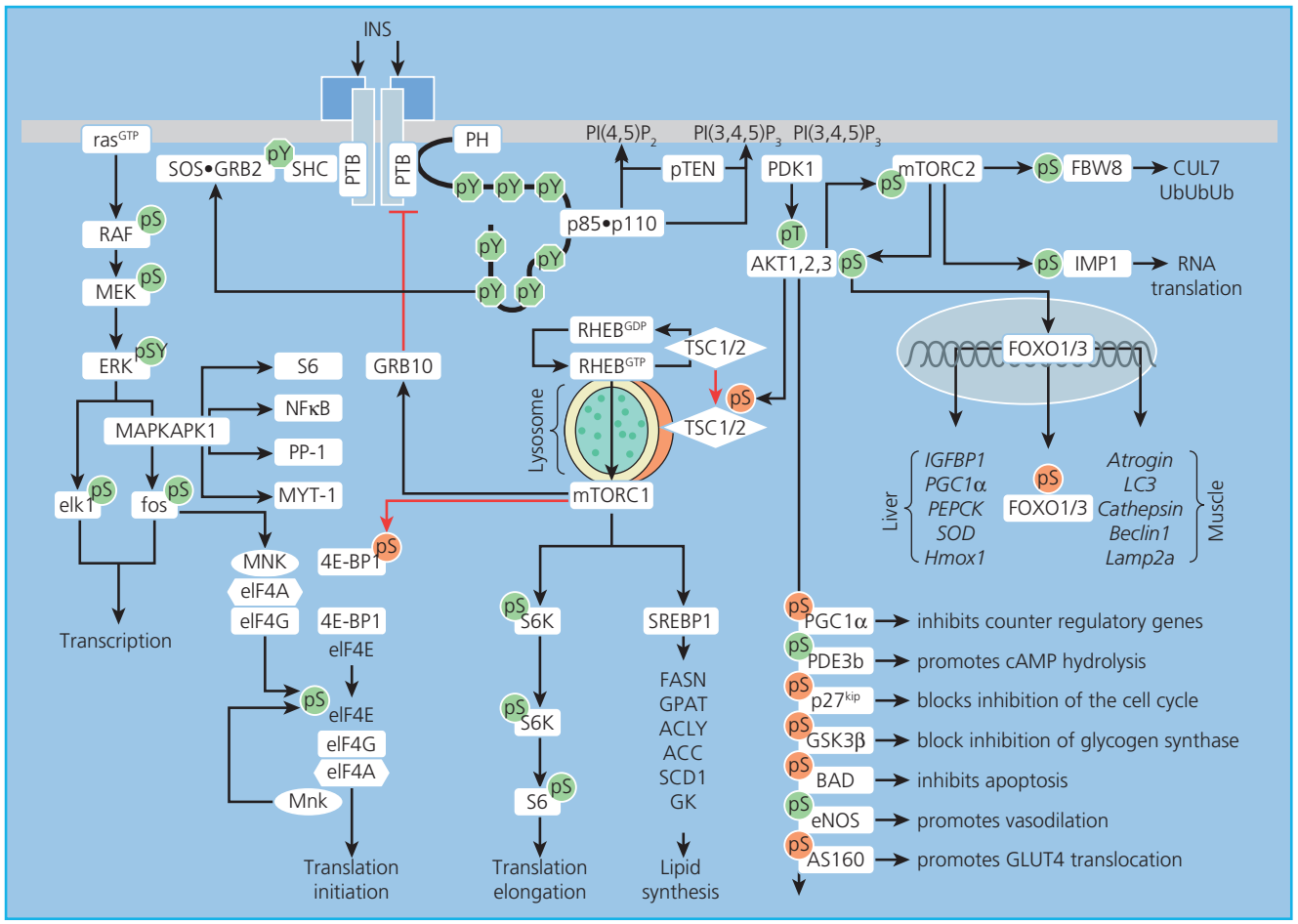

Figure 8.4 A canonical insulin/IGF signaling cascade. Two main branches propagate insulin signals generated via the IRS-proteins initiated by PI3K and GRB2•SOS. Activation of the receptors for insulin and IGF1 results in tyrosine phosphorylation of the IRS proteins, which bind PI3K and Grb2/SOS. The Grb2/SOS complex promotes GDP/GTP exchange on $p21^{ras}$, which activates the ras→raf→MEK→ERK1/2 cascade. Activated ERK stimulates transcriptional activity by direct phosphorylation of ELK1 (ETS domain-containing protein) and by indirect phosphorylation of cFOS through MAPKAPK1 (MAPK-activated protein kinase-1). MAPKAP1 also phosphorylates other proteins, including S6 (ribosomal protein S6), NFκB, PP1, and MYT1 (myelin transcription factor 1). The activation of PI3K by recruitment to IRS1 or IRS2 produces $PI3,4P_2$, and $PI(3,4,5)P_3$ (antagonized by the action of PTEN or SHIP2), which recruits PDK1 and AKT to the plasma membrane. AKT is activated upon phosphorylation at T308 by PDK1 and at S473 by mTORC2. mTORC1 is activated by $Rheb^{GTP}$, which accumulates upon inhibition of the GAP (GTPase-activating protein) activity of the TSC1•TSC2 complex following AKT-mediated phosphorylation of TSC2. The S6K is primed through mTORC1-mediated phosphorylation. AKT phosphorylates many cellular proteins, inactivating PGC1α, $p21^{kip}$, GSK3β, BAD, and AS160, and activating PDE3b and eNOS. AKT-mediated phosphorylation of forkhead proteins, including FOXO1, results in their sequestration in the cytoplasm, which inhibits their influence upon transcriptional activity. Insulin stimulates protein synthesis by altering the intrinsic activity or binding properties of key translation initiation and elongation factors (eIFs and eEFs, respectively) and also critical ribosomal proteins. Components of the translational machinery that are targets of insulin regulation include eIF2B, eIF4E, eEF1, eEF2, and the S6 ribosomal protein [215].

promote signaling by opening the catalytic site without insulin-stimulated tris-autophosphorylation. In the latter case, a basal level of insulin signaling might be sustained through IRS2 during starvation through a mechanism that depends more on the cellular concentration of IRS2 than the basal level of insulin.

Systemic inactivation of IRS genes

IRS1 and IRS2 are broadly expressed in mammalian tissues, whereas IRS4 is largely restricted to the CNS, mainly the hypothalamus [82, 83]. The IRS proteins are arguably the most important adapter molecules linking the InsR and IGF1R to downstream signaling cascades and heterologous regulatory components used by many signaling systems (Figure 8.4). Work with transgenic mice reveals that all insulin responses, especially those that are associated with somatic growth, carbohydrate, protein, and lipid metabolism, hepatic, adipose, skeletal muscle, and cardiovascular physiology, pancreatic β−cell function, and central nutrient homeostasis, are mediated through IRS1, IRS2, or both [84].

In many cell-based assays, IRS1 and IRS2 have similar roles to couple the receptors for insulin and IGF1 to the PI3K→Akt

and GRB2•SOS→RAS cascades. However, IRS1 and IRS2 can display unique signaling properties in various tissues, apparently owing to different regulation, function, or expression [85]. In this regard, the deletion of one or both alleles of IRS1 or IRS2 has been especially informative. Systemic deletion of IRS1 produces small insulin-resistant mice with nearly normal glucose homeostasis owing to β-cell expansion and life-long compensatory hyperinsulinemia [86]. These results suggest that IRS1 mediates most of the IGF1 signal for somatic growth, but is not essential for β-cell growth during insulin resistance. By contrast, mice lacking IRS2 display nearly normal body growth and even gain fat mass; however, male $IRS2^{-/-}$ mice develop life-threatening diabetes between 8 and 15 weeks of age owing to the progressive loss of β-cell mass that disrupts compensatory hyperinsulinemia [87]. Female mice progress more slowly to diabetes, developing severe hyperglycemia around 6 months of age, but the mechanism remains unknown. Whereas the complete deletion of IRS1 and IRS2 is embryonic lethal, littermates retaining one allele of IRS1 ($IRS1^{+/-}$•$IRS2^{-/-}$) or one allele of IRS2 ($IRS1^{-/-}$•$IRS2^{+/-}$) can be born alive [88]. $IRS1^{+/-}$•$IRS2^{-/-}$ mice develop severe fasting hyperglycemia and die by 4 weeks of age because IRS2 is required for pancreatic β-cell survival and growth. By contrast, $IRS1^{-/-}$•$IRS2^{+/-}$ mice reach only 30% of normal size, but display nearly normal glucose tolerance and circulating insulin concentrations at 6 months of age [88]. Regardless, the small $IRS1^{-/-}$•$IRS2^{+/-}$ mice are very fragile and require extraordinary care to live beyond this age. Hence IRS1 and IRS2 are essential for development and nutrient homeostasis.

Inactivation of IRS in liver

The central role of IRS in the PI3K→AKT signaling cascade is validated by a wide array of cell-based and mouse-based experiments (Figure 8.4). The simplest experiments employ an intraperitoneal injection of insulin into ordinary mice, or mice lacking hepatic IRS1, IRS2, or both [89, 90]. Insulin rapidly stimulates AKT phosphorylation and the phosphorylation of its downstream substrates FOXO1, GSK3α/β, and mTORC1 (mechanistic target of rapamycin complex 1) in wild-type mice (Figure 8.4). Although the deletion of the InsR alone can uncouple the PI3K→PDK1→AKT cascade from these downstream effectors, both IRS1 and IRS2 must be deleted before the InsR is uncoupled from the PI3K→PDK1→AKT cascade in hepatocytes [91]. These results reveal the shared but absolute requirement for IRS1 or IRS2 for the hepatic insulin response in mice. In general, IRS1 plays a dominant role in the liver because most nutrient sensitive transcripts, including gluconeogenic and lipogenic genes, are expressed nearly normally in liver lacking IRS2, whereas these transcripts are dysregulated significantly in liver lacking IRS1—or IRS1 and IRS2 together [92]. Even 50% less IRS1 in the absence of IRS2 is sufficient to maintain nearly normal gene expression, fasting glucose concentrations, and postprandial glucose tolerance [92]. Thus, IRS1 appears stronger than IRS2 for glucose tolerance, at least during nutrient excess. This distinction appears to be related to the stability of IRS1 expression compared with the progressive depletion of IRS2 during metabolic stress. Other aspects are also involved, including differential transcriptional regulation. Hence hepatic IRS1 is a principal mediator of the transition between fasting and postprandial glucose homeostasis, especially during chronic nutrient excess [92]. Regardless, IRS2 is important for normal metabolic regulation as its upregulation during fasting opposes the unrestrained counter-regulatory hepatic glucose production during fasting.

Inactivation of IRS in muscle

Like the liver, IRS1 and IRS2 display similar but not identical signaling functions in skeletal muscle. Insulin and insulin-like growth factor signaling in skeletal muscle is initiated by the activation of the insulin and/or IGF1 receptor tyrosine kinases [93], which can exist as hybrids linked to the downstream pathways through the IRS1 and IRS2 branches of the cascade. Based upon insulin- or IGF1-stimulated AKT→mTORC1 signaling, IRS1 has a stronger role than IRS2 for IIS in muscle. Without IRS1, AKT phosphorylation at $T308^{AKT}$ and $S473^{AKT}$ is mildly impaired, but AKT phosphorylation is nearly normal without muscle IRS2. Regardless, deletion of both IRS1 and IRS2 is necessary to eliminate insulin-stimulated phosphorylation of $T308^{AKT}$, which suggests that both IRS1 and IRS2 can promote AKT activity in muscle [94]. Consistent with these results, young mice without IRS1 display a small reduction in skeletal muscle mass and protein content, whereas no reduction is detected without IRS2 [94]. However, the deletion of both IRS1 and IRS2 strongly reduces skeletal muscle growth and causes cardiac arrest between 3 and 4 weeks of age owing to left ventricular failure. Since a single allele of either IRS1 or IRS2 in cardiac muscle can prevent sudden death, we conclude that either IRS1 or IRS2 contributes sufficient insulin-like signaling in muscle [94]. How IRS1 and IRS2 stabilize heart function during cardiovascular stress needs to be investigated.

PI3K→AKT cascade

The PI3K→AKT cascade begins when insulin stimulates tyrosyl phosphorylation of YMPM motifs in the IRS proteins (Figure 8.3), which directly recruit and activate the PI3K (Figure 8.4). PI3Ks are lipid kinases central to numerous signaling pathways, which are organized into three classes, I, II, and III [95]. The growth factor-regulated class IA PI3Ks are composed of two subunits. The catalytic subunit, p110α (PIK3CA), p110β (PIK3CB), or p110δ (PIK3CD), is inhibited and stabilized during association with one of several homologous 85 kDa regulatory subunits encoded by PIK3R1 (p85α) or PIK3R2 (p85β). Alternative splicing of PIK3R1 produces p55α or p50α, or a third gene PIK3R3 encodes p55γ, all of which lack some N-terminal regulatory features of p85 while retaining affinity towards the catalytic subunits [96–98]. All of the regulatory subunits contain two SH2 (src homology 2) domains that bind phosphorylated YMPM motifs in IRS to disinhibit the catalytic domain that produces PI(3,4,5)P3 (phosphatidylinositol 3,4,5-trisphosphate) [95, 99, 100]. Inhibition of the PI3K by

chemical or genetic means blocks almost all metabolic responses stimulated by insulin including glucose influx, glycogen and lipid synthesis, and adipocyte differentiation, confirming that the PI3K is a critical node coordinating insulin action [101].

Upon binding of p85 to phosphorylated YMPM motifs in IRS, the activated PI3K produces PI(3,4,5)P3, which binds to the PH (pleckstrin homology) domains in various signaling proteins to recruit and activate them at the plasma membrane including PDK1 (3′-phosphoinosotide-dependent protein kinase-1) and AKT (v-akt murine thymoma viral oncogene). AKT is activated by phosphorylation of Thr_{308} in its activation loop by the juxtaposed membrane-bound PDK1 (Figure 8.4). AKT isoforms have a central role in cell biology as they regulate by phosphorylation many proteins that control cell survival, growth, proliferation, angiogenesis, metabolism, and migration (Figure 8.4) [99, 102, 103]. More than 100 AKT substrates are known and several are especially relevant to insulin signaling including GSK3α/β (blocks inhibition of glycogen synthesis), AS160 (promotes GLUT-4 translocation), the BAD•BCL2 heterodimer (inhibits apoptosis), the FOXO transcription factors (regulates gene expression in liver, β cells, hypothalamus and other tissues), $p21^{CIP1}$ and $p27^{KIP1}$ (blocks cell cycle inhibition), eNOS (stimulates NO synthesis and vasodilatation), PDE3b (hydrolyzes cAMP), and TSC2 (tuberous sclerosis 2 tumor suppressor) that inhibits mTORC1 (Figure 8.4). An unbiased tandem mass spectrometry (MS/MS) approach implicates many more AKT substrates in insulin action, suggesting that the majority of PI3K-mediated growth factor (insulin) signaling is coordinated through AKT-dependent mechanisms (Figure 8.4) [104].

The mammalian genome contains three genes encoding AKT1, -2, and -3. The analysis of knockout mice shows that each isoform regulates important biological functions, including cell proliferation, cell growth and survival and differentiation, and glucose metabolism *in vivo*; however, the AKT isoforms are not redundant components of the insulin-like signaling cascade [95, 105, 106]. AKT1 has a major role in embryonic development, growth, and survival, but minor effects upon metabolism [107]. By comparison, systemic AKT2-deficient mice display metabolic defects, whereas AKT3-deficient mice display neural defects [102]. AKT2 is important for metabolic regulation largely because it mediates insulin-stimulated GLUT-4 translocation and regulates liver glucose and lipid metabolism [108, 109]. Humans with a dominant negative mutation in AKT2 display many features of type 2 diabetes including hyperglycemia, increased lipogenesis, elevated liver fat content, triglyceride-enriched very low-density lipoprotein, hypertriglyceridemia, and low HDL cholesterol levels [11, 110]. Consistent with this finding, targeted disruption of AKT2 impairs insulin-stimulated glucose uptake in murine muscle and adipocytes, and prevents the suppression of hepatic glucose output by insulin [111, 112]. Systemic AKT2 deletion causes glucose intolerance and insulin resistance that progress to diabetes and β-cell failure [107]. The related SGK3 (glucocorticoid-regulated kinase 3) synergizes with AKT2 in pancreatic β cells to stimulate proliferation and insulin release [112].

Work with IRS1/2 and AKT1/2 hepatic-specific knockout mice reveals their important role in the inactivation of FOXO1. As expected, mice without hepatic AKT1 and AKT2, or without IRS1 and IRS2, are glucose intolerant, insulin resistant, hyperinsulinemic, and defective in their transcriptional response to feeding in the liver [91, 113]. Remarkably, in both cases these defects are normalized upon concomitant liver-specific deletion of FOXO1. In the absence of both AKT1/2 and FOXO1, or without IRS1/2 and FOXO1, mice are no longer hyperinsulinemic and adapt appropriately to both the fasted and fed state even though insulin fails to promote a hepatic response [91, 113]. Gene expression analysis reveals close concordance for dysregulation of FOXO1-dependent gene expression upon deletion of AKT1/2 or IRS1/2, whereas deletion of FOXO1 restores a nearly normal metabolic response to nutrient intake. These results show that a major role of hepatic IRS→AKT signaling in the liver is to restrain the activity of FOXO1. Remarkably, in the absence of FOXO1, IRS→AKT signaling is largely dispensable for *in vivo* systemic insulin- and nutrient-mediated hepatic metabolic regulation [114]. The same result is observed upon deletion of the InsR and FOXO1 [115, 116]. It is unclear how liver metabolism can be normalized without direct insulin signaling, unless other insulin-dependent signals generated in heterologous tissues have indirect effects upon hepatic metabolism [117].

AKT→mTORC1 cascade

mTOR (mechanistic target of rapamycin) is a Ser/Thr kinase that is regulated through multiple mechanisms. It belongs to the PI3K-related kinase family and forms two large functionally distinct protein complexes, mTORC1 and mTORC2, composed of common and unique subunits. Both complexes are controlled by growth factors and insulin through the PI3K→AKT cascade, but are recruited to different compartments and respond distinctly to nutrients, stress, hypoxia/energy status, and other stimuli to coordinate a diverse array of biological processes including protein and lipid synthesis, liposome biogenesis, autophagy, and cell migration, growth, and proliferation [118]. In addition to the common catalytic subunit, mTORC1 and mTORC2 share mLST8 (mammalian lethal with sec-13 protein 8), DEPTOR (Dishevelled, Egl-10 and Pleckstrin domain containing mTOR-interacting protein), and Tti1 (telomere maintenance 2 interacting protein 1). However, mTORC1 is distinguished by two specific components, including RAPTOR (RPTOR, regulatory associated protein of mTOR, complex 1) and AKT1S1 (PRAS40, AKT1 substrate 1 proline-rich). mTORC2 lacks the mTORC1-specific components, but includes RICTOR (RAPTOR independent companion of mTOR, complex 2), SIN1 (MAPKAP1, mitogen-activated protein kinase associated protein 1), and PRR5 (protor1/2, protein observed with Rictor 1 and 2) [118]. mTORC1 is strongly regulated by nutrient concentration and inhibited by rapamycin, whereas mTORC2 is inhibited variably by rapamycin and appears to be insensitive to nutrient levels.

mTORC1 coordinates many growth factor (insulin) responses owing to its regulation by AKT, nutrient/amino acid concentrations, and subcellular/lysosomal targeting [118]. In addition to the stable complex of mTORC1 components, several additional proteins regulate mTOR activity. AKT-dependent activation begins with the phosphorylation of at least five sites (Ser_{939}, Ser_{981}, Ser_{1130}, Ser_{1132} and Thr_{1462}) on TSC2 (tuberin), which in complex with TSC1 (hamartin) functions as a GTPase-activating protein for the small G protein RHEB (Ras homolog enriched in brain) (Figure 8.4) [118]. AKT-mediated phosphorylation inhibits TCS1/2, allowing RHEB to accumulate in its GTP-bound form, which activates mTORC1 (Figure 8.4). In one possible mechanism, FKBP38 (FK506 binding protein 8) inhibits mTOR until RHEB-GTP promotes its dissociation from mTORC1 [119]. Regulation by TSC1/2→RHEB is also augmented by AKT-mediated phosphorylation of AKT1S1 [AKT1 substrate 1 (proline-rich); PRAS40], which promotes its dissociation from RAPTOR to activate mTOR [102]. Proinflammatory cytokines can activate mTORC1 through a similar mechanism where IKKβ (IκB kinase) phosphorylates TSC1/2, leading to the accumulation of RHEB-GTP [120].

The second important level of mTORC1 regulation by growth factors (insulin) depends upon its localization to the surface of lysosomes [118]. Lysosomal targeting of mTORC1 is coordinated by amino acid-dependent GTP loading of the RAGA•RAGB (Ras-related GTP binding) complex, which interacts with both RAPTOR and a multisubunit complex called RAGULATOR that is located on the lysosome surface [121]. RHEB resides on endomembranes including lysosomes where it can interact with mTORC1 only if sufficient amino acids are available to promote RAGA•RAGB-mediated recruitment (Figure 8.4) [118].

mTORC1 regulates various cellular anabolic and synthetic processes needed for growth and proliferation including the stimulation of glycolytic flux and mitochondrial function, protein and lipid synthesis, and the inhibition of autophagy and lysosomal biogenesis [122]. Protein synthesis is one of the best understood mTORC1-regulated processes that is controlled, at least in part, through the phosphorylation/activation of S6K1 and S6K2 (the ribosomal protein S6 kinases) and phosphorylation/inhibition of 4E-BP1 (eukaryotic translation initiation factor 4E binding protein 1) (Figure 8.4). The dependence upon amino acids and energy for full mTORC1 activity ensures that the cellular environment is sufficient to support growth factor (insulin) stimulation. At the whole animal level, the mTORC1→S6K cascade increases cell and animal size, including pancreatic β-cell growth that is needed for insulin action [123]. Although disruption of the *S6k1* gene in mice enhances peripheral insulin sensitivity, the reduced size of pancreatic islet β cells leads to glucose intolerance.

mTORC1 also promotes lipid synthesis required for membrane biogenesis in proliferating cells, and for energy storage and lipid secretion from the liver. mTORC1 promotes the expression of SREBP1 and its proteolytic cleavage to mediate translocation of the active transcription factors to the nucleus where they promote the expression of genes involved in hepatic fatty acid or cholesterol synthesis (Figure 8.4). mTORC1 also inhibits autophagy, which ordinarily degrades damaged proteins, lipid particles, and organelles to recycle nutrients required to maintain critical cellular functions. Thus mTORC1 controls many key cellular processes that balance cellular integrity and long-term survival.

AKT→mTORC2→AKT cascade

mTORC2 plays an important role in insulin signaling because it is a key regulator of ATK [122, 124]. Like most insulin responses, mTORC2 activation requires PI3K, but its role in insulin action has been difficult to understand owing to variable effects observed upon deletion of specific components. However, a central role for mTORC2 growth factor (insulin) signaling emerged when it was found to control several members of the AGC subfamily of kinases, including AKT and SGK1 [125]. Upon the initial step to activate AKT by PDK1-mediated phosphorylation at $T308^{AKT}$, some AKT substrates are phosphorylated, including TSC2, GSK3, and SIN1 (MAPKAP1) [118]. Judging from temporal dependence upon insulin stimulation, the SIN1 component of mTORC2 might be recruited to the plasma membrane by PI(3,4,5)P3, where it is phosphorylated at T86 by $pT308^{AKT}$ [124]. Phosphorylated SIN1 activates mTORC2, which promotes $S473^{AKT}$ phosphorylation [124]. Upon bisphosphorylation, AKT can phosphorylate a wider array of substrates, including FOXO transcription factors (Figure 8.4) [103]. This model fills a conspicuous gap in our understanding of PI3K-sensitive mTORC2 activation during insulin stimulation and its role in AKT regulation. The potential regulation of mTORC2 activity through multisite SIN1 phosphorylation reveals how mTOR signaling can be coordinated through feedforward and feedback mechanisms [122].

Much less is understood about downstream signaling mediated by mTORC2. mTORC2 plays a role in mRNA processing when it phosphorylates IMP1 (insulin-like growth factor 2 mRNA-binding protein 1) at Ser_{181}, which strongly enhances IMP1 binding to enable IGF2-leader 3′-mRNA translational initiation by internal ribosomal entry (Figure 8.4) [126]. Thus, mTORC2-catalyzed cotranslational IMP1 phosphorylation can promote organismal growth by regulating IGF2 production that can activate IRA in the mouse embryo. mTORC2 also regulates protein ubiquitinylation by phosphorylating FBW8 (F-Box And WD Repeat Domain Containing 8), a Cullin 7 E3 ubiquitin ligase recognition subunit (Figure 8.4). The phosphorylation of FBW8 stabilizes and promotes ubiquitinylation of targeted substrates, including IRS1 that contributes to insulin resistance in certain tissues and cells (Figure 8.5) [127]. Thus, important mTORC2 signaling might be mediated through its direct effect upon the activity of the PI3K→AKT cascade, and its indirect control of important regulatory points to integrate the insulin/IGF signaling cascade fully [126].

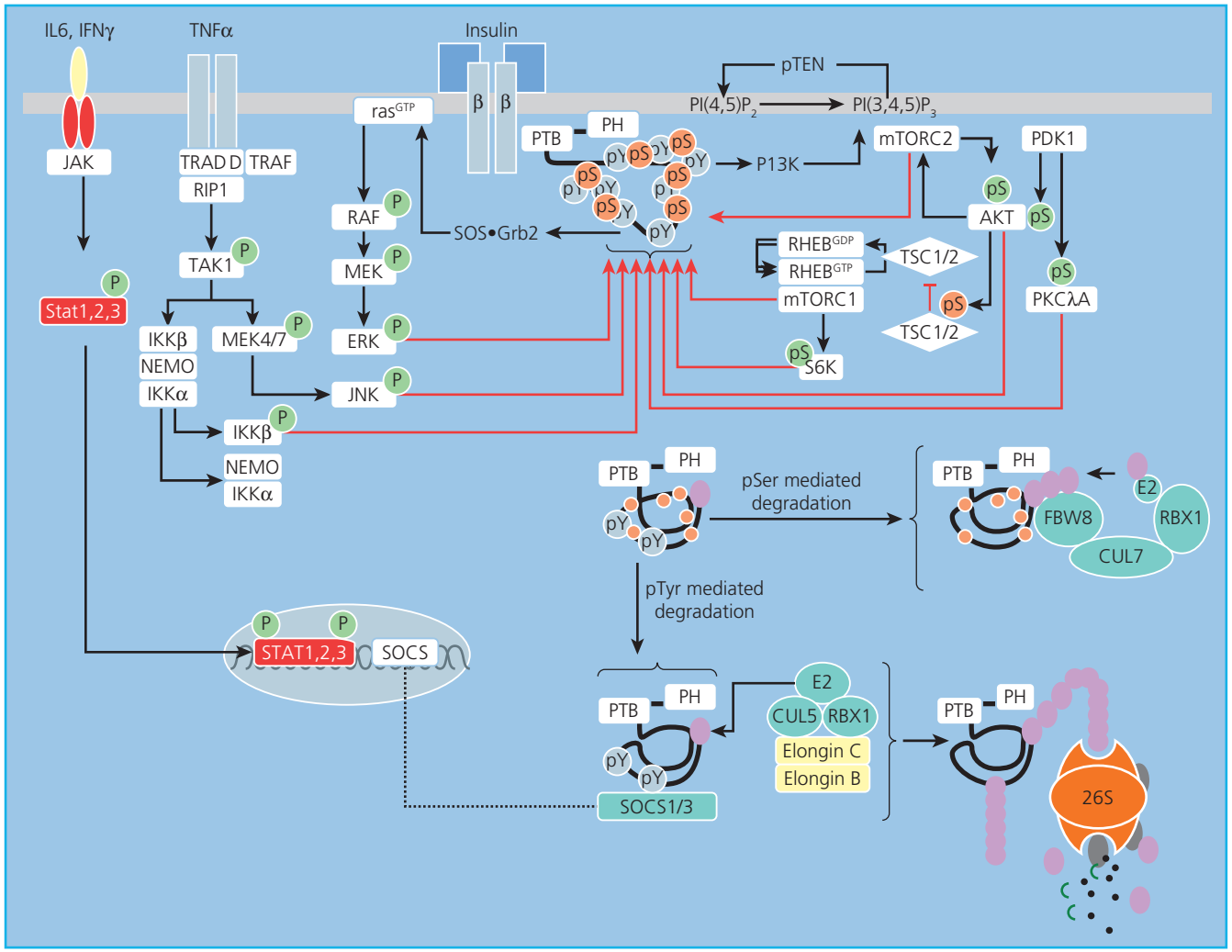

Figure 8.5 Schematic diagram of heterologous and feedback inhibition of insulin signaling mediated by Ser/Thr-phosphorylation and degradation of IRS1/IRS2. Various kinases in the insulin signaling cascade are implicated in this feedback mechanism, including PKB, mTOR, S6K, ERK, AKT, and atypical PKC isoforms. Other IRS kinases are activated by heterologous signals, including lipids, TNFα or other cytokines. Serine phosphorylation of IRS1 can recruit CRL7 ubiquitinylation (purple oval) complex to mediate degradation of IRSs through the 26S proteasome. Proinflammatory cytokines that cause insulin resistance also induce the expression of SOCS family members, which contain an N-terminal SH2 domain and a C-terminal SOCS box [216, 217]. SOCS1 or SOCS3 can target phosphotyrosine residues in IRS1 or IRS2 for ubiquitinylation and degradation, because the SOCS box associates with elongin BC-containing ubiquitin ligase E3 [218–220].

AKT→FOXO cascade

The forkhead box O (FOXO) subfamily of transcription factors, including mammalian FOXO1, FOXO3a, FOXO4, and FOXO6, regulate expression of target genes involved in DNA damage repair response, apoptosis, metabolism, cellular proliferation, stress tolerance, and longevity [128–130]. Nuclear FOXO regulates the transcription of target genes containing a consensus DNA binding sequence (TTGTTTAC). Nuclear localization is regulated by several post-translational modifications, including AKT-mediated phosphorylation, or by acetylation, methylation, glycosylation, and ubiquitinylation [131–133]. The modifications affect protein–protein and protein–DNA interactions that alter the DNA-binding characteristics that regulate transcriptional activity [131, 133–137]. AKT-mediated phosphorylation of FOXO1, FOXO3a, and FOXO4 causes their nuclear exclusion, leading to their sequestration by 14-3-3 proteins, or ubiquitinylation and degradation in the cytoplasm. Moreover, FOXO transcriptional activity can be inhibited by IKK (IκB kinase) and SGK (serum/glucocorticoid-inducible protein kinase) that also causes phosphorylation and nuclear exclusion [131, 138]. By comparison, methylation of arginine residues in FOXO blocks AKT-induced phosphorylation and inactivation [133], whereas addition of *O*-linked β-*N*-acetylglucosamine to FOXO promotes the expression of its target genes involved in stress resistance during hyperglycemia and cell stress [139]. Lysyl acetylation of FOXO can play both positive and negative regulatory roles, which appear

to depend upon effects to modify localization, AKT-mediated phosphorylation, or DNA binding [140, 141]. It appears that a specific pattern of FoxO post-translational modifications by acetylation or phosphorylation fine tunes interactions with specific binding partners to mediate cell- and tissue-specific effects [140].

Evidence from genetically modified mouse models suggests that the FOXOs have a distinct function during development, but considerable redundancy in adults [142–144]. Through the IR→IRS→PI3K→AKT signal cascade, FOXO integrates insulin action with the systemic nutrient and energy homeostasis and organism growth. FOXOs can regulate genes controlling hepatic glucose production, insulin secretion in β cells and β-cell growth and differentiation, survival and function, and fat and muscle mass (Figure 8.4) [145]. FOXO1 coordinates decreased nutrient availability with reduced somatic growth by increasing the hepatic expression of IGFBP1 (insulin-like growth factor-binding protein 1), a liver-secreted protein that binds to circulating IGF1 to limit its systemic availability [146]. FOXO could be a therapeutic target for metabolic disorders of insulin resistance, including β-cell function, obesity, diabetes, and non-alcoholic fatty liver diseases [130].

Heterologous regulation and dysregulation of the insulin and insulin-like growth factor signaling cascade

Concerted regulation of proximal insulin signals

Over a decade of genetic experiments in mice have established that changes in the relative function of a broad array of insulin signaling components, nutrient sensors, and their downstream metabolic effectors can have profound effects upon insulin sensitivity and nutrient homeostasis. Although this work is remarkably informative, the complexity of heterologous regulation complicates the identification and design of strategies for the treatment of insulin resistance and its pathological sequelae. Although the list of insulin signaling components and their interactions continues to grow, the IRSs retain a special position as a common integrating node that coordinates insulin responses in all tissues and cells. Indeed, a 50% reduction in the concentration of the IR, IRS1, and IRS2 achieved by genetic methods causes growth deficits and diabetes in mice [147]. We are now aware of many heterologous pathways that regulate the concentration and function of these proximal insulin signaling components, but how dysregulation of these mechanisms contributes to the progression of insulin resistance, metabolic disease, and type 2 diabetes is not understood well enough to guide the development of efficacious and safe treatments.

Many insulin and insulin-like growth factor signaling components are regulated by YY1 (Yin Yang 1), including IGF1 and IGF2, IRS1 and IRS2, and AKT1, -2, and AKT-3 in skeletal muscle [148]. YY1 is a ubiquitous homeobox transcription factor related to the polycomb family that can activate or repress these genes and many others. YY1 has many functions, including interactions with histone acetyltransferase and histone deacetylase complexes, which alter chromatin structure and function. In its active state, YY1 recruits PRC (polycomb repressive complex), PC2 (polycomb protein 2) and EZH2 (enhancer of zeste homolog 2) to the promoters of the proximal insulin signaling genes to promote histone acetylation that prevents the binding of the "transcription activator complex." YY1 also interacts with other proteins, including mTORC1, which phosphorylates and disrupts the acetylation complex leading to increased transcription of its target genes [148, 149]. This unexpected "feed forward" mechanism can explain, at least in part, why people treated with mTOR inhibitors might develop glucose intolerance, insulin resistance, and dyslipidemia, which compromises the long-term use of these drugs for the treatment of metabolic disease [148].

Transcriptional control of IRS1

Although the concerted repression of multiple signaling components can have strong effects, reduced expression of individual signaling molecules can also lead to insulin resistance. Decreased expression of IRS1 in humans and rodents is associated with diabetes, but few studies have investigated whether dysregulated transcription of IRS1 might be involved. Few studies have described transcription factors that promote IRS1 expression, leading to the view that IRS1 is a constitutive mediator of long-term insulin action. Regardless, recent work suggests that IRS1 expression might be regulated by transcriptional repressors, including AP2β (transcription factor AP-2-beta), or the p160 family of nuclear receptor coactivators p/CIP (p300/CBP/cointegrator-associated protein) and SRC1 (steroid receptor coactivator-1) [150, 151]. AP2β is expressed in adipose tissue, where it promotes adipocyte hypertrophy, inhibits adiponectin expression, and enhances the expression of inflammatory adipokines such as IL6 and MCP1 [150]. AP2β binds directly to the IRS1 promoter and decreases IRS1 mRNA and protein concentration in adipocyte cell lines [150]. Interestingly, GWAS reveals AP2β as a candidate gene for the risk of obesity and type 2 diabetes, which might involve negative regulation of IRS1 expression [152].

p/CIP and SRC1 serve as transcriptional coactivators for nuclear hormone receptors and certain other transcription factors [153]. Compound knockout of p/CIP and SRC1 in mice prevents obesity and increases energy expenditure, consistent with a role of nuclear hormone receptor target genes in these processes. Without p/CIP and SRC1, mice display increased glucose uptake and enhanced insulin sensitivity in white adipose tissue and skeletal muscle. Interestingly, IRS1 expression increases significantly in p/CIP and SRC1 knockout mice, suggesting that steroid-regulated nuclear receptors can regulate IRS1 transcription through the action of p160 coactivators [151].

Multiple factors regulate IRS2 transcription

IRS2 transcription is regulated by multiple factors, including CREB (cAMP response element binding protein) and its coactivator CRTC2 (CREB regulated transcription coactivator 2),

FOXO1/3, NFAT (nuclear factor of activated T cells), TFE3 (transcription factor E3), HIF2α (hypoxia-inducible factor-2α encoded by Epas1), and SREBP1 (sterol regulatory element binding protein 1) [154, 155]. Under fasting conditions, the cAMP-responsive CREB coactivator CRTC2 promotes glucose homeostasis by stimulating gluconeogenesis in liver upon assembly of CREB•CRTC2 on relevant CRE promoter sites, including a half-CRE on IRS2 [155]. The induction of hepatic IRS2 during fasting appears to modulate glucose homeostasis as it mediates a feedback response that limits glucose output from the liver even when the insulin concentration is low.

The IRS2 promoter also includes elements that bind FOXO family members. Upon deletion of AKT1/2 in the liver, nuclear FOXO accumulates and promotes IRS2 transcription, whereas the deletion of FOXO1/3 strongly reduces IRS2 transcription [113]. Thus, regulation of IRS2 transcription by AKT→FOXO establishes a direct feedback loop in the liver to promote insulin signaling during fasting and inhibit it during prolonged hyperinsulinemia. Moreover, an E-box overlapping the FOXO site binds TFE3 (basic helix–loop–helix transcription factor E3), which converges with FOXO to promote IRS2 expression [156]. These elements also overlap with an SRE that binds the SREBP-1c (sterol regulatory element-binding protein 1). SREBP-1c is an important transcriptional activator of lipid synthesis [157]. Active SREBP-1c concentrations increase during nutrient excess and chronic insulin stimulation [158, 159]; however, elevated hepatic SREBP-1c decreases IRS2 expression [159]. Upregulation of IRS2 expression by TFE3/FOXO and downregulation by SREBP-1c appear to coordinate starvation-induced glycogenolysis and gluconeogenesis with postprandial lipogenesis. However, an imbalance in this reciprocal regulation might contribute to pathophysiological effects of over-nutrition, leading to the development of insulin resistance, metabolic syndrome, and diabetes.

HIF2α also induces transcription of mouse or human IRS2 in the liver [160]. Under normal oxygen tension, HIF1α and HIF2α are destabilized upon hydroxylation of critical proline residues by prolyl hydroxylase domain-containing proteins (PHD1, -2, and -3). Interestingly, acute inhibition of hepatic PHD3 improves insulin sensitivity and resolves diabetes by specifically stabilizing HIF2α, which increases IRS2 transcription that promotes insulin-stimulated AKT activation [160]. Physiologically, the HIF2α-mediated mechanism of IRS2 transcriptional regulation might be important in the perivenous zone of the liver, which displays more hypoxia and less gluconeogenesis compared with other zones in the liver [161]. These results reveal the intersection between hypoxic sensing and IRS2-mediated hepatic insulin action.

miRNA-mediated post-transcriptional regulation

miRNAs are short (~20 nucleotides), non-coding RNA molecules that act as post-transcriptional regulators of gene expression, and bind to target sites in the 3′-untranslated regions (3′UTR) to form a complex that inhibits translation and renders the target mRNA molecule unstable. Several proximal components of the IR→PI3K→mTOR signaling cascade can be regulated by miRNAs. The LIN28a/b⊣ LET7 axis is a recent example [162]. LET7 miRNA interferes with many targets, including the translation of several proximal insulin signaling proteins, including IGF1R, INSR, IRS2, PIK3IP1, AKT2, TSC1, and RICTOR [162]. LIN7 interference is inhibited by the RNA-binding proteins Lin28a and Lin28b, which block the production of mature LET7 and increase translation of the insulin signaling components. LIN28 overexpression in mice can cause gigantism and a delay in puberty onset, consistent with human genome-wide association studies suggesting that polymorphisms in the human LIN28B gene are associated with human height and puberty timing [163]. Moreover, LIN28a/b can promote glucose homeostasis in mammals by increasing insulin→PI3K→mTOR signaling and insulin sensitivity [162].

Several other miRNAs can suppress the translation of IRS1, including miRNA-96, miRNA-128a, miRNA-126, miRNA-143, miRNA-144, miRNA-145, miRNA-487b, and miRNA489. In one example, chronic angiotensin II-induced hypertension can increase the expression of miRNA-487b in rat aorta [164]. In this case, down regulation of IRS1 might contribute to hypertension-induced cardiovascular disease, including aortic aneurysm formation due to the loss of medial smooth muscle.

Post-translational regulation of insulin and insulin-like growth factor signaling

Degradation of the IRS-proteins

Proteasome-mediated degradation regulates many biological processes, including signal transduction, gene transcription, and cell cycle progression [165]. Proteins targeted for destruction by the 26S proteasome are polyubiquitinylated by various complexes containing a ubiquitin-activating enzyme (E1), ubiquitin-conjugating enzyme (E2), and ubiquitin–protein ligase (E3). IRS1 and IRS2 can be polyubiquitinylated during chronic inflammatory states, nutrient excess, and hyperinsulinemia through various tissue-specific mechanisms [166]. One of the pathways is associated with proinflammatory cytokine-mediated upregulation of SOCS1/3 (suppressors of cytokine signaling). Cytokines such as INFγ or IL6 bind to receptors that recruit and activate JAK kinases, which promote phosphorylation and dimerization of STAT transcription factors that migrate into the nucleus to induce SOCS1/3 expression (Figure 8.5) [167]. SOCS1/3 can act as an adapter protein that uses an SH2 domain to bind to phosphotyrosine residues in IRS while its conserved "SOCS box" recruits an elongin BC-containing E3 ubiquitin ligase to ubiquitinylate IRS (Figure 8.5) [168–171]. Mutations in the "SOCS box" prevent degradation of IRS1 or IRS2 [168], and inhibition of SOCS1/3 expression by antisense oligonucleotides improves insulin sensitivity in obese and diabetic mice [169]. Thus, SOCS-mediated polyubiquitinylation can promote insulin resistance and glucose intolerance during infection, inflammation, or metabolic stress (Figure 8.5).

In another mechanism, the cullin-RING E3 ubiquitin ligase 7 (CRL7) can mediate IRS1 degradation downstream

of feedback serine phosphorylation signals generated by an PI3K→AKT→mTORC1 cascade [172]. CRL7 is a member of the Cullin-RING finger E3 ligases, which comprise the largest E3 family responsible for directing the polyubiquitinylation of substrate proteins for degradation by the 26 S proteasome [173]. The CRL7 complex contains CUL7 (cullin 7), a molecular scaffold to assemble FBW8 (F-box/WD repeat-containing protein 8) to recruit phosphorylated substrates, and Rbx1 (RING-box protein 1) associated with an E2 conjugating enzyme (Figure 8.5). FBW8 apparently binds to IRS1 through phospho-S/T residues generated by an mTORC1→S6K cascade including human pS307^{IRS1}, pS312^{IRS1}, and pS527^{IRS1}, but possibly also others, which leads to polyubiquitinylation of IRS1 that progresses to degradation (Figure 8.5) [172, 173]. However, ordinary mTORC1→S6K activity appears insufficient to engage the CRL7 pathways against IRS1, as unusually high levels of mTORC1→SK6 activity is required to drive IRS1 degradation [173].

Chronic consumption of high-calorie diets upregulates CBLB (Cbl proto-oncogene B), a RING-type E3 ubiquitin ligase that belongs to the Casitas B-lineage lymphoma family of proteins [6]. CBL proteins share a conserved N-terminal region containing a tyrosine kinase binding domain and a RING-finger domain to facilitate E3 ubiquitin ligase activity. Calorie excess induces ChREBP (carbohydrate-responsive element-binding protein) and SREBP1c, which upregulates in murine muscle and liver MSTN (myostatin) that induces CBLB expression to drive insulin resistance through the polyubiquitinylation and degradation of IRS1 [174].

Finally, MG53 (mitsugumin 53), a TRIM (tripartite motif-containing) family E3 ubiquitin ligase, can promote IRS1 and InsR degradation in muscle during calorie excess. MG53 is found in kidney, skeletal muscle, and heart, where it can act as a scaffold for assembly of repair complexes [175, 176]. However, metabolic stress induces MG53, which targets InsR and IRS1 for polyubiquitinylation and degradation [177, 178]. Although it is unclear how high-calorie diets upregulate MG53, mouse studies show that MG53-deficient mice fed a high-calorie diet are protected from degradation of InsR and IRS1 and insulin resistance [178]. Hence MG53 appears to play important repair functions during acute damage, whereas it might have detrimental metabolic effects during chronic inflammatory stress.

Multisite Ser/Thr-phosphorylation of IRS-proteins

IRS1 and IRS2 can be regulated through a complex mechanism involving phosphorylation of more than 50 serine/threonine residues (phospho-S/Ts) located in the long tail regions (see Figure 8.3) [179]. Understanding how phospho-S/Ts regulate signaling is a difficult problem because so many sites and phosphorylation mechanisms appear to be involved. Heterologous signaling cascades initiated by proinflammatory cytokines or metabolic excess, including tumor necrosis factor-α (TNFα), endothelin-1, angiotensin II, excess nutrients (free fatty acids, ceramides, amino acids, and glucose) or endoplasmic reticulum stress, are implicated in IRS1 phospho-S/Ts [180, 181]. Many biochemical and genetic experiments in cell-based systems suggest that individual phospho-S/T sites throughout the structure of IRS1 are associated with a reduction of insulin-stimulated tyrosine phosphorylation by up to 50% [182]. This level of inhibition is sufficient to cause glucose intolerance that could progress to diabetes, especially if pancreatic β cells fail to provide adequate compensatory hyperinsulinemia [147].

Numerous cell-based studies reveal IRS1 phospho-S/T to be a physiologically integrative mechanism modulating insulin sensitivity [179]. Insulin is clearly an important agonist of IRS1 phospho-S/T, as most sites are stimulated by insulin and diminished by inhibition of the PI3K→Akt→mTOR cascade [183]. Moreover, the IRS1 phospho-S/T patterns produced during drug-induced "metabolic stress" correlates significantly with that stimulated by insulin. These results suggest that IRS1 phospho-S/T is first and foremost a feedback mechanism that develops during insulin stimulation, which can be co-opted by metabolic stress to inhibit insulin signaling and promote metabolic disease (Figure 8.5) [179]. An implicit corollary is that hyperinsulinemia may be an important physiological mediator of insulin resistance in animals, and there is some experimental evidence that this is so [184].

Mouse S307^{IRS1} (human S312^{IRS1}) is one of the best studied regulatory phosphorylation sites in IRS1 that is often used as barometer of insulin resistance. Phosphorylation of S307^{IRS1}, located near the PTB domain, can inhibit insulin-stimulated IRS1 tyrosine phosphorylation by disrupting the association between the InsR and IRS1, which decreases the activation of the PI3K→Akt pathway during insulin stimulation [185, 186]. Insulin itself promotes rat/mouse S307^{Irs1} phosphorylation through activation of the PI3K revealing feedback regulation that can be mediated by many kinases, PKCζ, IKKβ, JNK, mTOR, and S6K1 (Figure 8.5) [183]. In some cases, PI3K-dependent degradation of IRS1 might depend on the pS307^{IRS1}, although other mechanisms can be involved [187]. Free fatty acids that contribute to insulin resistance promote pS307^{IRS1}; however, associated hyperinsulinemia has not been excluded as the principal agonist of IRS1 phospho-S/T levels [179]. S307^{Irs1} is poorly phosphorylated in *ob*/*ob* (obese) mice that lack Jnk1, suggesting that this kinase might be involved [188]. IRS1 can be phosphorylated by PKCδ on at least 18 sites in BL21 DE3 cells, including S307^{IRS1}, S323^{IRS1}, and S574^{IRS1}, which appear to play an inhibitory role [189]. Hyperactivated mTOR also promotes S307^{IRS1} phosphorylation, which is diminished in mice lacking S6K [190–192]. IKKβ inhibitors (aspirin and salicylates) block S307^{IRS1} phosphorylation [193], which is associated with improved insulin sensitivity in obese rodents and in persons with type 2 diabetes [194–196].

Regardless, only two studies have investigated directly the function of IRS1 phospho-S/T in mice using transgenesis or genetic knock-in to augment or replace endogenous (wild-type) IRS1 with a mutant version. In the first report, transgenic mice are generated to have moderate overexpression in skeletal muscle (about twofold versus littermates) of non-mutant IRS1 or mutant IRS1 with alanine substitutions to block phosphorylation at three serine

residues: S302/307/612A (hS307/312/616A) [197]. In the triple-mutant transgenic mice, possibly half of the total muscle IRS1 protein is endogenous in origin. Compared with mice expressing a wild-type IRS1 transgene, mutant mice fed a high-fat diet showed better glucose tolerance, increased total and muscle glucose disposal during clamp, and enhanced muscle IRS1 tyrosine phosphorylation and p85 binding in response to insulin. This experiment is consistent with the notion that $S302^{Irs1}/S307^{Irs1}/S612^{Irs1}$ phosphorylation in skeletal muscle contributes to the development of insulin resistance in animals and humans.

However, genetic knock-in experiments to replace wild-type IRS1 in mice with a single mutant ($A307^{IRS1}$) do not support this result [198]. Given the apparent sensitizing effect of the $A307^{IRS1}$ mutation in cell-based assays, homozygous $A307^{IRS1}$ mice show increased fasting insulin versus control mice, mild glucose intolerance, and decreased PI3K binding (p85 and p110) in insulin-stimulated primary hepatocytes. During the high-fat diet, $A307^{IRS1}$ mice exhibit higher fasting insulin and more severe glucose intolerance than wild-type mice. Thus, $S307^{Irs1}$ appears permissive rather than inhibitory for insulin signaling in mice. Among other, less prosaic explanations, it is possible that a serine is structurally required at $S307^{Irs1}$ for normal signaling. Alternatively, S307 phosphorylation could have a partial positive effect on insulin signal transduction that is more important in tissues or primary cells than its desensitizing function in continuous cell lines. $A307^{IRS1}$ phosphorylation might have mixed tissue-specific effects that are obscured by the standard knock-in approach [199]. In any case, the phenotype of $A307^{IRS1}$ mice confirms that S/T sites on IRS1 can affect whole-body insulin sensitivity.

Modulation of insulin signaling by protein and lipid phosphatases

Many phosphatases can modulate the action of insulin by dephosphorylating key proteins or lipids in the signaling cascade including PTP1B (PTPN1, tyrosine–protein phosphatase

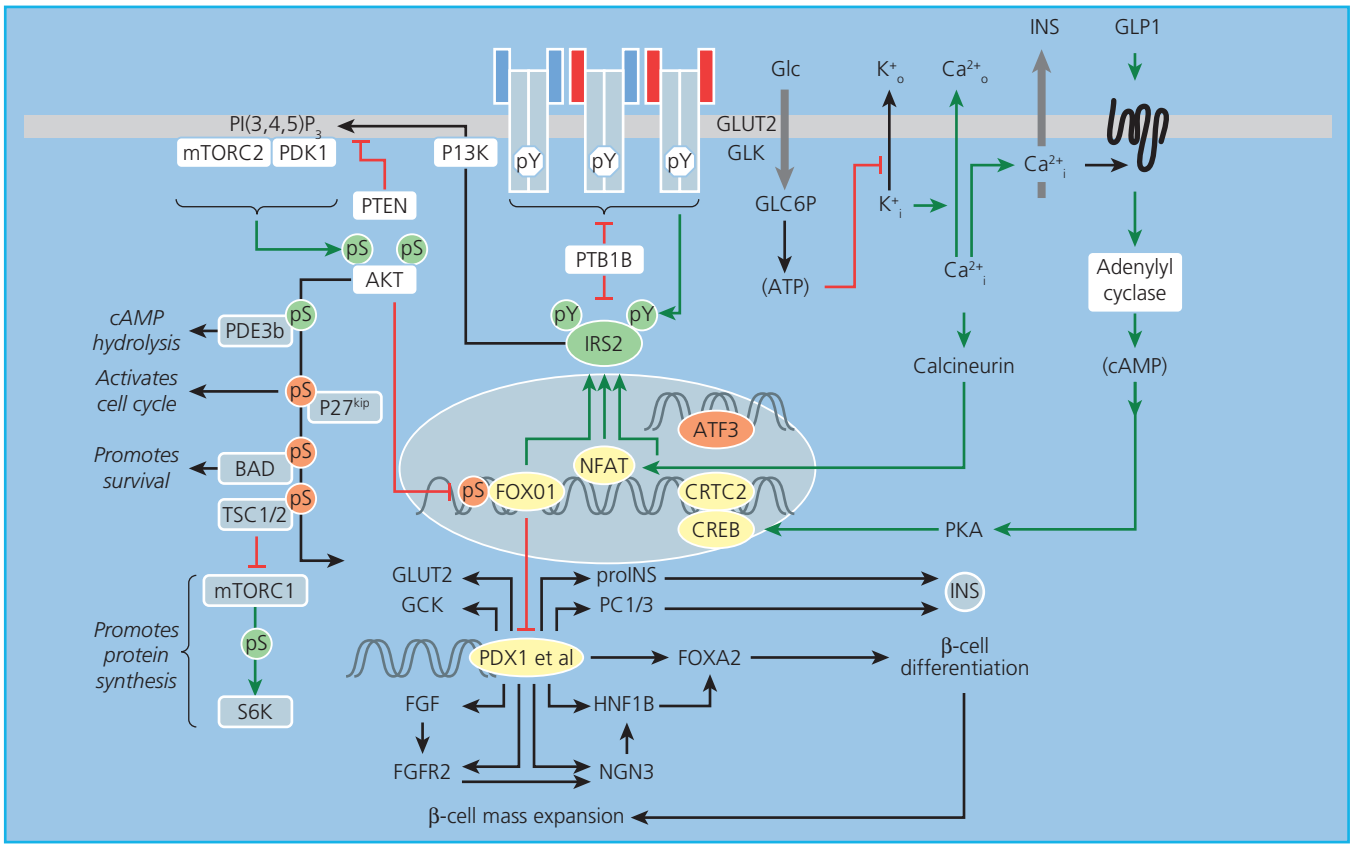

Figure 8.6 The integrative role of IRS2 signaling in pancreatic β-cell function. The diagram shows the relation between the IRS2 branch of the insulin signaling pathway and upstream and downstream mechanisms regulating β-cell growth and function. The production of $PI(3,4,5)P_3$ by the PI3K recruits the Ser/Thr-kinases PDK1 and AKT to the plasma membrane where AKT is activated by PDK1 and mTORC2-mediated phosphorylation. AKT phosphorylates many proteins that play important physiological roles in β cells including GSK3β (glycogen synthesis), the BAD•BCL2 heterodimer (apoptosis inhibition), TSC1/2 (protein synthesis and nutrient sensing), and FOXO (transcriptional regulation). Activation of GLP1→cAMP→PKA→CREB, glucose→Ca^{2+}→CRTC2 and calcineurin→NFAT induce IRS2 expression in β cells, revealing a mechanism that places β-cell growth, function, and survival under the control of glucose and incretins. Since insulin and IGF1R are constitutively active, IRS2 expression can act as the regulatory gateway to mTORC1, FOXO1, and $p27^{kip}$. Together, this integrated pathway shows how signals known to promote β-cell and islet growth and function can be integrated by the IRS2 signaling cascade into a common pathway.

non-receptor type 1), PTPN2, pTEN (phosphatase and tensin homolog), and PP2A (protein phosphatase 2A). PTP1B and PTPN2 are related phosphotyrosine phosphatases that attenuate insulin signaling by dephosphorylating the bisphosphorylated regulatory loop of the InsR [200]; however, their biological effects appear distinct owing to a different time course of action and differential expression (muscle expresses PTP1B, whereas liver expresses both enzymes) [201]. Both PTP1B and TCPTP can be inactivated by reactive oxygen species generated during insulin stimulation, which provides an additional level of regulation [20, 202]. $PTP1B^{-/-}$ mice display increased insulin sensitivity, lower circulating insulin concentrations, and decreased pancreatic β-cell mass [203]. Furthermore, PTP1B is a selective inhibitor of leptin signaling (LepRb→JAK2) as it dephosphorylates JAK2, but not JAK1 or -3, whereas TCPTP dephosphorylates JAK1/3, but not JAK2 [200]. Thus, CNS inhibition of PTP1B can protect against obesity, whereas peripheral inhibition of PTP1B promotes glucose tolerance [204]. In pancreatic β cells, PTP1B attenuates the IRS2→PI3K→AKT cascade that is important for growth, function, and survival of these cells [205]. The deletion of PTP1B maintains β-cell mass in mice lacking IRS2, which prevents the early onset of diabetes. Regardless, without IRS2 even the $IRS2^{-/-}$•$PTP1B^{-/-}$ mice lose β-cell mass between 8 and 9 months of age, suggesting that IRS1 alone is inadequate throughout life.

PTEN (phosphatase and tensin homolog) is a potent negative regulator of insulin action and cellular proliferation, and one of the most frequently mutated genes in many forms of human cancer [206, 207]. PTEN attenuates downstream insulin-like signaling by dephosphorylating $PI(3,4)P_2$ and $PI(3,4,5)P_3$ at the 3-position, which reduces the recruitment and activation of PDK1 and AKT (Figure 8.5) [207]. $PTEN^{+/-}$ mice are glucose tolerant even as β-cell mass and circulating insulin levels decrease [208]. PTEN heterozygosity also increases peripheral insulin sensitivity in $IRS2^{-/-}$•$PTEN^{+/-}$ mice and normalizes glucose tolerance, as the small islets in these mice produce sufficient insulin until death from lymphoproliferative disease between 10 and 12 months age. These experiments highlight the complex relation between nutrient homeostasis, insulin sensitivity and secretion, and cancer that emerges in rodents and humans. Despite this complexity, mild inhibition of PTEN, especially if it can be accomplished in a tissue-specific way, might have therapeutic value.

The serine–threonine phosphatase PP2A also plays an important regulatory role for insulin signaling as it dephosphorylates Ser/Thr residues on IRS1 and other proteins. By contrast, the inhibition of PP2A by okadaic acid strongly increases phospho-S/T and degradation of IRS-1, which is associated with reduced tyrosine phosphorylation and decreased insulin signaling [209]. Thus, compared with the effects of PTP1B, PP2A generally displays the opposite effect upon insulin signaling. The specificity of PP2A is largely coordinated through a scaffolding unit that recruits various substrates. The scaffolding unit is composed of HEAT (huntingtin-elongation-A subunit-TOR) repeats, which are thought to target PP2A to its substrates to confer specificity upon the constitutive catalytic domain.

IRS2 as a gateway to β-cell function

Pancreatic β cells have a special place in nutrient homeostasis as the unique source of insulin secretion, and, like other cells, they also require insulin and insulin-like growth factor signaling for growth, function, and survival. However, β cells are always exposed to insulin and IGF, so insulin and insulin-like growth factor signaling appears to be regulated through multifactor transcriptional control of IRS2 through the action of FOXO1/3, NFAT, and the CREB•CRTC2 (Figure 8.6) [154, 210–212]. In β cells, FOXO can account for as much as 80% of the basal IRS2 expression [210]. Since the IRS2→PI3K→AKT cascade phosphorylates and inhibits FOXO, insulin and IGF1 have inhibitory effects on FOXO-mediated transcription of IRS2, which can attenuate IRS2 expression. Since β cell mass and function must be protected during chronic nutrient excess, other mechanisms promote IRS2 expression, including glucose-stimulated Ca^{2+} influx and cAMP production. In addition to its immediate role in insulin secretion, Ca^{2+} activates calcineurin, which dephosphorylates NFAT to facilitate its entry into the nucleus, where it induces expression of IRS2 and other genes [211]. Glucose, glucagon-like peptide-1, and other GPCR agonists also increase the cAMP concentration in β cells, which has many important effects, including the activation of CREB•CRTC2 that promotes IRS2 transcription [213, 214]. Through this mechanism, the responsibility for insulin or IGF1 itself to trigger downstream insulin and insulin-like growth factor signaling in β cells has been replaced by indirect control through glucose, incretins, or neuronal signals, the physiologically relevant regulators of pancreatic β-cell function (Figure 8.6).

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9 Control of Weight: How Do We Get Fat?

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Key points

- The current obesity epidemic is a consequence of a positive "energy gap" arising from an imbalance between energy intake and expenditure.
- Complex genetic, environmental, behavioral, and neuroendocrine factors are responsible for this abnormal energy homeostasis.
- Environmental risk factors such as sedentary lifestyle, dietary consumption patterns, and the impact of advertising and globalization remain most responsible for the current obesity epidemic.
- Emerging pathophysiological mechanisms implicated in obesity include common single-nucleotide polymorphisms (obesity susceptibility genes), epigenetics, endocrine disruptors, neuroendocrine pathways, and the gut microbiome.
- Evolutionary counter-regulatory neuroendocrine pathways are a key factor in protecting against weight loss and promoting weight regain by decreasing energy expenditure and influencing appetite regulation and fat storage.

Introduction

The current obesity epidemic can be broadly conceptualized as the result of a positive "energy gap": the consequence of the progressive imbalance between energy intake and expenditure at a population level [1]. The underlying cause of this "energy gap" is complex, arising from the interplay of genetic, environmental, behavioral, and neuroendocrine determinants which are becoming better characterized.

This chapter provides a broad overview of several of these etiological factors that are implicated in the development of weight gain and obesity from either an epidemiological or an individual homeostatic and behavioral perspective.

Genetic factors

Heritability of obesity

Genetic factors have a major role in the development of overweight and obesity, although it is increasingly recognized that the gene–environment relationship frequently moderates the influence of these genetic factors. Early twin studies identified the heritability of obesity to be in the order of 40–70% [2–5]. Nonetheless, environmental factors such as physical activity and age are important genetic modifiers: for example, the heritability of fat mass in Finnish twins with low levels of physical activity is reported to be 90%, compared with only 20% amongst pairs of twins with high levels of physical activity [6]. Moreover, the heritability of body mass index (BMI) appears strongest in young adulthood [7].

Monogenic obesity

Monogenic and syndromic forms of obesity are rare but provide exceptions to the gene–environment obesity paradigm; in these conditions, genetic factors have such potent effects that their effect on body weight supersedes the influence of the environmental context. Examples include leptin deficiency caused by mutations in the leptin gene (*LEP*) or receptor (*LEPR*) or other genes involved in the hypothalamic leptin-melanocortin signaling pathway regulating appetite and satiety (i.e. *POMC* [pro-opiomelanocortin], *PCSK1* [prohormone convertase 1] and *MC4R* [melanocortin 4 receptor] [8–14]. *MC4R* mutations are the most common of these gene defects, with a prevalence of 0.5–1.0% in obese adults and 1.0–6.0% in obese children [15].

Common obesity "susceptibility" genes

More recently, genome-wide association studies (GWAS) have identified obesity "susceptibility" genes: common single-nucleotide polymorphisms (SNPs) associated with obesity within a population. However, so far these genes account for <2% of BMI variability within a population [14]. There are currently at least 75 obesity susceptibility loci that have been identified by GWAS [16, 17]. Interestingly, several of these loci are found near genes linked to severe monogenic obesity (i.e. *MC4R*, *SH2B1*, *BDNF*, *POMC*) [14]. The fat mass and obesity-associated (*FTO*) gene was the first to be identified and remains the most

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common. It has been replicated across different ethnicities (with the strongest association seen in European followed by Asian and African populations), and has the largest effect on BMI and obesity risk, with each minor risk allele associated with a 0.39 kg/m^2 higher BMI and 1.2-fold increase in obesity risk within a population [18, 19]. Nonetheless, it accounts for only 0.34% of the variability in BMI in a population [20]. Evidence derived from animal studies suggests that *FTO* and other obesity susceptibility genes are principally involved in the regulation of food intake [14]. However, evidence is conflicting in human studies on the association of *FTO* with increased energy or fat intake [21–24], increased appetite [25, 26] and reduced satiety [27].

"Missing heritability"—epigenetics and intrauterine imprinting

Given the discrepancy between the estimated effect of these obesity "susceptibility" gene loci (<2%) and the known heritability of obesity (40–70%), there is increasing focus on the impact of gene–environment interactions via epigenetic and intrauterine effects on gene expression that may account for this "missing heritability" [14].

Prader–Willi syndrome is an extreme example of epigenetic-induced obesity, most frequently due to loss of expression of imprinted paternal genes on chromosome 15q11–13. Gene methylation is another example of epigenetic modification, and can be altered by maternal diet [28, 29]. Decreased methylation due to exercise has also been demonstrated in skeletal muscle biopsies of sedentary adults undergoing acute exercise, correlating with the degree of exercise intensity [30].

More broadly, the concept of intrauterine imprinting is also implicated in the development of obesity. The Barker-Hales Developmental Origins of Health and Disease hypothesis proposes that intrauterine and/or early childhood undernutrition lead to adult obesity and related cardiovascular sequelae [31]. This was first evident in the Dutch famine study, which found that nutrient deprivation during the first trimester, compared with later in pregnancy, increased the risk of obesity in the offspring in the long term [32]. Conversely, maternal obesity and increased gestational weight gain, especially in the first trimester, are associated with fetal macrosomia, large-for-gestational age (LGA) [33–35] and subsequent obesity in the offspring in the long-term [36]. Overall, higher rather than lower birth weight appears to be a much stronger predictor of high adult BMI [37].

Similarly, offspring of mothers with gestational diabetes mellitus (GDM) and pre-existing diabetes are more likely to be macrosomic and LGA at birth, with an increased risk of subsequent childhood and adolescent obesity and diabetes [38–40]. Moreover, offspring exposed to both maternal obesity and GDM are at an even greater risk of obesity in adolescence than that seen in those with GDM alone, suggesting that alterations in fatty acid metabolism and circulating inflammatory markers play a critical role in the development of obesity in the offspring [41]. From a pathophysiological perspective, maternal hyperglycemia causes fetal hyperglycemia, hyperinsulinemia, and increased leptin synthesis, influencing intrauterine hypothalamic energy homeostasis [42]. Moreover, maternal hyperglycemia may also alter the fetal epigenome, resulting in the expression of genes that regulate accumulation of body fat [43].

Antenatal maternal smoking has long been associated with subsequent risk of obesity in the offspring. For example, smoking in early pregnancy is associated with a more than twofold risk of overweight and obesity in the offspring at age 3 years [44]. Smoking throughout pregnancy increases the risk of elevated BMI in the offspring at the age when commencing school from <10% to >15%. This risk remains largely unchanged even if smoking is discontinued after the first trimester, indicating that the effect of smoking on fetal programming occurs predominantly early in pregnancy [45].

Environmental factors

Epidemiological evidence suggests that environmental changes promoting positive energy balance are those most responsible for the current obesity epidemic. These environmental risk factors include our increasingly sedentary lifestyle, the cost, quality, quantity, and changing patterns of dietary consumption, and the impact of advertising and globalization leading to progressively increased energy intake at a population level. Other environmental factors implicated in the obesity pathway include sleep and work patterns, medications, and environmental toxins.

Sedentary lifestyle

Epidemiological evidence indicates that moderate to high levels of physical activity protect against weight gain and obesity [46, 47], with physical activity particularly important for weight maintenance following initial weight loss [48]. Despite this, physical activity has been increasingly engineered out of our lifestyle, leading to the increasing prevalence of obesity via reduced energy expenditure.

Our increasingly sedentary lifestyle, from both occupational and recreational perspectives, arises from greater urbanization and technological advances that promote convenience and efficiency. Examples are the development of transport systems in which driving in cars or other transport is readily available, the mechanization and computerization of the workforce, and the increase in passive recreation and entertainment (e.g. shopping centers, television and movie watching, and the use of computers and other electronic devices).

The impact of such technological changes and urbanization on physical activity levels has been significant. A comparison of physical activity among Amish versus Colorado populations revealed that Amish men and women walk 18,000 and 14,000 steps daily, respectively [49], in contrast to men and women in Colorado who walk on average 6733 and 6284 steps daily, respectively; this equates to a difference in daily energy expenditure of 400–600 kcal/day [50]. Similarly, evidence shows that individuals in US

cities where more walking is required weigh less than those in other cities [51].

Energy intake—quantity of food consumed

Evidence suggests that a positive energy imbalance gap of 100–200 kcal/day is sufficient for body weight gain [52], although a recent US population-based study suggests that a mean daily energy imbalance gap of only 7 kcal/day could account for the current obesity epidemic [52]. Indeed, the increase in average daily energy intake since 1970 greatly exceeds these figures. Globally, the availability of calories per capita increased by ~450 kcal/day in developed countries and by over 600 kcal/day in developing countries [53], whereas the US National Health and Nutrition Examination Survey (NHANES) reported that the increase in average energy intake in the United States between 1971 and 2000 for men and women was 168 and 335 kcal/day, respectively [54].

This energy imbalance appears to be due predominantly to alterations in dietary composition, specifically the increased availability of foods, increased portion size, and the reduced cost of high-fat, energy-dense food (e.g. refined carbohydrates/sugar and vegetable oils).

Dietary composition: sugar versus fat

The impact of dietary composition on body weight remains controversial. It has been argued that as excess energy from dietary fat is more effectively stored than energy from carbohydrates, high dietary fat content may be a key factor driving weight gain [50]. Other postulated mechanisms include the high palatability of dietary fat and its associated weak impact on satiety, which can lead to overconsumption and increased energy intake [55]. This contention is supported by epidemiological studies correlating dietary fat intake with the percentage of the population that is overweight [56]. Longer term *ad libitum* feeding studies of high-fat diets also demonstrate a positive correlation between high fat intake and weight gain [55, 57]. However, there is evidence to suggest that obesity is more strongly associated with animal fat, saturated fat, and trans fat intake rather than total fat intake per se [58]. Despite this evidence, it appears that average daily fat intake has in fact remained relatively stable since the 1970s, with the net increase in energy intake instead likely accounted for by the increase in refined carbohydrate consumption [50].

US data reveal that of the 14.7% estimated increase in daily caloric intake (equivalent to 340 kcal/day) from 1984 to 1994, refined carbohydrates accounted for 6.2%, fats and oils 3.4%, fruits and vegetables 1.4%, and meat and dairy products 0.3% [59]. Despite this, studies consistently demonstrate an inverse relationship between sugar intake as a percentage of energy intake and obesity [60]. Possible explanations for this discrepancy include the inherent difficulty of differentiating between the relative influence of percentage dietary fat and carbohydrate owing to their reciprocal relationship in dietary intake; in combination, they contribute >80% of total energy intake [55]. Accurate assessment of dietary composition is also confounded by the known phenomenon of dietary under-reporting, particularly amongst the overweight and obese [61].

Calorically (sugar) sweetened beverages

Overall, there appears to be a positive association between calorically sweetened beverages (soda/soft drinks, fruit drinks or juice, and sports energy drinks) and weight gain, assuming that sugar (fructose) in beverages adds, rather than replaces, calories derived from other sources [50]. In the United States, calorically sweetened beverages are the fourth highest contributor of calories to energy intake [62]. NHANES data indicate that the mean energy intake from calorically sweetened beverages is ~180 kcal/day for children and 340 kcal/day for young adults [63].

A recent systematic review reported that after adjustment for energy intake and expenditure, the strength of evidence for the relationship between calorically sweetened beverages and obesity is inconclusive [64]. However, several cross-sectional and longitudinal studies have reported a positive association between calorically sweetened beverages and increased body weight, particularly in children and adolescents [65]. There is also evidence to suggest that in adults, soft drink consumption correlates with long-term increases in body weight [66]. Moreover, a randomized controlled intervention trial demonstrated that the use of a high-fructose soft drink increased total energy intake by 335 kcal/day, corresponding to a significant mean weight gain of 0.66 kg over 10 weeks. This compared with the weight loss seen in participants randomized to consumption of artificially sweetened (aspartame) soft drink [67].

Eating out and portion size

The increase in consumption of food that is prepared outside the home and the associated increased portion size are also significant contributors to the current obesity epidemic [68]. This relates particularly to the impact and influence of fast food establishments. Meals prepared outside the home are generally higher in total energy and fat, cholesterol, and sodium and consist of larger portion sizes (including snack foods), which promote a higher total energy intake [55, 68]. Studies have shown that those who tend to consume food prepared outside the home have a higher BMI [69] and that consumption of fast food is associated with corresponding overall unhealthier dietary intake for that day [70, 71].

The provision of unhealthy meals and the accessibility of vending machines at schools may also contribute to weight gain in children and adolescents [55]. Conversely, the availability and range of fruits and vegetables in the home have been shown to correlate with their consumption [72], and the mother's nutrition knowledge and behavior influence their children's dietary composition [73], which may have either positive effects with the presence of fruits and vegetables or better nutrition knowledge or behavior, or obviously the converse with the presence of less fruits and vegetables and lower nutrition knowledge or poorer behaviors.

Snacking

Snacking has a role in weight gain because of the high energy density of highly processed snack foods and their increasing

portion size, which result in increased daily energy intake [74]. In the United States, the prevalence of snacking is increasing, which has led to a greater contribution of snack foods to total energy intake, which is of the order of 20–25% of daily energy [75].

Eating patterns

The pattern and frequency of food consumption also influence weight gain. In particular, consuming smaller portions (as opposed to *ad libitum* consumption) more frequently throughout the day is associated with both normal BMI and maintenance of weight loss [76, 77]. In one study, adolescent boys who ate more than six times per day were more likely to have a BMI within the normal range compared with those who generally ate fewer than six times per day, and who were more likely to be overweight [78]. More generally, "binge-eating" behavior is associated with weight gain and this disordered pattern of eating is significantly more common in obesity [55].

Advertising

Highly visible advertising for fast food restaurants and energy-dense foods and beverages is also thought to contribute to their increased consumption, resulting in increased energy intake and weight gain [79]. This holds particularly true for children, with both the exposure to and the energy content of foods advertised to children being disproportionately high compared with their required daily energy intake.

Globalization and government regulation

Globalization, multilateral free trade agreements, and market liberalization have significantly impacted the global food system, promoting consumption-based growth. This has led to the greater availability and thus overconsumption of convenient, energy-dense processed foods [29], with processed foods now accounting for >80% of global food sales [80].

The overall effect of such trade and agricultural policies is a reduction in cost of processed energy-dense food, leading to their increased consumption [81, 82]. For example, between 1985 and 2000, the cost of fruit and vegetables rose by 188%, fish 77%, and dairy 56% compared with sugar, fats and oils, and calorically sweetened beverages, the cost of which rose by only 46, 35, and 20%, respectively [83].

More generally, globalization has led to the increasing presence of multinational retailers, manufacturers, and fast food chains in developing countries, heightening the influence of Western culture across the world [80]. This has resulted in the homogenization and westernization of traditional diets, with a transition towards energy-dense processed foods [84].

Government regulation of the food industry and the initiation of preventive public health policy in the midst of the obesity epidemic continue to be limited, in part because of the above economic policies that promote market and trade liberalization and the primacy of individual autonomy. Importantly, a recent systematic review concluded that government food policy is indeed effective in promoting improved dietary consumption, with taxes on soft drinks and subsidies for healthier food options particularly effective [82]. This also emphasizes the impact of cost of food on consumption. Specific examples include the enactment of legislation in Denmark in 2003 regulating the sale of many foods containing trans fats, essentially banning partially hydrogenated oils, and the 2013 proposed limit on soft drink size in New York, prohibiting the sale of calorically sweetened beverages of more than 16 oz (0.5 L) in volume, although this regulation was rejected by the New York judicial system in 2014.

Sleep patterns

The quality and duration of sleep are also implicated in weight gain and other metabolic and psychological adverse sequelae, through effects on appetite and energy homeostasis [85]. The factors contributing to chronic insufficient sleep are pervasive in modern society and include the use of electronic media, caffeine consumption, shift work, mental illness, and psychotropic medication [85].

Insufficient sleep is associated with alterations in hormonal mediators of appetite and metabolism, such as insulin, ghrelin, leptin, and cortisol [86], leading to insulin resistance, sympathetic nervous system overactivity, increased hunger, particularly for energy-dense food, reduced satiety, and decreased physical activity [86, 87].

This association between insufficient sleep and obesity appears particularly strong among children and adolescents, with an inverse dose-dependent relationship evident in several studies. For example, it has been estimated that for each hour of lost sleep, the odds of obesity in adolescents increase by 80%, and this appears most directly related to the influence of sleep loss on reduced physical activity [88]. Conversely, there is a positive correlation between longer sleep duration and lower BMI in children, with the prevalence of increased BMI in those who slept for less than 10 hours per night being 5.4% compared with 2.1% in children who slept more than 11.5 h per night [89].

Medications and toxins

Medications

Several classes of pharmacotherapy are associated with significant weight gain, including certain antidiabetes therapies, corticosteroids, anticonvulsants, antipsychotics, and antidepressants. Antihypertensives (α- and β-blockers), the oral contraceptive, and antihistamines have also been associated with lesser degrees of weight gain [90].

Older generation sulfonylureas such as chlorpropamide and glyburide are associated with significant weight gain over time (up to 5 kg) [91] compared with second-generation sulfonylureas such as gliclazide, which are associated with weight gains ~0.5–2.0 kg [92]. Similarly, insulin therapy can cause weight gains of between 2 and 10 kg generally within the first 12 months of therapy, correlating with glycemic control and insulin dose [91]. The mechanism of weight gain with these agents is multifactorial and includes appetite stimulation, increased snacking to prevent hypoglycemia,

reduced energy loss following correction of glycosuria, and the anabolic effect of insulin on muscles and adipose tissue [90].

Weight gain is the most frequent adverse effect associated with chronic corticosteroid therapy, with low-dose prednisone (5–10 mg daily) associated with a 4–8% mean increase in body weight [93]. Corticosteroids cause weight gain via several central and peripheral mechanisms, including effects on glucose, protein, and lipid metabolism and stimulation of reward and feeding pathways which promote increased appetite for energy-dense food [90, 94].

Several anticonvulsant agents are associated with significant weight gain. Sodium valproate causes progressive weight gain of up to 5.8 kg throughout the duration of treatment [95], whereas carbamazepine, gabapentin, and pregabalin are associated with lesser degrees of weight gain. Weight gain due to these agents results from a variety of mechanisms, including direct appetite stimulation via alterations to leptin synthesis, hyperinsulinemia, and their sedative effects, which result in decreased physical activity [95, 96].

Antipsychotic therapy is also strongly associated with weight gain in the order of 2–17 kg over the course of treatment [97]. This is most commonly a feature of the atypical (second-generation) antipsychotic, particularly clozapine and olanzapine. Antipsychotic-induced weight gain correlates with a significant increase in appetite for energy-dense foods, involving central serotonergic, histamine, and catecholamine pathways regulating appetite and reward pathways [98].

Antidepressants as a class have a variable impact on weight gain. Tricyclic antidepressants (TCAs) and monoamine oxidase inhibitors (MAOIs) are most frequently associated with significant weight gain. Selective serotonin reuptake inhibitors (SSRIs) can often induce initial weight loss, but generally lead to weight gain in the longer term. The mechanism of antidepressant-induced weight gain appears to be increased appetite mediated via serotonergic pathways [99].

Toxins and endocrine disruptors

Adipose tissue can store toxins, which are mobilized following weight loss. For example, organochlorine compounds are implicated in decreasing basal metabolic rate and their storage is reduced following bariatric surgery [100]. Pesticides, flame retardants, plasticizers, and polychlorinated biphenyls (PCBs) have also been implicated in obesity in epidemiological and animal studies [101]. Potential mechanisms include inducing adipogenesis [102], altering sex hormone metabolism and thyroid hormone synthesis, and effects on fetal development [103].

From an epidemiological perspective, the decline in smoking prevalence since the 1970s corresponds to the increase in obesity rate, and it is thought that the weight gain associated with smoking cessation could account for approximately one-quarter to one-sixth of this increased prevalence [104]. Smoking is an established appetite suppressant, potentially mediated by the thermogenic effect and influence on eating behavior and resting metabolic rate of nicotine [105, 106]. Conversely, smoking cessation is associated with gender-specific effects on weight gain, with studies reporting weight gains of 3.8–4.4 and 2.8–5.0 kg for men and women, respectively [104, 107]. The weight gain is predominantly due to increased snacking. Predictive factors for weight gain following smoking cessation include younger age, lower socioeconomic status, previous heavy smoking, and genetics [105].

Neuroendocrine and behavioral regulation of energy homeostasis and the gut microbiome

Neuroendocrine and behavioral pathways

The relationship between energy intake, expenditure, and regulation of body weight is moderated not only by the above genetic, environmental, and behavioral factors but also by complex neuroendocrine feedback mechanisms that fundamentally seek to promote energy intake and protect against weight loss.

The hypothalamus is the central site for homeostatic regulation of body weight. It integrates peripheral homeostatic hormonal signals from the gastrointestinal tract (e.g. ghrelin, cholecystokinin, peptide YY, pancreatic polypeptide, and glucagon-like peptide 1 [GLP-1]), pancreas (insulin), and adipose tissue (leptin, adiponectin), with hedonic peripheral (e.g. leptin, ghrelin and insulin influence central dopaminergic and opioidergic pathways) and central reward pathways (cortex and reward circuits in the limbic system). The latter hedonic pathways strongly influence appetite behavior, particularly the consumption of energy-dense, highly palatable foods [108].

Arguably the key factor when considering regulation of body weight is that although weight loss can be readily achieved, maintenance of weight loss is inherently difficult owing to the above complex evolutionary counter-regulatory neuroendocrine mechanisms. These pathways are fundamentally protective against weight loss and promote weight regain by decreasing energy expenditure and influencing appetite regulation and fat storage [108]. A recent study demonstrated that by 1 year after initial weight loss, levels of the circulating mediators of appetite that encourage weight regain, such as leptin, peptide YY, cholecystokinin, insulin, ghrelin, gastric inhibitory polypeptide, and pancreatic polypeptide had not returned to their pre-weight loss levels, and increased hunger also persisted [109].

Endocrine feedback mechanisms regulating growth hormone (GH), thyroid hormone (thyroxine), gonadal and adrenal steroids (testosterone, estrogen, and adrenal androgens and glucocorticoids) are also critical in regulating weight gain. GH and thyroxine are predominantly responsible for regulating growth, while gonadal steroids during puberty alter the ratio and distribution of lean muscle mass to body fat: testosterone increases lean muscle mass and reduces visceral adiposity whereas estrogen has the opposite effect.

Gut microbiome

The role of the gut microbiome in regulating fat storage, obesity, and insulin resistance has become a burgeoning area of recent research. Obesity appears to be associated with alterations in the

ratio of the dominant gut microbiota, the Bacteroidetes and the Firmicutes [110]. It has been shown that colonization of germ-free mice with an "obese microbiota" results in a significantly greater increase in total body fat, despite an associated decrease in food consumption. This suggests that the obese microbiome has an increased capacity to obtain energy from the diet [111]. In animal studies, altering the gut microbiota via probiotic therapy has been shown to reduce fat mass and increase muscle mass, but does not impact overall body weight [111]. In humans, intervention studies assessing the role of probiotics (beneficial microorganisms) in weight loss suggest that *Lactobacillus gasseri* SBT 2055, *Lactobacillus rhamnosus* ATCC 53103, and the combination of *L. rhamnosus* ATCC 53102 and *Bifidobacterium lactis* Bb12 may reduce body weight and prevent weight gain in humans, potentially via effects on short-chain fatty acid production and low-grade inflammation that influence metabolism and affect body weight [112]. Additional information on the influence of the microbiome is diabetes is covered in Chapter 17.

Conclusions

This chapter has aimed to provide an overview of the multiple factors implicated in weight gain and obesity. As demonstrated, the regulation of energy intake and expenditure and consequently energy homeostasis is influenced by a complex interplay of genetic, environmental, neuroendocrine, and behavioral mechanisms operating at both individual and population levels. In consequence, addressing the current obesity epidemic requires multifaceted long-term strategies that target the multifactorial causes of obesity. In particular, a population perspective on the current drivers of weight gain requires policies that address the environmental context promoting excessive energy intake and sedentary lifestyle. From an individual standpoint, there is a need to conceptualize obesity as a chronic disease requiring long-term intervention and to develop treatment strategies that target the multiple complex counter-regulatory neuroendocrine mechanisms which continue to promote weight regain.

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3 Pathogenesis of Diabetes

10 Autoimmune Type 1 Diabetes

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Key points

- The prevalence and incidence of autoimmune type 1 diabetes mellitus (T1DM) continues to increase worldwide and the clinical onset tends to occur in younger children.
- Autoimmune T1DM is characterized by the appearance of a first β-cell autoantibody against either insulin (IAA) or GAD65 (GADA), or both, in early childhood.
- The etiopathophysiology of T1DM may be divided into three distinct stages: β-cell autoimmunity, asymptomatic loss of β-cell secretory capacity, and loss of β-cell function along with diabetes symptoms.
- Autoimmune T1DM results from a loss of immunological tolerance to β-cell autoantigens.
- HLA genes represent the strongest genetic determinants for the risk of both β-cell autoimmunity and T1DM.
- Environmental factors may trigger β-cell autoimmunity, accelerate the pathogenic process, or both.
- β-Cell destruction may occur prior to β-cell autoimmunity but the mechanism is not yet fully clear.
- β-Cell destruction occurs during the pathogenesis of β-cell autoimmunity mediated by cytotoxic T cells.
- Multiple β-cell autoantibodies (≥2) usually appear within 6–12 months following the appearance of the first autoantibody and markedly increase the risk for progression to T1DM.
- The appearance of either IA-2A, ZnT8A, or both, in IAA- or GADA-positive children is a strong marker of rapid progression to clinical onset of T1DM.
- The progressive destruction of β cells is likely to vary in intensity and duration, affecting the time of clinical diagnosis.

Introduction

The differentiation between the two main forms of diabetes mellitus, type 1 (previously known as insulin-dependent or juvenile-onset diabetes) and type 2 diabetes (non-insulin-dependent or adult-onset diabetes), has been deliberated for almost 50 years. In 1965, insulitis was rediscovered [1], supporting the view that autoimmune islet inflammation was associated with the etiopathology in type 1 diabetes mellitus (T1DM), a phenomenon absent in type 2 diabetes mellitus (T2DM) [2]. The evidence for islet autoimmunity was further supported during the last decade by the identification of cellular reactivity with islet autoantigens [3] and the association between T1DM and other organ-specific autoimmune disorders [4]. More importantly, long sought after antibodies against islet cells (ICAs) were finally detected in the sera of people with concomitant T1DM and autoimmune polyendocrine syndrome [5, 6]. At the same time, T1DM was found to be strongly associated with the human leukocyte antigen (HLA) [7]. It was also noted, however, that around 10% of adults classified with T2DM who were not achieving adequate glycaemic control with sulfonylurea treatment [8] were positive for ICA, a group of people now commonly known as having latent autoimmune diabetes of adults (LADA) [9]. Several genetic and autoimmune similarities are found between childhood T1DM and LADA; nevertheless, these two entities differ in other genetic and autoimmune processes [10]. Recent research, including studies of children followed from birth and extensive genetic studies, have resulted in a paradigm shift of the etiology and pathogenesis of type 1 diabetes [11–13]. In this chapter, we therefore summarize current knowledge of possible trigger(s) of β-cell autoimmunity (etiology) and factors affecting progression to clinical onset in individuals who have developed one or several β-cell autoantibodies (pathogenesis).

Autoimmune T1DM is characterized by the appearance of a first β-cell autoantibody against either insulin (IAA) or GAD65 (GADA), or both, in early childhood [11–13]. Rarely, the first islet autoantibody is directed against IA-2 (IA-2A) or ZnT8 (ZnT8A). These four biomarkers of T1DM (Table 10.1) are strong, since it has been found that the development of a first autoantibody (IAA or GADA) and the appearance of a second, a third, and often a fourth autoantibody will result in T1DM in 100% of subjects when followed for 20 years [11]. The epidemiology in different countries of β-cell autoantibodies in children or in the adult population is currently not known, as population screening for IAA, GADA, IA-2A, and ZnT8A is yet to be implemented.

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Table 10.1 Characteristics of β cell autoantigens and autoantibodies.

	GAD65	IA-2	Insulin	ZnT8
Chromosome	10p11	IA-2: 2q35-36 IA-2β: 7q36	11p15	8q24
Molecular weight (kD)	64	IA-2: 40 IA-2β: 37	5.8	67
Tissue specificity	Pancreas, neuron, ovary, testis, kidney	Neuroendocrine cells (pancreas, brain, pituitary)	β-cell specific	β-cell specific
Function	GABA production (an inhibitory neurotransmitter)	Not clear (lack enzymatic activity)	Regulates glucose metabolism	Zn^{2+} transport and accumulation in β-cell vesicles
Genetic association	DR3 - DQ2 DR4-DQ8	DRB1*0401	INS - VNTR, DR4	SLC30A8
Antibody abbreviation	GAD65Ab	IA-2Ab	IAA	ZnT8Ab
Standardized assay	RBA, ELISA	RBA	RBA	RBA
Sensitivity (%)	RBA: 80 ELISA:89	RBA: 70 ELISA: 65	RBA:>60	RBA: 50 (C terminal)
Specificity (%)	RBA:96 ELISA:98	RBA: 99 ELISA: 99	RBA: 95	RBA: 98 (C terminal)
Variation with age	Higher detection with increase age	Less with increasing age	Higher predictivity in children	Increasing predictivity with age
Variation with gender	Female preference if onset <10 years	Male preference	None	None

ELISA, enzyme linked immunosorbent assay; RBA, radiobinding assay.
Workshop sensitivity and specificity for GAD65Ab and IA-2Ab were from the Diabetes Antibody Standardization Program [70].
Diagnostic sensitivity at 95% diagnostic specificity for insulin autoantibodies (IAA) were from [71].

It remains to be determined in multiple populations whether the incidence of β-cell autoantibodies eventually equals that of T1DM.

Epidemiology

The epidemiology of T1DM is detailed in Chapter 3. Briefly, the incidence of T1DM varies 50–100-fold worldwide, with the highest rates occurring in individuals of northern European descent. Both sexes are equally affected in childhood, but men are affected more commonly in early adult life [14]. The incidence of childhood T1DM is rising rapidly in all populations, especially in the age group younger than 5 years, with a doubling time of less than 20 years in Europe [15]. The increasing incidence of T1DM suggests a major environmental contribution, but the role of specific pathogenic factors remains largely unsettled. The distinction between T1DM and T2DM can become blurred in later life, and the true lifetime incidence of the condition is therefore unknown.

In Europe, the highest rates of childhood diabetes are found in Scandinavia, with an incidence for children from birth to 14 years of age ranging from 57/100,000 per year in Finland to 4/100,000 in Macedonia [15, 16]. In the United States, the overall annual incidence in young people is about 19/100,000. Prevalence rates are strikingly different among ethnic groups living in the same geographic region, probably because of genetic differences in susceptibility to the disease. Early-onset diabetes carries a higher familial risk, and affected fathers are more likely to transmit the risk for T1DM to their offspring than affected mothers are, with risks being 6–9% and 1–3%, respectively[15, 16].

The SEARCH for Diabetes in Youth multicenter study (funded by the US Centers for Disease Control and Prevention and the National Institutes of Health) examined diabetes among children and adolescents in the United States [17]. During 2008–2009, an estimated 18,436 people younger than 20 years in the USA were newly diagnosed with T1DM annually, and 5089 people younger than 20 years were newly diagnosed with T2DM annually. The prevalence estimates indicate that there are almost 500,000 children aged under 15 years with T1DM worldwide, the largest numbers being in Europe (129,000) and North America (108,700). Countries with the highest estimated numbers of new cases annually were the USA (13,000), India (10,900), and Brazil (5000) [18].

Etiopathophysiology

The etiopathophysiology of T1DM may be divided into three distinct stages in genetically susceptible individuals (Figure 10.1). Individuals are born with HLA-DR-DQ genotypes that confer risk for T1DM. The next step is that the individual is exposed to one or more environmental factors that trigger the immune system to mount an autoimmune reaction towards pancreatic β-cell autoantigens. At present, the β-cell autoimmunity is reflected by the appearance of a first autoantibody to either insulin (IAA), GAD65 (GADA), or both of them simultaneously [12, 13]. The disease then progresses in three stages:

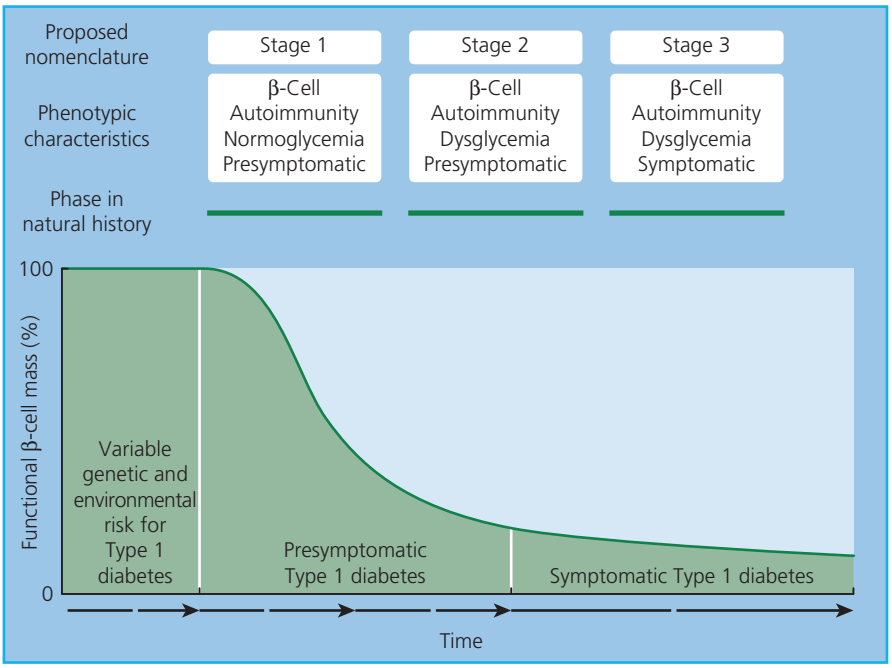

Figure 10.1 Schematic presentation of the early natural history of T1DM divided into three different disease stages.

Stage 1: Triggering of β-cell autoimmunity resulting in one or multiple β-cell autoantibodies associated with gradual β-cell destruction but no dysglycemia or symptoms of diabetes.

Stage 2: Loss of β-cell secretory function in autoantibody-positive individual. It may be manifested by a slowly increasing HbA_{1c} [19], loss of first-phase insulin release (FPIR) after intravenous glucose tolerance test (IVGTT), or reduced C-peptide levels, impaired glucose intolerance after an oral glucose tolerance test (OGTT) [20, 21], all referred to as dysglycemia, but still with no symptoms.

Stage 3: Loss of β-cell secretory capacity in β-cell autoantibody-positive individuals to the extent that symptoms of diabetes are discernible (Figure 10.1).

The continuing progress in the understanding of the natural history of T1DM will be dependent on several longitudinal studies starting from birth, aimed at detecting factors that predict (1) β-cell autoimmunity and (2) the clinical onset among β-cell autoantibody-positive individuals. The approach will permit both primary (prevention in the persons at genetic risk) and secondary (preventing diabetes onset in β-cell autoantibody-positive individuals) prevention or intervention (stop further loss of functional β cells after the clinical diagnosis).

Etiology

The etiology of T1DM is multifaceted and may be divided into genetic and environmental etiology and possible gene–environment interactions. Genetic susceptibility increases predisposition for a hypothetical trigger of β-cell autoimmunity (Figure 10.2). Genetic factors may also to contribute to either an accelerated β-cell failure in response to exogenous environmental factors such as obesity or to slowing down the process.

Genetic etiology

Longitudinal studies of newborns at increased genetic risk have demonstrated strong genetic association between HLA and the first β-cell autoantibody (Figure 10.2). IAA as a first islet autoantibody was strongly associated with HLA-DR4-DQ8. GADA as a first islet autoantibody was associated with HLA-DR3-DQ2 [12, 13]. The paradigm shift is that the primary association with HLA would be β-cell autoimmunity and not diabetes as such, as has been traditionally claimed since 1974 [7, 22, 23].

Throughout the years, the genetics of T1DM have been studied extensively despite the fact that the mode of inheritance remained uncertain. In persons with T1DM, the HLA genes represent almost 50% of the familial risk of T1DM [24]. Certain alleles of the HLA region, such as the HLA class II DR and DQ alleles, are mainly present in specific association with each other, a phenomenon known as linkage disequilibrium. The HLA association of T1DM is therefore often described by haplotype or genotype of the individual [25].

The genotype that confers the highest risk of T1DM is the heterozygosity of the two high-risk HLA class II haplotypes: DR3-DQ2 (*DRB1*03-DQA1*0501-B1*0201*) and DR4-DQ8 (*DRB1*04-DQA1*0301-B1*0302*) (Table 10.1) [25, 26]. One or both of these haplotypes were found in more than 95% of individuals with T1DM younger than 30 years but also in ~40–50% of the general population [26]. The concomitant inheritance of high-risk alleles and haplotypes appears to increase the risk of T1DM significantly through synergistic association of their single risks. For example, in persons with T1DM, DQ8 (*DQA1**

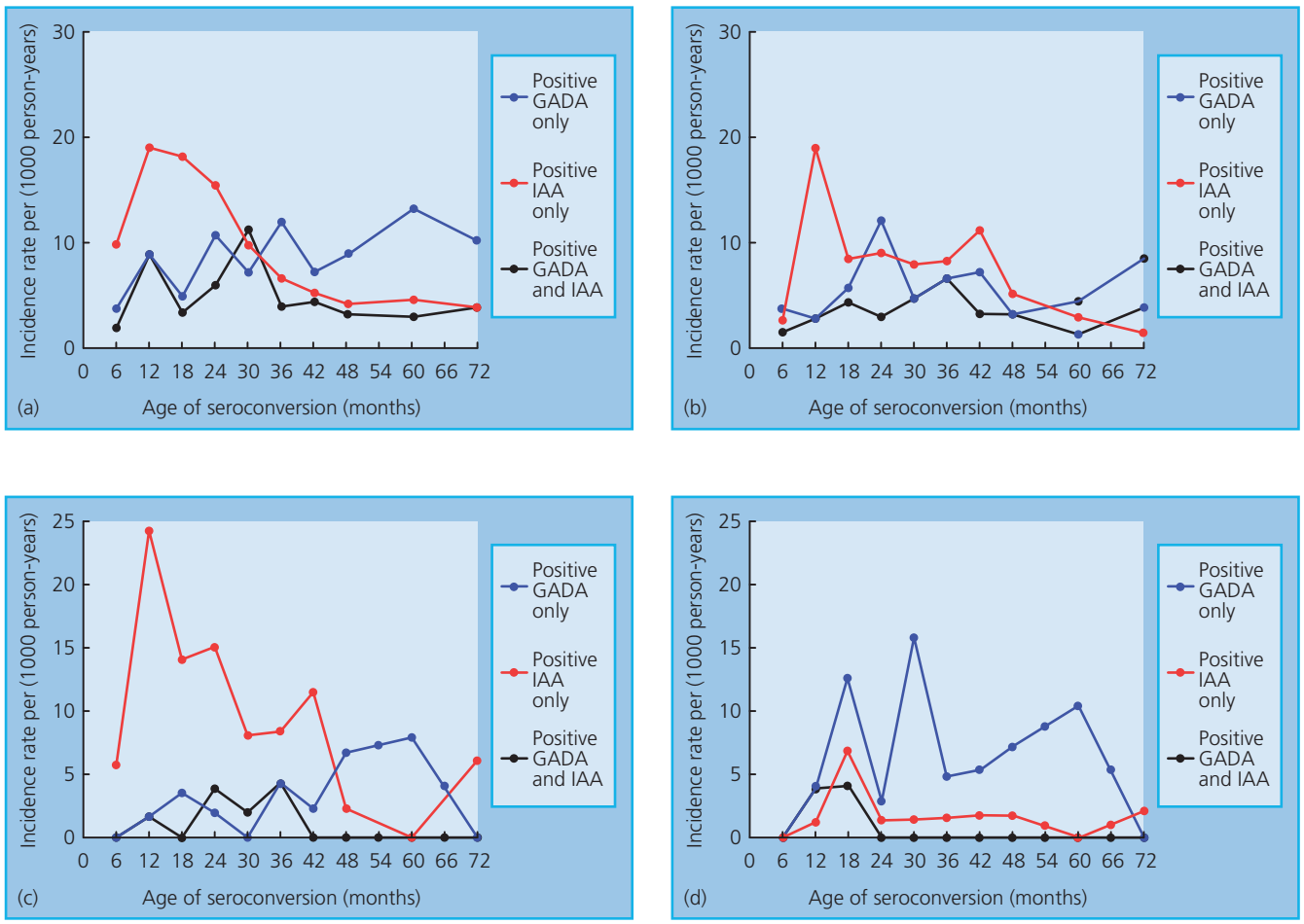

Figure 10.2 Incidence of the first islet autoantibody in relation to HLA-DQ genetic risk. In all four panels the red line represents IAA as the first β-cell autoantibody, the blue as GADA and the black simultaneously GADA and IAA. The Environmental Determinants of Diabetes in the Young (TEDDY) children in (a) were HLA-DQ2/8, in (b) HLA-DQ4/8, in (c) HLA-DQ8/8 and in (d) HLA-DQ 2/2. Source: Data from [12].

*0301-B1*0302*) is mostly inherited with certain variants of *DRB1*04*, especially *DRB1*0401*, *DRB1*0404*, and *DRB1*0402*, but not *DRB1*0403*, which has negative association [27] (Table 10.1). It cannot be excluded that the presence of the DR4-DQ8 haplotype in many people at the time of clinical diagnosis reflects the triggering of IAA by an environmental factor years before the clinical diagnosis of T1DM [11–13].

DQ2 (*DQA1*0501-B1*0201*) is mostly inherited with *DRB1*03* [25, 28]. Whereas certain alleles confer higher risk, such as *DQB1*0302*, *DRB1*03* and *DRB1*04:01*, which possesses an independent risk, others confer protection and may "neutralize" high-risk alleles when they are inherited together [29]. In this case, it cannot be excluded that one or more environmental factors triggered GADA as the first sign of β-cell autoimmunity years before the clinical diagnosis [12]. The most common protective haplotypes are DQ6 (*DQA1*0102-B1*0602* and *DQA1*0102-B1*0603*) and also *DQA1*0101-B1*0503* and *DQA1*0202-B1*0303* [25, 30]. Furthermore, other HLA class II (such as DPB1) and class I alleles have also been associated with T1DM risk and the search for new associations is continuing (for a review, see [28]).

The HLA-associated triggering of β-cell autoimmunity may reflect differences in the way in which children with DR4-DQ8 and DR3-DQ2 respond to virus infections, for example. It is well established that HLA-DR-DQ types are related to the immune response against virus or vaccines [31–34]. It cannot be excluded that the early sharing of environment contributes to the risk for β-cell autoimmunity, T1DM, or both, in families who are carriers of T1DM HLA risk haplotypes.

The sequencing of the entire human genome has made it possible in large genome-wide association studies (GWAS) to confirm the strong association with HLA but also to identify more than 50 non-HLA genes that are associated with the risk for T1DM (Figure 10.3) [35–38]. Their relative contribution to the risk in an individual is minor. It is notable that the T1DM non-HLA genetic factors are essentially all related to the function of immunocytes such T and B lymphocytes [39]. None of the T1DM genetic factors are shared with those identified in T2DM [40], which underscores the notion that T1DM and T2DM are two distinct entities with little genetic overlap. It cannot be excluded that some of the T1DM non-HLA genes are more

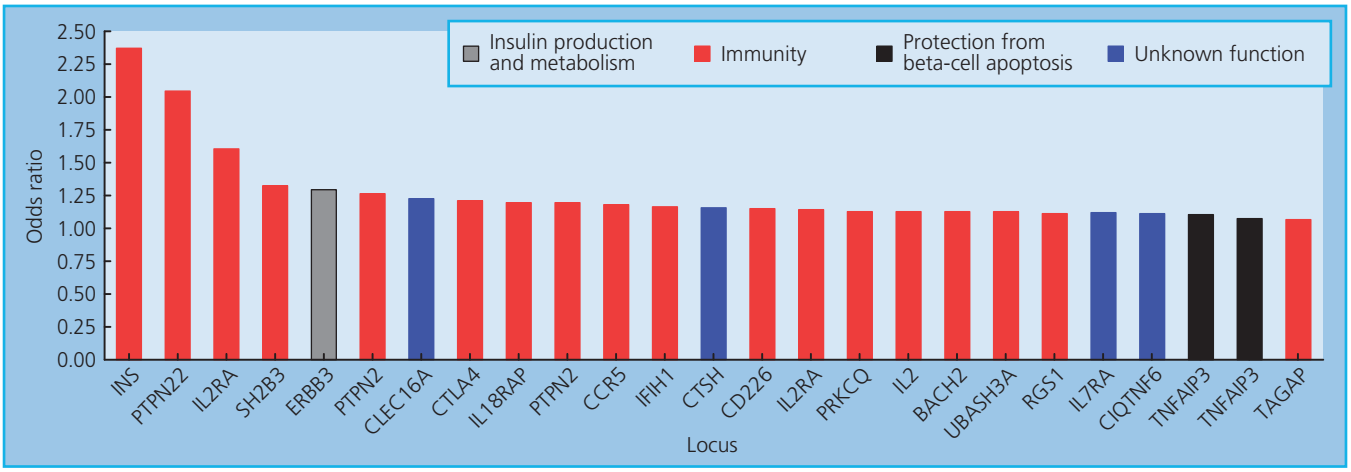

Figure 10.3 Putative genetic factors and proposed function for non-HLA type 1 diabetes genes determined by the Type 1 Diabetes Genetics Consortium.

important in triggering β-cell autoimmunity (stage 1) rather than diabetes [41] and that some contribute to stage 2 and stage 3 (Figure 10.1). Some genetic variants may slow (decelerate) or accelerate the disease pathogenesis during stages 2 and 3.

Environmental factors

Possible effects of environmental factors on the risk for T1DM will be considered in two parts. First, environmental factors may be important to the appearance of β-cell autoimmunity, i.e. to explain why children at increased genetic risk develop a first islet autoantibody. Recent data suggest that IAA only (Figure 10.2) in predominantly children with HLA DR4-DQ8 may appear as early as the first years of life but rarely after 5 years of age [12, 13]. Little is known about the role of environmental factors but enterovirus or upper respiratory virus are candidates [42, 43]. GADA only as the first islet autoantibody in children with DR3-DQ2 appears later, at 3–4 years of age (Figure 10.2). The incidence of GADA only seems to attain a steady state. It remains to be determined if environmental factors are able to trigger the appearance of GADA only. After the appearance of IAA only or GADA only, children may develop a second, third, or fourth islet autoantibody. The pattern of sequential appearance of islet autoantibodies is poorly understood and further studies are needed to determine the possible role of environmental factors when a child is progressing from a single autoantibody to multiple autoantibodies.

In children with multiple β-cell autoantibodies, it was reported that infection by Coxsackie virus accelerated progression to clinical onset [44]. It therefore cannot be excluded that a virus or perhaps other infections may have an accelerating effect on the disease pathogenesis, i.e. progression from β-cell autoimmunity to clinical onset of T1DM. It is speculated that the vast literature on infections prior to the clinical onset of T1DM is related to "accelerating infections" rather than to "triggering infections." Children with multiple β-cell autoantibodies are expected to have lost significant numbers of β cells. At the time of an infection, the insulin demand will increase and it is speculated that the conversion to clinical onset of T1DM may be explained by β-cell fatigue. Earlier literature on the concordance rate of 50–70% among identical twins [45, 46] and the seasonality of diabetes incidence may therefore be explained by an accelerating effect rather than by infections that may induce β-cell autoimmunity.

Environmental factors (Table 10.2) also include maternal factors [47], viral infections [48], dietary [49, 50] high birth weight and growth rate, psychological stress [51] and toxic substances [52]. The concurrent association of β-cell autoimmunity and factors increasing insulin resistance such as obesity and accelerated growth may boost the autoimmune destruction of β-cells [53]. The hygiene hypothesis proposes that better sanitation created a pathogen-free environment reducing the exposure to pathogens and their products. According to this hypothesis, the immune systems of children tend to be underdeveloped and therefore prone to autoimmune reactions. Additionally, it was also proposed that younger children received low-level antibodies from their mothers and, when exposed to infections such as enterovirus, it increased their T1DM risk [54]. It will be important in the future to distinguish environmental factors that trigger β-cell autoimmunity from those that accelerate the disease process in children with multiple islet autoantibodies.

Pathogenesis

Cellular autoimmunity

The genetic susceptibility of T1DM predisposes for a loss of immunological tolerance to certain β-cell autoantigens. The predisposition also include an eventual autoimmune killing of β cells perhaps explained by a disordered antigen presenting mechanism [55]. The HLA class II molecules are heterodimers that regulate the immune response and are expressed on the surface of APC such as macrophages. The heterodimer binds peptides generated intracellularly either from self-proteins or from exogenous antigens taken up by phagocytosis. The resulting

Table 10.2 The main putative environmental risk factors associated with T1DM.

Factor	Proposed effect mechanisms	Examples
Maternal factors	Triggering autoimmune response	Gestational infections
	Unknown	Higher maternal age
	Unknown	Higher birth order
	Unknown	ABO blood group incompatibility
Virus infections	Direct β-cell killing (cytolysis)	Mumps virus
	Mimicry of β-cell autoantigens	Rubella virus
	Autoreactive T- cell activation and subsequent β-cell killing	Enterovirus/Coxsackie B virus
	Inhibition of insulin production through inducing expression of HLA genes and interferon	Rotavirus
		Cytomegalovirus
		Epstein – Barr virus
Dietary factors	Triggering autoimmune response	Bovine milk/short breastfeeding
	Triggering autoimmune response	Cereals
	Unknown	High protein content
	Lack of possible protective effect of vitamin D	Vitamin D deficiency
Factors related to insulin sensitivity and/or resistance	Stressing β cells with excess demands "accelerator hypothesis"	Puberty
		High energy food
	Increased insulin resistance	Weight gain
Psychologic stress	Affect hypothalamic-pituitary-adrenal axis leading to disturbance in autonomic nervous system and autoimmune dysregulation	Stress during pregnancy
		Child – parent separation
		Behavioral deviances
		Difficult adaptation
Toxic substances	Direct damage to β cells	Alloxan
		Streptozocin
		Vacor

trimolecular complex represents the ligand for the T-cell receptor (TCR). The interaction between the trimolecular complex and the TCR activates the T lymphocyte. The HLA class II molecules on APC are responsible for antigen presentation to T-helper lymphocytes ($CD4^+$). Upon non-antigenic stimulation, macrophages from people with T1DM and the high-risk HLA DQB1*0201/*0302 genotype showed excessive secretion of proinflammatory cytokines and prostaglandin E_2 [56]. Cytokines may damage β cells directly or indirectly by activating other cells such as T and B lymphocytes [57]. The APC presenting β-cell autoantigens may thus be actively involved in the anti-self-autoimmune response that may result from failure to sustain self-recognition or from promoting an anti-self-response. APC, $CD4^+$ and $CD8^+$ T lymphocytes were all detected in pancreatic autopsies of people who died shortly after the onset of T1DM [58], indicating their role in insulitis. Autoreactive $CD8^+$ T lymphocytes may have the most significant role in the autoimmune destruction of β cells [59]. Natural killer (NK) cells [60] and also mast cells [61] may be found with abnormal activity and count. The detection of autoreactive T lymphocytes in insulitis and in the circulation at the time of diagnosis, in addition to the notion that immunosuppressive drugs such as cyclosporine or anti-CD3 monoclonal antibodies can temporarily abort disease progression, are all considered to support the role of cellular immunity in β-cell destruction [62].

The mechanism involved in β-cell destruction is not yet fully clear. Prior to stage 1 (Figure 10.1), one possible scenario is that β cells are first destroyed by an environmental factor such as a virus. The dying or dead β cell is next phagocytized by local dendritic cells (APC), which are then activated and migrate through the lymphatics to a pancreatic draining lymph node. The antigen presentation to and activation of $CD4^+$ T lymphocytes takes place in the lymph node to include activation of $CD8^+$ T lymphocytes specific for islet autoantigens. These β-cell autoantigen-specific $CD8^+$ T lymphocytes return to the blood circulation, eventually ending up in islets to destroy β cells. The β-cell killing will generate a new cycle of islet autoantigen presentation known as epitope spreading [57, 63]. $CD4^+CD25^+$ regulatory T lymphocytes are also thought to play an important role in the pathogenesis of T1DM as they may inhibit β-cell autoantigen-specific $CD4^+$ T lymphocytes [63, 64]. These cells express FOXp3 from the X chromosome and are important in the development of peripheral tolerance.

The identification of β-cell autoantigen-specific T lymphocytes has been challenging and the development of standardized assays of T lymphocytes specific to islet autoantigens (insulin, GAD65 and IA-2) is still difficult to achieve [62, 64]. Soluble HLA class II tetramer assays to assess autoantigen-specific T lymphocytes [65] and ELISPOT (enzyme-linked immunospot) [66] assays to measure cytokines of each T lymphocyte are tests to assess

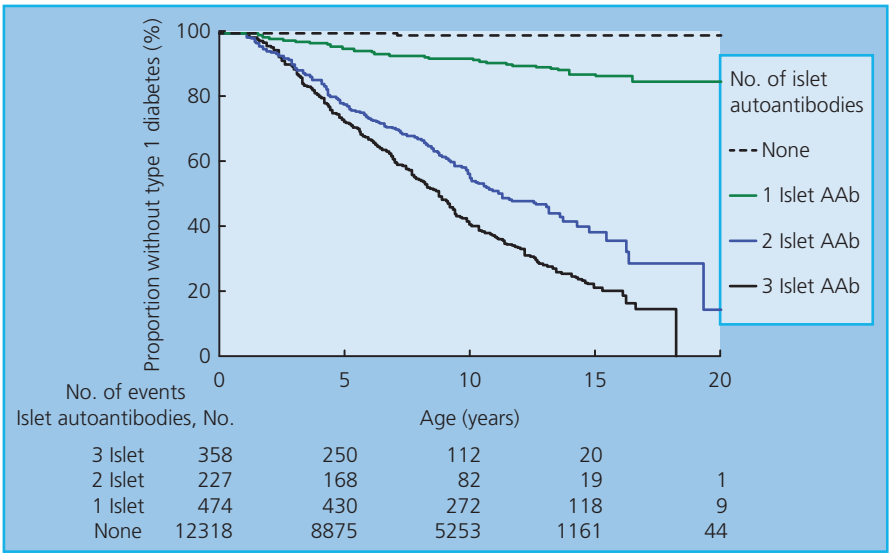

Figure 10.4 Probability of progression to symptomatic T1DM in relation to number of β-cell autoantibodies analyzed from birth. Source: Data from [11].

β-cell autoantigen T-lymphocyte reactivity. During β-cell autoimmunity prior to the clinical onset, these autoantigen-specific T lymphocytes may not be found in peripheral circulation; rather, they may accumulate in islets and are therefore difficult to detect [67]. More recent evidence indicates that B lymphocytes play a critical role in disease. This conclusion is based in part on the success of anti-CD20 (rituximab) therapy, which by broadly depleting B cells delays disease progression in people with new-onset T1DM [68, 69].

Humoral autoimmunity

Standardized assays specifically to detect autoantibodies to individual autoantigens are used to detect autoantibodies against GAD65, IA-2 [70], insulin [71], and ZnT8 (Table 10.1) [72, 73]. Multiple β-cell autoantibodies (≥2) usually appear within 6–12 months following the appearance of the first autoantibody (Figure 10.2) [13, 74] and markedly increase the risk for progression to T1DM (Figure 10.4). Nevertheless, some individuals develop transient islet autoantibodies but they are usually solitary and associated with lower risk [75], possibly because of the presence of protective genes [76]. One or more of these autoantibodies can be detected months to years before clinical onset in more than 95% of persons with newly diagnosed T1DM, even as early as the perinatal period [54]. Moreover, the detection of all four β-cell autoantibodies in addition to ICA demonstrate a diagnostic sensitivity of 91% [77].

Insulin autoantibodies

The most highly specific autoantigens of β cells are insulin and its precursor proinsulin. In 1983, using radioligand-binding assays, insulin autoantibodies (IAAs) were first identified in 50% of persons with newly diagnosed diabetes before initiating treatment with exogenous insulin [78]. IAAs, which react with both insulin and proinsulin, tend to be the earliest marker of islet autoimmunity [12, 13]. The predictive value for T1DM using IAAs alone appears to be related to age; it is higher among younger children, possibly related to a higher rate of β-cell destruction. IAAs are detectable in 90% of children who progress to T1DM before the age of 5 years compared with only 40–50% of adolescents older than 15 years (Table 10.1) [11].

DR4 is associated with a higher frequency of IAAs, which may be related to the linkage disequilibrium with the high-risk DQ8 haplotype [79]. IAAs are also associated with the insulin gene on chromosome 11p15 [80], where the number of tandem repeats (VNTRs) were found to be associated with T1DM whether IAAs were present or not.

Antibodies against exogenous insulin showed no correlation with IAA levels detected at the clinical onset of T1DM and appear to be independent of autoimmunity [81]; however, they do share some similar binding features [82]. Unlike IAAs, antibodies against exogenous insulin shows higher specificity, hence they may be detected using the enzyme-linked immunosorbent assay (ELISA) test, which does not predict T1DM [83]. The IAA fluid-phase radioimmunoassay shows high sensitivity and specificity to detect T1DM [71, 84]. Nevertheless, poor inter-laboratory concordance remains a problem that has delayed standardization of IAAs [71].

Glutamic acid decarboxylase autoantibodies

The enzyme glutamic acid decarboxylase (GAD) is found in neurons and β cells and produces γ-aminobutyric acid (GABA), which is a major inhibitory neurotransmitter. The 64K protein identified with GAD enzymatic activity after immunoprecipitation of human islets [85] was found to represent GAD65, not the previously known GAD67 isoform, which shares 65% of the GAD65 amino acid sequence [86]. Unlike GAD67 (encoded on chromosome 2q31.1), GAD65 (encoded on chromosome 10p11) is expressed primarily in human β cells [87].

Autoantibodies against GAD are most commonly to the GAD65 isoform (GADA), which were found in 70–80% of children with new-onset T1DM and 8% of T1DM first-degree relatives but also in about 1% of the general population [77, 88]. Unlike ICAs, GADA remain detectable for many years even after considerable loss of β-cell function [89]. Additionally, the GADA detection rate rises with age in new-onset T1DM (Figure 10.2). If the onset was before 10 years of age, some gender differences with female preference is observed [12]. Because GADA levels are persistent, more prevalent, and correlate well with plasma levels of C-peptide [90], they are currently considered good markers for both prediction and follow-up of β-cell dysfunction among individuals at risk.

GADA was the first islet autoantibody found to be associated with the high-risk HLA haplotype DR3-DQ2 (*DRB1*03-DQA1*0501-B1*0201*) [12, 13] Figure 10.2). Anti-idiotypic GADA were found to be markers that have lower frequency in T1DM and their absence was more predictive than the presence of GADA [91]. GADA can be detected with both radiobinding assays and ELISA, and these assays have been assessed and standardized in the Diabetes Antibody Standardization Program (DASP) [70]. The high and improved performance of these assays emphasizes the value of these autoantibodies in the prediction and classification of T1DM and also their value as screening tools in individuals at risk (Table 10.1).

Islet antigen-2 autoantibodies IA-2Ab and IA-2βAb

This autoantigen is a member of the plasma membrane protein tyrosine phosphatase family [92]. It is composed of two isoforms: IA-2 (formerly known as ICA512), which is a 40K protein encoded on chromosome 2, and IA-2β (phogrin), which is a 37K protein encoded on chromosome 7 (Table 10.1) [93]. The two isoforms share many common epitopes and are present in several neuroendocrine tissues in addition to pancreatic islets, with no clear function because they lack enzymatic activity.

The autoantibody reactivity of IA-2A is directed to the cytoplasmic portion of the autoantigen and the immunoreactivity in T1DM is directed against the C-terminal region of IA-2 [94]. IA-2A is detected in about 60–70% of people with new-onset T1DM and in less than 1% of the general population [30, 77]. IA-2A are often preceded by IAA, GADA, and ICA, respectively [12, 13], and the frequency decreases with increased age of onset [30]. This indicates that the predictive and screening abilities of IA-2A are more useful for younger children, especially when combined with IAA and GADA.

Using radiobinding assays to determine epitope-specific IA-2Ab/IA-2βAb among healthy siblings of children with T1DM, it was found that progression to T1DM was more common with autoantibodies to the juxtamembrane region of IA-2 (IA-2-JM-Ab) while IgE-IA-2A conferred protection even when IA-2-JM-Ab were positive [95]. Higher frequencies of IA-2A were found in association with *DRB1*0401* rather than with DQ8 [96]. Furthermore, persons with DQ2 had less association with IA-2A, indicating a role for additional mechanisms related to the HLA genetic component [30].

Assays to identify IA-2A were developed and standardized using radiobinding tests that can precipitate IA-2A and IA-2βA along with GADA. These assays have high levels of diagnostic sensitivity and specificity and were improved in subsequent DASP workshops [97]. Similarly, ELISAs combining IA-2A and GAD65A using biotin-labeled preparations were also standardized (Table 10.1) [97].

ZnT8 transporter (SLC30A8) autoantibodies ZnT8Ab

The zinc transporter (ZnT8 isoform-8 transporter) has developed into the fourth β-cell-specific autoantigen [72]. A polymorphism in the gene encoding this autoantigen, SLC30A8, is also associated with the risk of T2DM [98, 99]. ZnT8 is important for zinc–insulin crystallization and insulin secretion. It facilitates transport and accumulation of cytoplasmic zinc into the secretory vesicles of β cells. Inside these vesicles, insulin molecules are co-crystallized with two Zn^{2+} ions to form solid hexamers.

Nearly 60–80% of individuals with new-onset T1DM react positively to ZnT8A [77, 99, 100], which was detected in around 26% of people who were negative for GADA, IA-2A, and IAA [101]. Additionally, ZnT8A were also detected in 30% of persons with other autoimmune diseases associated with T1DM [72]. Being a target of humoral immunity in T1DM, the high β-cell specificity of ZnT8 is seen as an advantage over other non-specific β cell autoantigens such as GAD65 and IA-2. This high specificity and independence from other islet autoimmune markers, in addition to the fact that ZnT8A titers increase with age, all emphasize the value of ZnT8Ab in predicting T1DM, especially among older children. Detecting ZnT8 contributes to increasing the overall diagnostic sensitivity from 85.9 to 90.6%. ZnT8A showed the same sensitivity (61.1%) at disease onset as GADA (61.1%) and higher than IA-2A (53.7%), with only GADA showing much persistence in the long-term follow-up [102].

The polymorphic *SLC30A8* gene located on chromosome 8 encodes the ZnT8 [103]. This locus and other chromosome 8 loci have not been associated with T1DM risk as such but were associated with the risk of ZnT8A [99]. ZnT8A were found to react with the C-terminus of the autoantigen and variation at amino acid position 325 determines two important susceptibility markers of ZnT8A, which can be either arginine (ZnT8-R), tryptophan (ZnT8-W), or glutamine (ZnT8-Q) [99, 104]. Immunoprecipitation assays for ZnT8Ab were developed and fluid-phase radioassays for the C-terminus of ZnT8Ab were standardized and validated in the DASP workshop [73] (Table 10.1).

Candidate (minor) autoantigens

Several studies have reported associations of a group of molecules and substances with T1DM. This group included a wide variety of minor or candidate autoantigens that are thought to be associated with T1DM, β-cell autoimmunity, or both. Examples are ICA12/SOX13 [105], glima-38 [106], vesicle-associated

Table 10.3 Candidate minor β cell autoantigens.

Autoantigen	Molecular weight (kD)	Description	Autoantibody frequency
ICA12(SOX13)	—	SOX family protein present in pancreas, kidney and placenta. Anti-SOX-13-Ab found more in children	T1DM: 10–30% T2DM: 6–9% Healthy controls: 2–4%
Glima-38	38	Amphiphilic glycated β3-cell membrane protein. Specific expression on islet and neuron cells	New-onset T1DM: 19% Prediabetes phase: 14% Healthy controls: missing
VAMP2	12.6	β-cell secretory vesicles-related protein	T1DM: 21% Healthy controls: 4%
NPY	10.9	β-cell secretory vesicles-related protein	T1DM: 9% Healthy controls: 2%
CPH	43.4	Carboxypeptidase B-like glycoprotein present in islets and brain. Related to cleavage of insulin from proinsulin	ICA^+ relatives: 20% Healthy controls: missing
GLUT-2	55	Glucose transporter type 2 of β cells	New-onset T1DM: 32–80% Healthy controls: 6.6%
HSP 60	60	A "stress" protein which is thought to be produced and upregulated in response to cellular stress	T1DM: 15% Rheumatoid arthritis: 20% Healthy controls: 1.2%
Imogen 38	38	A protein found in β-cell mitochondria and to a lesser extent in α cells	No antibodies found
ICA 69	69	A peptide mainly present in islets and neuroendocrine, but also brain, kidney and lung	New-onset T1DM: 5–30% Healthy controls: 6% Rheumatoid arthritis 20%

membrane protein-2 (VAMP2) [107], neuropeptide Y [108], carboxypeptidase H [109], GLUT-2 [110], heat shock protein 60 [111], imogen 38 [112], ICA69 [113], INS-IGF2 [114, 115], and others (Table 10.3).

Pancreatic islet pathology before clinical diagnosis

During the period preceding the clinical onset, autoantibodies targeting specific β-cell autoantigens such as insulin, glutamic acid decarboxylase (GAD65), islet antigen-2 (IA-2), and zinc transporter (ZnT8) may be detectable for months to years before hyperglycemia becomes overt [11]. Autoimmune T1DM therefore results from a loss of immunological tolerance to β-cell autoantigens. The selective destruction of β cells implies specific mechanisms targeting these cells by autoimmune reactions. The process of β-cell killing seems not immediately to be associated with an infiltration by immune cells of the pancreatic islets [116, 117]. As the pathogenesis is progressing, more and more pancreatic islets are infiltrated by $CD4^+$ and $CD8^+$ T lymphocytes and macrophages, eventually leading to insulitis [1, 117]. It has been observed in IA-positive individuals that HLA Class I expression and also expression of INF-α were upregulated in pancreatic islets, but with no sign of a major mononuclear cell infiltration [58]. It has been assumed that the occurrence and number of islet autoantibodies were associated with insulitis [117]. Islet autoantibodies were detected among 62 (4%) individuals of 1507 pancreatic donors aged 25–60 years [117]. Although those 62 individuals also had HLA susceptibility, only two of them showed insulitis, indicating that the presence of islet autoantibodies was not a marker of insulitis. It needs to be established whether islet autoantibodies are more than biomarkers of β-cell destruction executed by $CD8^+$ T cells or if the cellular and humoral autoimmunity complement each other [117].

It has been widely claimed, based on autopsy studies, that around 80–90% of β cells are already lost at clinical onset [118]. Recent reanalysis of people who died soon after diagnosis, however, revealed that the level of β-cell loss required for hyperglycemia was age dependent, being about 40% in individuals aged 20 years [119]. Additionally, there are suggestions that β-cell regeneration may have taken place, contributing to the ~50% of viable β cells present at diagnosis [119]. The progressive destruction of β cells is likely to vary in intensity and duration depending on the age at diagnosis [120, 121].

Conclusions

Considerable progress has been made in the understanding of T1DM etiology and pathogenesis as it relates to the appearance of β-cell autoimmunity prior to the clinical onset of the disease. The development of standardized islet autoantibody tests (GADA, IA-2A, ZnT8A, and IAA) has made it possible to begin screening for people at risk to be included in clinical trials aimed at preserving residual β-cell function. Analyses of cell-mediated immunity need further development and standardization to be useful in clinical

trials. HLA-DQ on chromosome 6 remains the most important genetic factor for T1DM risk. It is well established that these HLA class II heterodimeric proteins are necessary but not sufficient for disease. Recent genome-wide association studies have provided a wide array of candidate factors to be explored for T1DM risk. We are still at a loss as to which environmental factors may be responsible for triggering β-cell autoimmunity and studies such as The Environmental Determinants of Diabetes in the Young (TEDDY) [12] are needed to test fully the multitude of candidate triggers.

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11 Other Disorders with Type 1 Phenotype

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Key points

- Persons with type 1 diabetes classically present early, require continuous insulin treatment, and carry autoimmune markers such as antibodies to glutamic acid decarboxylase (GAD).
- There are other types of diabetes with a type 1 phenotype due to heterogeneous etiologies, including maturity-onset diabetes of the young (MODY) and other forms of monogenic diabetes caused by mutations of mitochondria or amylin or pathways implicated in pancreatic β-cell function, latent autoimmune diabetes in adults (LADA), fulminant type 1 diabetes presenting with diabetic ketoacidosis after viral infections, and another form that reverts to a clinical course resembling type 2 diabetes after the initial ketotic presentation.
- Correctly diagnosing these disorders from a type 1 phenotype is clinically important owing to their different clinical courses, prognosis, and management.

Introduction

Classical type 1 diabetes mellitus is considered an autoimmune disease with pancreatic β-cell destruction. Those affected typically have onset of their disease at a young age with an acute presentation including diabetic ketoacidosis, requiring continuous insulin treatment [1]. However, with better understanding of the epidemiology and molecular mechanism of diabetes, clinical features such as the younger age of onset (e.g. less than 35 years old) or dependence on insulin treatment cannot adequately define the etiology of individuals presenting with hyperglycemia.

Furthermore, there are major ethnic differences in disease pattern in terms of presentation and natural progression. In white Europeans, over 90% of persons with diabetes diagnosed before the age of 35 years have type 1 disease [1]. By contrast, classical autoimmune type 1 diabetes with ketotic presentation is uncommon in non-white European populations [2–5]. Using as an example Hong Kong, which has a relatively homogeneous southern Chinese population leading an affluent lifestyle, fewer than 10% of adults presenting with diabetic ketoacidosis had autoimmune markers. Even among Hong Kong Chinese individuals with young onset of disease, only 10% had a classical type 1 diabetes presentation with antibodies to glutamic acid decarboxylase (GAD) [5]. Similar epidemiological findings have also been reported in other Asian populations in India, Malaysia, Singapore, and mainland China [7]. In most case series, 60–80% of white Europeans with type 1 diabetes had autoimmune markers such as autoantibodies to GAD and/or islet cell antigens (e.g. ICA-512). Despite the rarity of classical type 1 diabetes, 5–20% of young Asians with non-ketotic presentation had autoimmune markers with a wide range of insulin reserve. These findings suggest that latent autoimmune diabetes in adults (LADA) is not uncommon in young people with diabetes, especially those of Asian ethnicity, with considerable overlap between type 1 and type 2 diabetes phenotypes [6, 8] (Figure 11.1).

Our current understanding of the molecular pathways involved in the neogenesis, differentiation, and maturation of pancreatic β cells and also the intracellular signaling mechanisms leading to insulin synthesis, secretion, and processing are summarized in Figure 11.2. This large body of knowledge has provided the basis for the discovery and description of subtypes of diabetes with predominant β-cell failure due to causes other than autoimmunity, such as monogenic diabetes. Persons with monogenic diabetes often have young onset of disease and lean body mass. They may also have delayed presentation with complications due to the insidious nature of their symptoms [9, 10]. With the rising prevalence of young-onset diabetes, especially in developing countries [11], there is a need for healthcare providers to be aware of these non-classical presentations of "type 1 diabetes" characterized by insulin insufficiency, since they have important implications for clinical management and family screening.

Textbook of Diabetes, Fifth Edition. Edited by R. Holt, C. Cockram, A. Flyvbjerg and B. Goldstein.

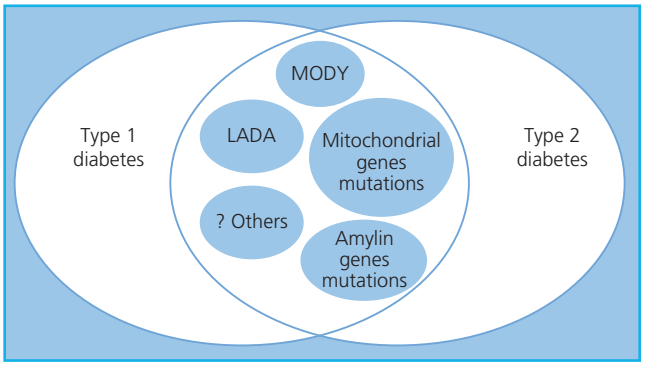


Figure 11.1 There are considerable overlaps between the phenotypes of type 1 and type 2 diabetes due to heterogeneous genetic and autoimmune etiologies. These include maturity-onset diabetes of the young (MODY), latent autoimmune diabetes in adults (LADA), and genetic variants affecting the insulin, amylin, and mitochondrial pathways. Other rare causes include fibrocalculous pancreatic diabetes and fulminant type 1 diabetes.

Atypical diabetes: heterogeneous etiologies of young-onset diabetes

In 1987, Winter et al. first described a cohort of 129 young African American with acute ketotic presentation, of whom 12 subsequently did not require insulin and followed a clinical course resembling type 2 diabetes [12]. Since then, a number of reports have shown that there is a poor correlation between the mode of presentation of hyperglycemia, clinical course, need for insulin treatment, and autoimmune status in different ethnic groups, including Asians [13–15]. Many of these individuals did not have human leukocyte antigen (HLA) genotypes or autoantibodies typical of autoimmune type 1 diabetes. Some individuals might be obese, with insulin resistance and glucotoxicity contributing to the initial ketotic presentation [16].

Monogenic diabetes due to genetic mutations encoding pathways implicated in insulin synthesis and secretion may lead to young-onset diabetes with atypical presentation. In young Chinese persons with diabetes, there is a higher prevalence of parental history of diabetes (32–47%), particularly a maternal history of diabetes, than in those with late onset of disease (12–19%) [10, 17, 18]. A progressively earlier age of onset of disease in successive generations has also been reported in some of these affected families [19]. These individuals may exhibit a mixed phenotype, including young age at diagnosis, insulinopenia, and normal body weight (as in type 1 diabetes), with a non-ketotic state typical of type 2 diabetes, despite a lack of insulin resistance and metabolic syndrome [20].

Monogenic diabetes

Maturity-onset diabetes of the young (MODY)

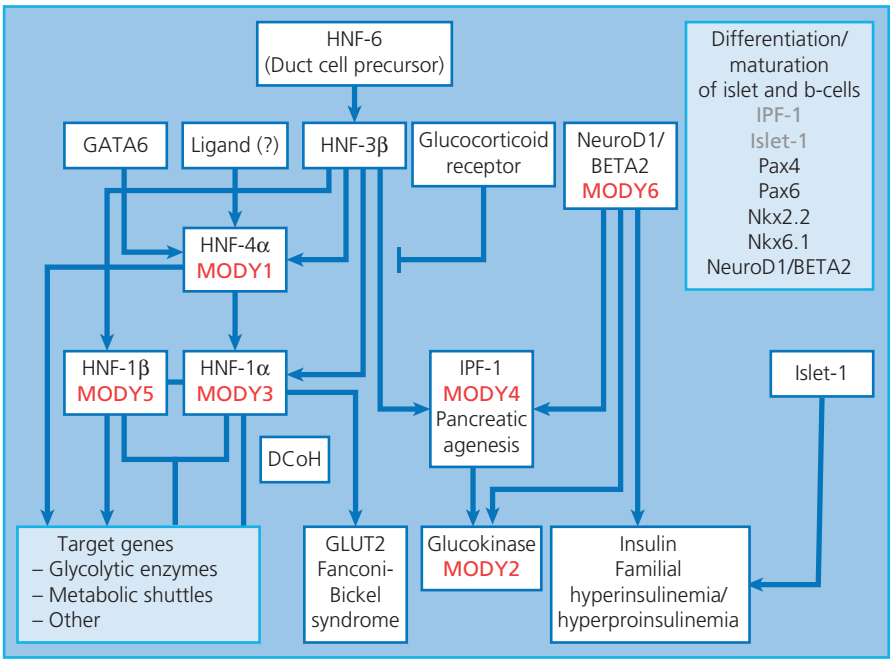
Persons with MODY typically present before the age of 25 years with a strong family history suggestive of autosomal dominant inheritance. Despite a non-ketotic mode of presentation, these individuals often have features of abnormal pancreatic β-cell function. Some people with MODY experience a rapid deterioration in glycemic control after initial presentation whereas others experience mild hyperglycemia and do not require insulin, despite having a long duration of disease.

To date, several subtypes of MODY have been reported (Chapter 18). These include mutations of transcription factors: *MODY 1*, hepatic nuclear factor (HNF) 4α; *MODY 3*, HNF-1α or transcription factor 1 (TCF1); *MODY 4*, insulin promotion factor 1 (IPF1); *MODY 5*, HNF-1β or transcription factor 2 (TCF2); *MODY 6*, neurogenic differentiation 1 (NeuroD1); and *MODY 7*, carboxyl ester lipase (CEL) and glucokinase, which is the glucose sensor of the pancreatic β cells (*MODY 2*). Transcription factors play key roles in pancreatic development, including differentiation and proliferation of β cells (Figure 11.2a). While genetic mutations in transcription factors typically cause significant insulin insufficiency and hyperglycemia, common polymorphisms of some of these transcription factors, e.g. HNF-1α [21], HNF-4α [22], and HNF-1β [23], have also been shown to be associated with increased risk of diabetes or metabolic traits that may interact with other genetic or environmental/lifestyle factors to give rise to overt diabetes. Interestingly, single-nucleotide polymorphisms in HNF-4α were associated with increased risk for type 2 diabetes in East and South Asians in genome-wide association studies [24, 25].

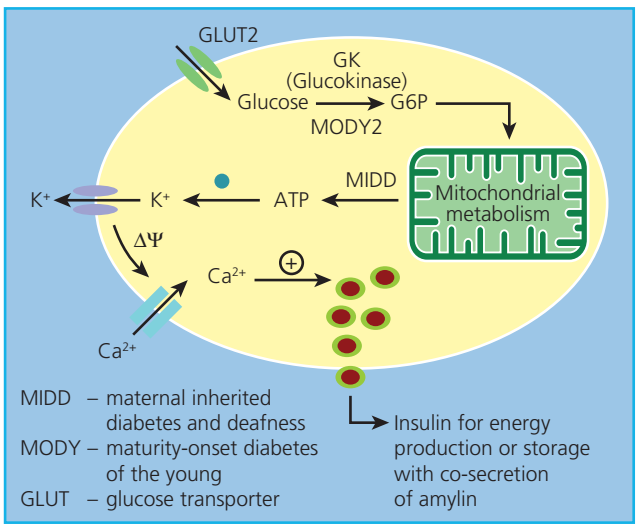
Over 80% of white European persons with classical MODY (i.e. age of onset less than 25 years with autosomal pattern of inheritance) have been reported to have mutations in HNF-1α or glucokinase, whereas other MODY subtypes (HNF-4α, HNF-1β and IPF-1 mutations) were less common [26]. There are clearly interethnic differences in MODY mutations. The frequencies of HNF-1α mutations ranged from 25 to 50% in French [27], 36% in German [28], 13–18% in British [29], 8% in Japanese [30], and 5% in Chinese people [9], although the selection criteria of index cases may influence these figures. In unrelated young Chinese people with type 2 diabetes, only 5–10% were found to have glucokinase or HNF-1α mutations [13, 31, 32]. This suggests that there may be other unidentified MODY genes in non-white European ethnic groups.

Given the mixed phenotypes, it is a clinical challenge to distinguish MODY from the large numbers of people with type 1 or young-onset type 2 diabetes. The costs of genetic analysis prohibit widespread screening for mutations in persons with diabetes. In 2008, a consensus group recommended clinical criteria for MODY testing that included onset of diabetes before age 25 years, parental history of diabetes, non-insulin dependence (for HNF-1α and HNF-4α MODY), and fasting plasma glucose of 5.5–8.0 and HbA_{1c} <8% (for GCK MODY) [33]. Although these criteria have high specificity, they have low sensitivity with other forms of familial monogenic diabetes yet to be discovered.

Extending the screening criteria to, for example, those diagnosed under the age of 30 years or with C-peptide positivity within 3 years of diagnosis (random or glucagon-stimulated C-peptide ≥0.2 nmol/L) may identify additional cases that were



(a)



(b)

Figure 11.2 (a) The cascade of transcription factors involved in pancreatic development and also neogenesis, differentiation, and maturation of pancreatic β cells. Maturity-onset diabetes of the young (MODY) includes subtypes with mutations in transcription factors, namely MODY 1 with mutations of hepatic nuclear factor (HNF-4α); MODY 3, HNF-1α; MODY 4, insulin promotion factor (IDF-1); MODY 5, HNF-1β; MODY 6, NeuroD1 (neurogenic differentiation 1); and MODY 7, carboxyl ester lipase (CEL), and also glucokinase, which is the glucose sensor of the pancreatic β cells (MODY 2). There are also involvement and interactions of glucose transporter 2 (GLUT-2) and endodermal factor, including GATA and various important genes and transcription factor governing the differentiation and maturation of pancreatic islet and β cells. These include Pax genes family and genes encoding the homeodomain transcription factors Nkx 2.2 and Nkx 6.1. In the Southern Indian population, interaction of the NeuroD1, neurogenin-3 (Neurog3), and HNF-1α genes has been observed to have a combined effect in controlling islet cell development and insulin secreting, thus contributing to the overall glucose tolerance [106]. (b) The multiple steps involved in regulation of insulin secretion commencing with sensing of ambient blood glucose level by GLUT-2, glycolysis by glucokinase (GK), and ATP production by mitochondria. The generated ATP particles then close the potassium channel, leading to membrane depolarization and opening of calcium channels. The intracellular calcium influx is associated with translocation of insulin- and amylin-containing vesicles to the cellular surface for extracytosis. During these processes, transcription factors are also activated, resulting in insulin gene transcription and production to replenish the insulin-containing vesicles and maintain continuous insulin secretion.

previously misdiagnosed [34]. Alternative biomarkers may help to distinguish MODY from other diabetes subtypes. For example, common variants near the HNF-1α gene have been shown to influence C-reactive protein (CRP) levels in healthy populations [35]. Low levels of high-sensitivity CRP (hsCRP) were found to distinguish HNF-1α MODY from type 1 and type 2 diabetes and increased the sensitivity of diagnosis up to 90% when combined with clinical criteria [36].

Accurate diagnosis of MODY has implications for choice of treatment. MODY is characterized by mild fasting hyperglycemia and does not necessitate treatment while HNF-4α and HNF-1α MODY are sensitive to sulfonylureas [37]. That said, many individuals with MODY may eventually require insulin with progressive β-cell failure due to factors such as aging, glucolipotoxicity, and inflammation. Although persons with some forms of MODY (e.g. *MODY 2*) show a mild clinical course and rarely develop complications, other forms of MODY may be associated with severe insulin insufficiency and complications often due to the late presentation and/or delayed use of insulin [10]. In light of the potential long duration of disease, young persons with diabetes are more prone to develop microvascular complications than those with late onset of disease [38], thus emphasizing the importance of family screening.

Furthermore, heterogeneous mutations in these transcription factors can be expressed sequentially in renal tubules with possible roles in various stages of their development [39]. Thus,

individuals with MODY may have heterogeneous phenotypes with metabolic and renal manifestations. Those with *MODY 3* due to mutations in HNF-1α were found to have a low renal threshold for glucose [40] whereas those with *MODY 5* due to mutations in HNF-1β may have mild diabetes, but increased susceptibility to severe renal disease and other urogenital malformations [41]. In a consecutive unrelated cohort consisting of 74 young Chinese persons with type 2 diabetes with nephropathy, a novel missense genetic variant in exon 3 (E260D, GAG→GAC) of the HNF-1β gene was identified. Extended family analysis revealed that four other siblings carrying this variant with heterogeneity in clinical presentation included one member with uncomplicated diabetes, one with impaired glucose tolerance, and one with microalbuminuria with normal glucose tolerance. A silent polymorphism Q378Q was identified in another unrelated person in this study. Although these findings will need replication in independent and larger cohorts, the phenotypic heterogeneity associated with these genetic variants is noteworthy [42].

Mitochondrial gene mutations

Mitochondria are important intracellular organelles in the maintenance of glucose homeostasis and energy balance. Mitochondria have their own genome and, unlike nuclear DNA, which is protected by histones, mitochondrial DNA is more vulnerable to oxidative stress and environmental toxins. Superoxide radicals generated by the mitochondrial respiratory chain are a major source of damage to mitochondrial DNA. Aged individuals with a positive family history of diabetes have a high frequency of mitochondrial mutations [43]. Owing to its maternal inheritance, mitochondrial DNA is a well-known cause of a subtype of maternally inherited diabetes mellitus [44].

In 1992, an A3243G mutation in the mitochondrial DNA coding for $tRNA^{Leu(UUR)}$ (mt3243) was first reported [45]. This form of diabetes was found in persons with both type 1 and type 2 diabetes and was characterized by maternal inheritance and deafness [45]. In a random cohort of Chinese individuals with diabetes, 1–3% had this mutation with either a type 1 or type 2 clinical course [46–48]. Other point mutations associated with increased risk of diabetes include sites at 3316, 3394, and 14577 and also deletion and rearrangement in mitochondrial DNA [43].

In keeping with its candidacy as a "thrifty gene," the frequency of a common polymorphism of the mitochondrial DNA (T16189C) is higher in Chinese people with metabolic syndrome than in those without (44% versus 33%), after adjustment for age and body mass index (BMI) [49]. In a meta-analysis, Asian people without diabetes had a higher frequency of the 16189C variant than their European counterparts (31.0% versus 9.2%) [50]. Despite negative reports in European populations [50], there are consistent data showing the risk association of the 16189C variant with type 2 diabetes in Asians [51, 52].

Amylin gene mutations

Amylin, a 37 amino acid polypeptide, is co-secreted with insulin by pancreatic β cells. It is the principal constituent of the amyloid deposits in the islets of Langerhans in type 2 diabetes [53, 54]. In autopsy series, pancreatic amyloidosis was associated with β-cell loss in both European and Chinese people [55–57]. It is now evident that the formation of intracellular islet amyloid polypeptide (IAPP) oligomers may contribute to pancreatic β-cell loss and progressive hyperglycemia [54]. Changes in metabolic milieu or genetic variants encoding proteins involved in amylin metabolism may lead to structural changes of amylin and increased oligomerization with β-cell death [58].

An S20G variant of the amylin gene has been shown to enhance cytotoxicity in transfected COS-1 cells and amyloidogenicity *in vitro* [59, 60]. This genetic variant is found in 2–3% of Japanese, Chinese, and Pacific Islanders with diabetes [9, 59, 61–64]. In Taiwanese Chinese, normoglycemic carriers of S20G variant had reduced early-phase insulin secretion [65]. However, cosegregation findings in family studies of S20G variant are inconclusive, suggesting that it is likely to be a risk-modifying factor rather than a major diabetes gene [9, 59, 65].

Other genetic mutations affecting pancreatic β-cell function

Genetic variants of transcription factors implicated in pancreatic β-cell development, structure, and function, such as Pax6, Nkx2-2, Nkx6-1, and NEUROG3, have also been reported in persons with type 1 or type 2 diabetes [66]. The Pax-4 gene is important for the differentiation of pancreatic β cells [67]; however, mutations in Pax4 have only been associated with monogenic diabetes in a few Asian families [68]. Recently, genome-wide analyses reported novel loci near Pax4 that may be associated with increased type 2 diabetes susceptibility in Chinese populations [69].

The pancreatic β-cell ATP-sensitive K^+ channels (K_{ATP} channels) comprise two subunits, the inwardly rectifying potassium channel Kir6.2 and the sulfonylurea receptor SUR1. This transmembrane channel plays an important regulatory role in insulin secretion (Figure 11.2b). Genetic variants encoding the K_{ATP} channel subunits Kir6.2 (KCNJ11) and SUR1 (ABCC8) are associated with reduced insulin secretion and diabetes in different ethnic populations [70–75] including Asians [66]. In the recent genome-wide association studies, polymorphisms encoding components of these K_{ATP} channels such as KCNJ11 and KCNQ1 have also been found to be associated with a 20–30% increased risk of diabetes in European and Asian populations [76, 77]. Additional information on genetic determinants of type 2 diabetes phenotypes is covered in Chapter 14.

Latent autoimmune diabetes in adults (LADA)

Autoantibodies to GAD are suggested to be sensitive markers of type 1 diabetes in white Europeans [13], although they can also be detected in individuals with type 2 diabetes such as those with LADA. In the UK Prospective Diabetes Study (UKPDS), ~10% of persons with type 2 diabetes had anti-GAD antibodies, the majority of whom eventually progressed to insulin dependence [78, 79].

Reports from different ethnic groups suggest an estimated 10% prevalence of LADA in populations with diabetes [78–80]. In Asians, 10–50% of persons with diabetes with acute or early onset of disease had anti-GAD antibodies depending on selection criteria of clinical definition, age at diagnosis, and assay methodologies [2, 6, 13, 81].

LADA is a slowly progressive form of autoimmune disease causing diabetes and is characterized by the presence of serum autoantibodies to pancreatic antigens [82, 83]. Similar to those with type 1 diabetes, individuals with LADA often carry other autoantibodies associated with celiac disease and adrenal and thyroid disorders [84, 85]. Hence it is plausible that LADA represents one end of a continuum of autoimmune diabetes with classical type 1 diabetes occupying the other end of the spectrum [86].

The nomenclature for this subtype of diabetes has been confusing, including type 2 diabetes with islet autoantibodies, slowly progressive insulin-dependent diabetes mellitus [87], type one-and-a-half diabetes [88, 89], latent autoimmune diabetes in children (LADC) [90], latent autoimmune diabetes in the young (LADY) [91], autoimmune diabetes [92], and autoimmune diabetes in adults with slowly progressive β-cell failure (ADASP) [80], although LADA remains the most commonly used term. The World Health Organization (WHO) and American Diabetes Association (ADA) acknowledged LADA as a slowly progressive form of type 1 diabetes [93, 94].

The correct diagnosis of LADA is clinically important since early use of insulin instead of sulfonylurea may prevent or reduce the rate of deterioration of β-cell function in these young persons with diabetes [95]. In individuals with LADA, impaired β-cell response is evident at diagnosis and early use of insulin may reduce the adverse effects of glucotoxicity on β cells [80, 92]. Apart from high clinical suspicions, HLA studies may distinguish LADA from classical type 1 diabetes. In white European populations, LADA is associated with HLA DQA1-DQB1*0102(3)-*0602(3)/X, which is uncommon in persons with typical type 1 diabetes [96].

Other subtypes of diabetes with type 1 phenotype

In 2000, a novel subtype of type 1 diabetes, known as fulminant type 1 diabetes in Japan, was reported [97]. Individuals with fulminant type 1 diabetes were characterized by a remarkably abrupt onset, absence of insulitis, non-autoimmune nature with negative autoantibodies, elevated pancreatic enzyme concentrations, and association with HLA haplotypes [97–99]. Since then, increasing numbers of cases have been reported in Japan and a nationwide survey found that ~20% of persons with type 1 diabetes in Japan indeed have fulminant type 1 diabetes [100]. Sporadic cases have also been reported in other Asian countries, including Korea, the Philippines, and China [98]. The pathogenesis of this new subtype of type 1 diabetes is not fully understood, with possible involvement of both genetic predisposition and viral infection in which antiviral immune responses lead to pancreatic destruction [98]. Diagnostic criteria were established by the Japan Diabetes Society [101] and intensive insulin therapy is the standard therapy.

In India, type 2 diabetes in youth often overlaps with monogenic forms of diabetes, fibrocalculous pancreatic diabetes, and diabetes associated with malnourishment, all of which are ketosis-resistant forms of youth-onset diabetes [102]. In Indian people with tropical calcific pancreatitis, the loss of endocrine function accompanying the exocrine damage may be an additional factor contributing to the clinical manifestation of diabetes in the presence of other stressors [103]. Using pancreatic specimens, Asian researchers have reported significant correlations between BMI and a relatively low volume of β cells [104], with amyloidosis, inflammation, and fibrosis as common pathological features [105].

Conclusion

Until recently, autoimmune type 1 diabetes was considered to be the predominant form of diabetes in children and young adults. With a better understanding of the pathogenesis of diabetes, it is now recognized that genetic or acquired factors that affect the pancreatic β-cell structure and function and also associated mechanisms such as amylin deposition and mitochrondrial damage may give rise to a broad range of clinical manifestations with considerable overlap between type 1 and type 2 phenotypes. Detailed medical history taking (e.g. family history of diabetes, mode of presentation, exposure to infection), a complete physical examination (e.g. body leanness, microvascular complications, metabolic syndrome, and associated cardiovascular risk factors), and the use of appropriate laboratory testing (e.g. hsCRP, autoantibodies against pancreatic antigens, and genetic markers) may help clinicians refine the diagnosis. This will help to guide correctly the treatment of these individuals, who are often young, with long disease duration, and with a high risk for complications of their diabetes.

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12 Abnormalities of Insulin Secretion and β-Cell Defects in Type 2 Diabetes

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Key points

- Type 2 diabetes mellitus (T2DM) is a heterogeneous, progressive disease due to the interaction of genetic and environmental factors, which adversely affect β-cell function and tissue insulin sensitivity.
- Physiological regulation of insulin secretion is controlled through a sophisticated integrated process encompassing finely tuned feedback mechanisms between the β cell, plasma glucose and other nutrient levels, insulin sensitivity, incretin hormones, neuropeptides, and neuronal control.
- β-Cell abnormalities are the main determinant of the rate of progression of T2DM. Worsening of the ability of the β cells to compensate for existing tissue insulin resistance sets the rate of progression of the disease.
- A predisposing genetic background is the most likely explanation for the evidence provided by multiple studies that β-cell function is altered well before the onset of overt T2DM.
- In predisposed normoglycemic individuals, loss of first-phase insulin secretion and loss of glucose sensitivity, i.e. the ability of the β cells to sense and respond properly to changes in glucose concentrations, represent the earliest abnormalities of β-cell function.
- An apparent reduction in β-cell volume of up to 60% has been found in people with prediabetes, with a further reduction in individuals with overt diabetes. The decrease in β-cell mass is the result of an increased rate of apoptosis, autophagy, and dedifferentiation. The increased β-cell death occurs without a compensatory increase in β-cell replication owing, at least in part, to the limited regenerative capacity of adult human β cells.
- Multiple factors contribute to the progressive loss of β-cell function and β-cell mass, including the characteristic alterations of the metabolic milieu of T2DM, i.e. hyperglycemia, hyperlipidemia, chronic β-cell stimulation, and impaired incretin effect.
- All factors that accelerate the decreased number and function of β cells promote common damage pathways, including oxidative stress, endoplasmic reticulum stress, inflammation, immune system activation, and amyloid deposition. These factors impair both the function and the survival of β cells, although abnormalities of β-cell function seem to be predominant compared with the reduction in the number of insulin-secreting cells.
- Preserving β-cell function is key to ensuring long-term glycemic control in people with T2DM.

Introduction

Type 2 diabetes mellitus (T2DM) is a complex, progressive disease. In the past 40 years or so, a number of alterations involving different tissues have been identified as contributing to the development and progression of hyperglycemia and concomitant metabolic disorders [1, 2]. Of the many pathogenic mechanisms, insulin resistance and impaired β-cell function remain the hallmarks of the condition. Insulin resistance is almost universally present in people with T2DM and it is already apparent in predisposed individuals. However, normal glucose tolerance is maintained in the face of insulin resistance provided that the β cell remains capable of compensating for the increased secretory demand. This simple observation highlights how the defect of insulin secretion plays a central role in the development of glucose intolerance, conversion to diabetes, and progression of the disease. Insulin secretion, indeed, is key to the maintenance of glucose homeostasis.

Physiological insulin secretion

Insulin is secreted from the β cells embedded in the islets of Langerhans of the pancreas, where they account for up to 60% of the entire islet cell population. The total weight of β cells in an adult of normal weight does not exceed 1 g. This minute amount of β cells contains sufficient insulin to ensure up to 8–10 days' supply of insulin [3]. Insulin is the key hormone maintaining

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daily plasma glucose concentration within a tight range in spite of wide fluctuations in carbohydrate supply (i.e. food ingestion) and demand (e.g. resting conditions vs. physical activity). This implies a tightly regulated, dynamic and rapidly acting feedback between insulin secretion and plasma glucose concentration and also adaptation to insulin sensitivity [4].

Glucose is actively transported inside the β cell in a linear manner with plasma glucose levels through the activity of glucose transporter 2 (GLUT-2). Once inside the cell, glucose is promptly phosphorylated by glucokinase, allowing its entry into the glycolytic pathway leading to generation of adenosine triphosphate (ATP), the main driver of glucose-induced insulin secretion. Increased cytosolic ATP levels cause the closure of ATP-sensitive K^+ channels and depolarization of the plasma membrane, causing the opening of the voltage-dependent Ca^{2+} channels and Ca^{2+} influx. The rise in intracellular Ca^{2+} concentration triggers the exocytosis of insulin granules and the release of insulin (Figure 12.1).

Insulin secretion in response to glucose is biphasic in nature with a short-lasting (a few minutes) first-phase increase in insulin secretion followed by a more sustained second phase increase, which lasts as long as the glucose level remains elevated [5, 6]. This pattern can be clearly appreciated using the hyperglycemic clamp technique depicted in Figure 12.2 [7]. The biphasic response of insulin secretion is believed to reflect the dynamics of spatially and functionally distinct intracellular insulin granule pools. According to this view, first-phase insulin secretion reflects fusion to the cell membrane of predocked granules from a readily releasable granule pool [8]. This pool accounts for no more than 5% of the total granules in the cell. The second-phase involves the recruitment of granules from a more distant and larger reserve pool and stimulation of *de novo* insulin synthesis [9].

Insulin is secreted into the portal vein, exerting an immediate biological action on the liver. In the fasting state, the portal levels of insulin limit the supply of glucose from the liver into the systemic circulation to match the need of glucose-dependent tissues, primarily the central and peripheral nervous system and red blood cells. Basal insulin secretion is characterized by rapid oscillations with a 3–4 min frequency [10]. In the absorptive state, insulin is secreted in proportion to the increments in plasma

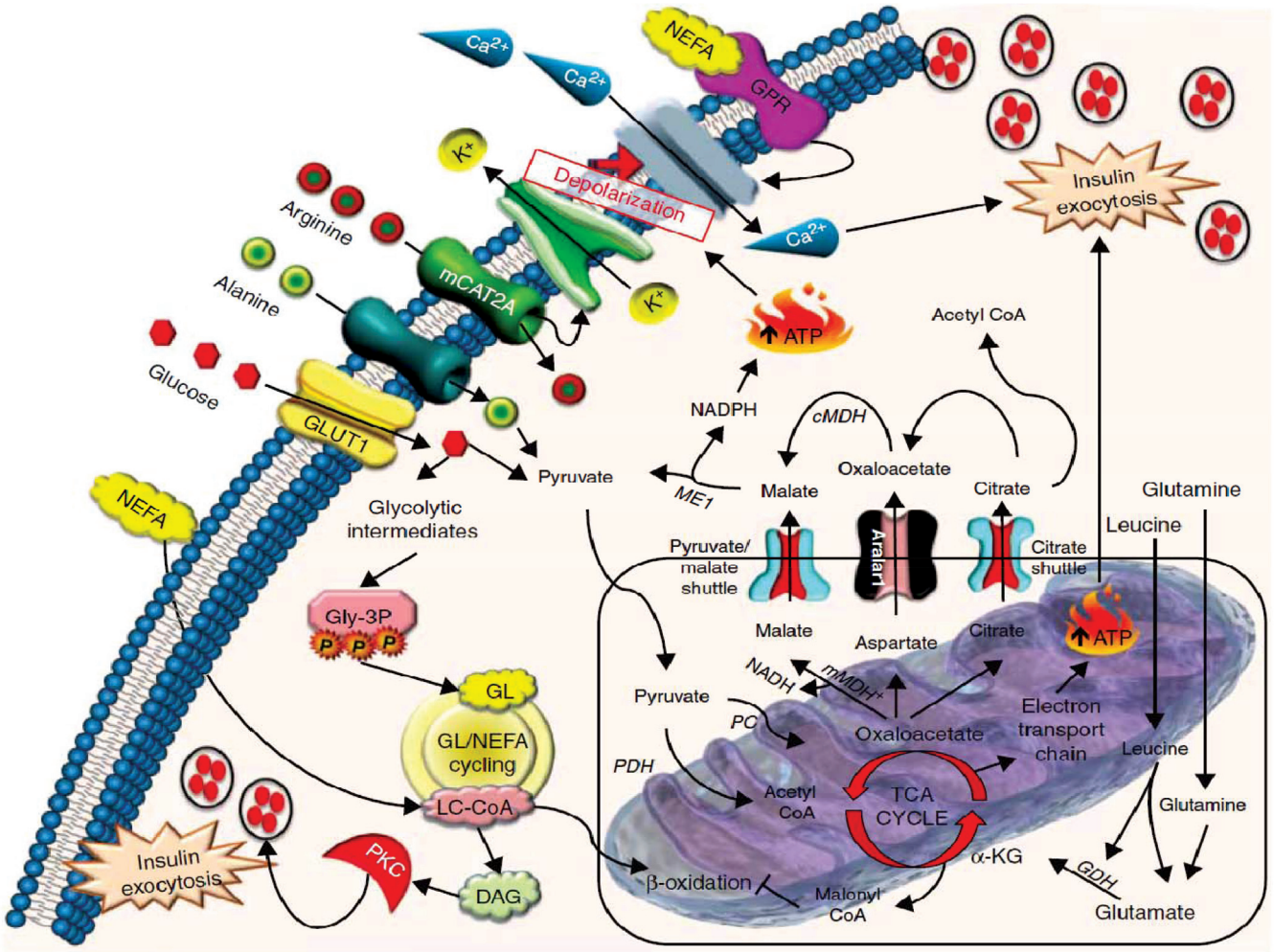

Figure 12.1 Mechanisms of nutrient stimulus–secretion coupling in the pancreatic β cell. Source: Newsholme et al. 2014 [14].

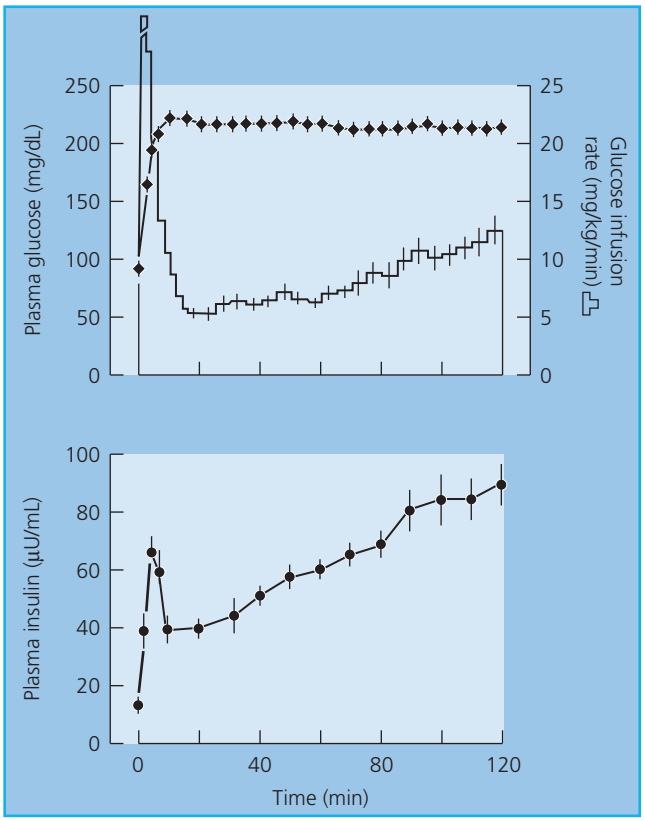

Figure 12.2 First- and second-phase plasma insulin response during hyperglycemic clamp in healthy individuals. Plasma glucose is acutely raised +125 mg/dL above baseline and maintained for the ensuing 2 h. Plasma insulin concentration is measured at regular intervals. Source: DeFronzo et al. 1979 [7]. Reproduced with permission of the American Physiological Society.

glucose levels subsequent to the entry of nutrients into the circulation following food digestion and absorption. The route of administration of glucose and other nutrients markedly influences insulin secretion. When glucose is administered via the gastrointestinal tract, a much greater stimulation of insulin secretion is observed compared with similar plasma glucose levels obtained with intravenous glucose infusion. This difference in insulin secretion between intravenous and oral glucose administration is referred to as the "incretin effect" [11]. Glucagon-like peptide 1 (GLP-1) and glucose-dependent insulinotropic peptide (GIP), the major incretin hormones in humans, play a predominant role in the postprandial incretin effect, thereby largely contributing to the maintenance of glucose homeostasis after the ingestion of a meal [12]. Other gut hormones, such as cholecystokinin (CCK), can contribute to the incretin effect, although the importance of these peptides is negligible under physiological conditions [13].

Insulin secretion is also stimulated by the ingestion of proteins and fat [14]. Amino acids regulate both the triggering and the amplification pathways of insulin secretion by acting as a substrate for the tricarboxylic acid cycle and/or redox shuttles with subsequent generation of ATP, and through direct depolarization of the plasma membrane (Figure 12.1). The latter is the consequence of the transmembrane transport of positively charged amino acids via specific amino acid transporters and Na^+ cotransport. Lipids and free fatty acids (FFAs) play a crucial role in β-cell function and insulin release [14]. In the presence of sufficient nutrients, FFAs influence insulin secretion through three distinct pathways: (1) tricarboxylic acid cycle/malonyl-CoA metabolic signaling, (2) glycerolipid/FFA cycling, and (3) direct activation of G-protein-coupled receptors [14]. Finally, many other factors, including neuropeptides and neuronal control, contribute to the modulation of insulin secretion through a sophisticated integrated process [15].

Long-term adaptation of insulin secretion is likely to be associated with changes in the number of β cells, as indicated by the progressive increase in β-cell mass occurring from birth to adulthood. Although β-cell mass expansion tends to become negligible after the age of 20–30 years [16, 17], an increase may occur under conditions of increased insulin demand such as obesity [18, 19] and pregnancy [20].

Although further details of the regulation of insulin secretion are given in Chapter 6, even from this brief discussion of the physiological regulation of insulin secretion, it is apparent how abnormal insulin secretion in T2DM may arise from defective β-cell function, reduced β-cell mass, or a combination of the two.

Natural history of β-cell failure

Because of its fine regulation, assessment of insulin secretion *in vivo* may require complex methodological approaches and sophisticated mathematical analysis [21, 22]. HOMA-B (homeostasis model assessment B) is a model-derived parameter reflecting β-cell function in the basal state [23]. This parameter has been instrumental in describing the natural history of β-cell dysfunction in T2DM in the United Kingdom Prospective Diabetes Study (UKPDS) [24]. The study showed that individuals with T2DM already had a significant reduction in β-cell function at the time of diagnosis. Moreover, it was apparent that β-cell function declined in an almost linear manner during the 10-year follow-up, irrespective of pharmacological treatment. Because of such a linear relationship, it was extrapolated that the defect in β-cell function was likely to antedate by many years the time of the development of hyperglycemia. By using the same HOMA-B parameter, a more articulated history of β-cell dysfunction was described in the Belfast Diet Study [25]. According to this analysis, individuals who eventually develop diabetes already have an intrinsic 40–60% reduction in β-cell function to start with. Over time, two phases were identified: phase A, which precedes overt diabetes and is characterized by a slow, constant decline of β-cell function (~2% per year), and phase B, characterized by a much faster decline (~18% per year), more commonly occurring with the development of diabetes. This view is of interest because it reflects three conditions that, in recent years, have received growing support and stronger evidence: (1) genetic predisposition, (2) early β-cell dysfunction, and (3) factors that accelerate the rate of loss of β-cell function.

Genetic predisposition

More light has been shed in recent years on the genetic predisposition to T2DM (See Chapter 14 and Figure 12.3). Early linkage and candidate gene studies and, more recently, genome-wide association studies (GWAS) have identified a large number of genetic variants associated with increased risk of developing T2DM, although most of them have limited size effects that seldom exceed 10–15% [26]. The only exception is represented by variants of the *TCF7L2* gene encoding for a transcription factor involved in the Wnt-β catenin-signaling pathway [27]. In particular, the T allele of the genotypes of the single-nucleotide polymorphism (SNP) rs7903146 confers a greater risk of developing T2DM in all the populations so far evaluated [27], except the Pima Indians [28]. More interestingly, the same genotype is associated with impaired *in vivo* [29, 30] and *ex vivo* [29] insulin secretion. The *TCF7L2* genetic variants may exert both direct and indirect effects on the β cell. Thus, the increased *TCF7L2* expression found in human pancreatic islets carrying the risk allele T was inversely correlated with glucose-stimulated insulin release [29]. Moreover, people carrying the risk alleles have impaired potentiation of insulin secretion in response to GLP-1 infusion [31] (Figure 12.4). In summary, the *TCF7L2* genetic variants may be associated with reduced insulin secretion in response to both glucose and incretin hormones. However, this is not clear cut as other studies have reported reduced expression of the *TCF7L2* gene in T2DM pancreatic islets along with impaired insulin secretion and β-cell survival [32].

A reduced early insulin response to both oral and intravenous glucose and greater susceptibility to diabetes have been reported for carriers of the SNP rs10830963 in the melatonin receptor gene (*MTNR1B*) [33]. These individuals have increased melatonin receptor expression in β cells, which may lead to increased melatonin binding and reduced cAMP/cGMP generation, accounting for impaired insulin secretion.

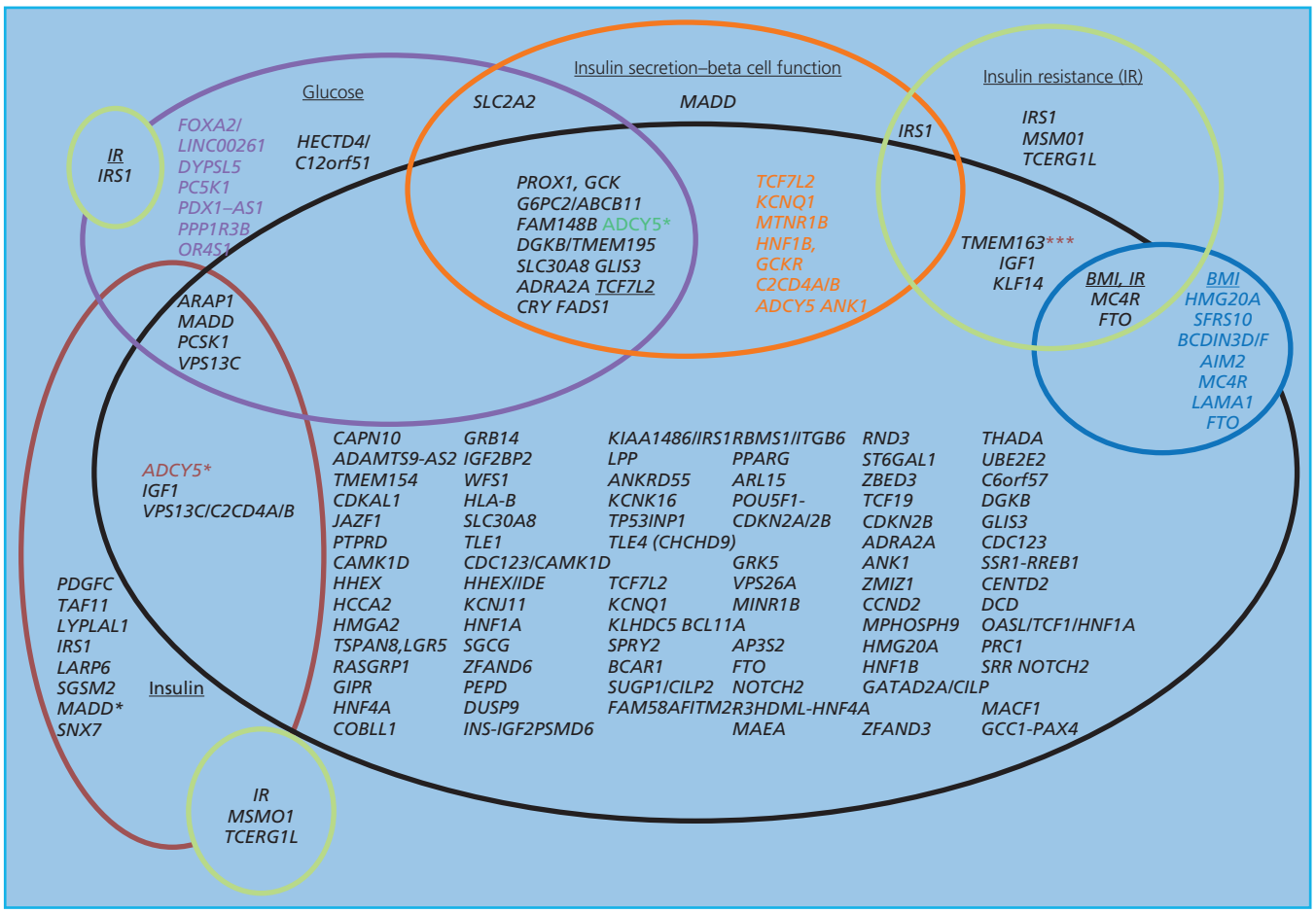

Figure 12.3 T2DM and glycemic trait-associated variants. The variants are represented by gene names here, which could indicate that the location is present either in the gene or in the vicinity of the gene. The white circle represents T2DM and the gene names in black in that circle represent variants only associated with T2DM. The overlapping circles indicate additional reporting associations for that variant. Source: Prasad and Groop 2015 [26] (this is an open-access article distributed under the Creative Commons Attribution License [CC BY]).

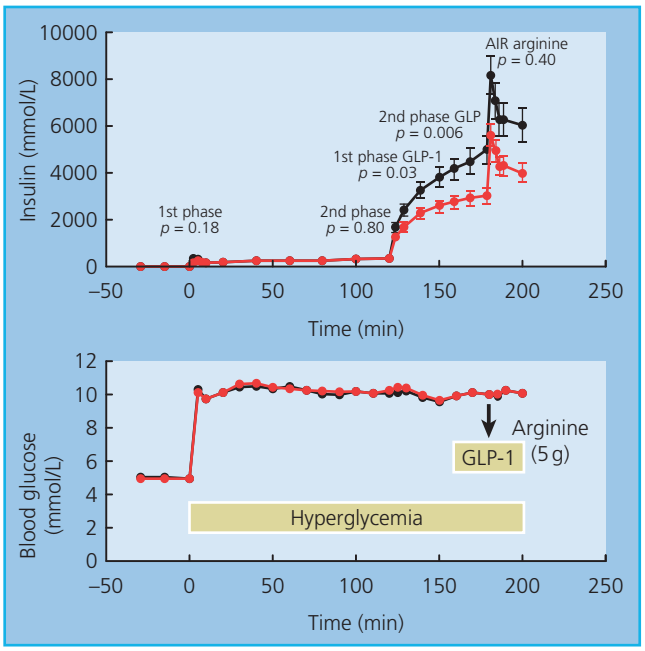

Figure 12.4 Associations between the genotypes of rs7903146 polymorphism in the *TCF7L2* gene with insulin secretion during a hyperglycemic clamp in 73 participants. Black lines, CC; red lines, CT and TT. AIR, acute insulin response. Arrow, administration of 5 g of arginine. The *p* values show the differences for the first- and second-phases of glucose-induced insulin secretion, first- and second-phases of GLP-1-induced insulin secretion, and acute insulin secretory response to arginine (AIR). Source: Schäfer et al. 2007 [31]. Reproduced with permission of Springer.

Other gene variants that have been associated with impaired insulin action include the G/G variants of calpain-10 gene (*CAPN10*) and *KCNJ11*. The G/G variant of SNP-43 of *CAPN10* was found to be associated with impaired insulin response to glucose in people without diabetes [34]. Variants of the *KCNJ11* gene may result in gain of function of the ATP-sensitive potassium channels, resulting in impaired depolarization of the β-cell membrane and altered insulin release, although such an effect becomes more apparent when the β cell is under stress conditions (i.e. glucotoxicity) [35].

Many other genes, including *HHEXZ/IDE*, *GIPR*, *PROX1*, *DGKB*, *CDKAL1*, *SLC30A8*, *CGK*, and *CDKN2A/2B*, have been associated with abnormalities of insulin secretion [36, 37]. Of interest, of the many gene variants so far associated with T2DM, the great majority seem to exert their main effect on insulin secretion, with only a minor proportion of genes being associated with insulin resistance [38]. However, some of the latter may also have an effect on the β cells as well. For instance, pancreatic islets carrying the $Gly^{972} \rightarrow Arg$ amino acid polymorphism of the insulin receptor substrate 1 (IRS-1) gene have impaired β-cell turnover [39] and reduced insulin secretion in response to glucose [40]. Similar findings have been reported for the ectonucleotide pyrophosphatase phosphodiesterase 1 (*ENPP1*) [41] and the *TRIB3* [42] genes. These observations not only support a genetic background associated with a "weaker" and more "vulnerable" β-cell phenotype but also point to a more complex picture where insulin secretion and insulin action might, to some extent, be dependent on a common genetic background.

In spite of the identification of many genes associated with impaired β-cell function and survival, they account for only a minority of the disease risk, suggesting that other mechanisms might be involved in the disease predisposition. Gene expression can be modified in the absence of alterations in the nucleotide sequence as occur with epigenetic DNA methylation and histone modifications triggered by nutritional, hormonal, and metabolic environments [43]. Impaired intrauterine environment and impaired fetal growth (small babies at birth) are associated with altered insulin secretion and/or reduced β-cell mass and increased risk of development of diabetes later in life [44]. Under these conditions, epigenetic modifications of key β-cell genes have been reported [45, 46]. Some evidence suggests that metabolic imprinting of offspring exposed to maternal undernutrition can be trans-generational, i.e. can be transmitted to offspring, generating a predisposition towards diabetes [47].

Overall, these observations suggest the existence, in predisposed individuals, of a genetic background that appears to be mainly associated with potential defects in β-cell function. In these individuals, insulin secretion, if properly assessed, can be expected to be impaired long before overt development of diagnostic hyperglycemia.

Abnormalities of β-cell function precede overt diabetes

A predisposing genetic background is the most likely explanation for the evidence provided by multiple studies that β-cell function is altered well before the onset of overt T2DM [48, 49]. For instance, abnormalities of β-cell function have been described in normoglycemic first-degree relatives of people with T2DM [50, 51]. These early alterations in insulin secretion are more qualitative than quantitative in nature. The plasma insulin concentration after an oral glucose load in predisposed individuals may not differ from those obtained in people with no such predisposition. Nonetheless, in white European people at risk for T2DM, β-cell response to oral glucose, adjusted for prevalent plasma glucose levels and insulin sensitivity, declines as a function of glucose tolerance [52]. Of interest, β-cell function worsens significantly with an increase in the 2-h plasma glucose level even in people with normal glucose tolerance (i.e. 2-h plasma glucose <140 mg/dL) [52, 53]. In both lean and obese individuals with 2-h plasma glucose levels of 120–140 mg/dL, β-cell function is already reduced by 60% compared with those with a 2-h plasma glucose level of <100 mg/dL (Figure 12.5) [53]. The abnormalities of β-cell function become fully apparent when the insulin secretion rate is plotted against prevalent plasma glucose levels [53, 54]. This analysis clearly shows how the β cells of people with a predisposition to diabetes secrete much less insulin than healthy individuals for

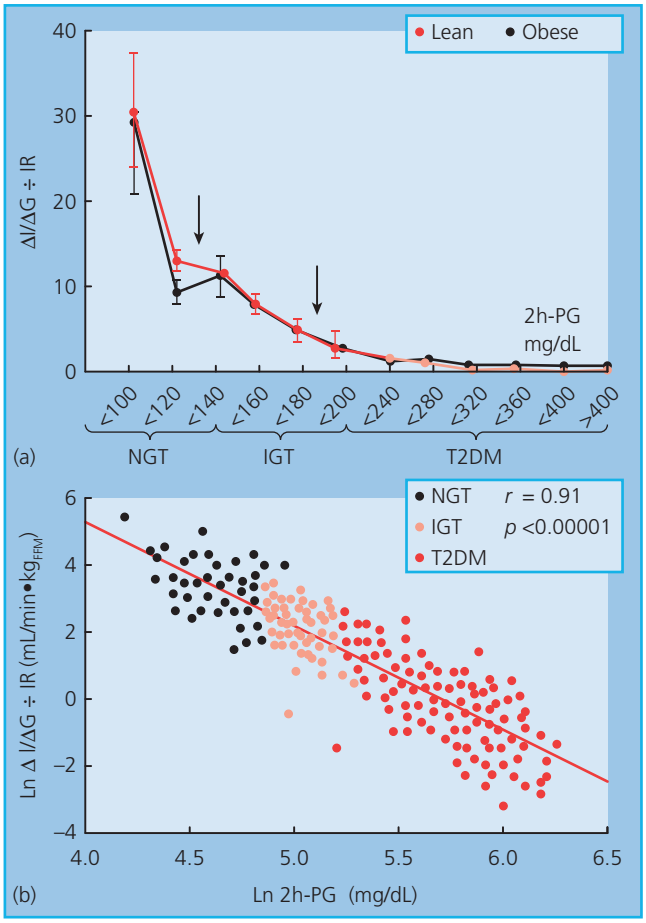

Figure 12.5 Relationship between the insulin secretion/insulin resistance index (ΔI/ΔG factored by the severity of insulin resistance measured with the euglycemic insulin clamp) and (a) the fasting plasma glucose (FPG) and (b) the 2-h plasma glucose (2-h PG) concentration (log–log scale). Source: Gastaldelli et al. 2004 [53], Figure 4. Reproduced with permission of Springer.

the same glucose stimulus [54]. This abnormality is often referred to as impaired glucose sensitivity [55] and it is better defined when mathematical modeling approaches are applied [56].

Loss of first-phase insulin secretion is a very early feature of β-cell dysfunction. Individuals with isolated impaired fasting glucose (IFG) show a decrease in first-phase insulin secretory response to intravenous glucose and early-phase insulin response to oral glucose [57]. The late-phase insulin response after an oral glucose tolerance test (OGTT) is less severely impaired than in people with impaired glucose tolerance (IGT) who have severe defects in both early- and late-phase insulin responses. First-phase insulin secretion plays an important role in priming the liver to inhibit endogenous glucose production in response to glucose or nutrient ingestion [58, 59]. Therefore, the defect in early-phase insulin secretion in IFG and IGT results in inadequate suppression of hepatic glucose production and contributes to an excessive early rise in plasma glucose in response to an oral glucose load. In people with IGT, the combination of deficient second-phase (late-phase during OGTT) insulin secretion and peripheral insulin resistance translates into less efficient glucose disposal. As a result, after the ingestion of a glucose load, the plasma glucose concentration will continue to increase after the initial 60 min to remain elevated at 120 min. The loss of first-phase insulin not only contributes to impaired hepatic glucose metabolism [60] but also is an independent predictor of development of T2DM [61, 62].

In summary, the natural course of β-cell function suggests that the acute insulin response and glucose sensitivity play a major role in determining glucose tolerance [63]. Longitudinal studies of Pima Indians relating changes in insulin sensitivity and acute insulin response have clearly demonstrated that it is the worsening of the latter rather than the development of insulin resistance that marks the progression from normal glucose tolerance to IGT and, eventually, T2DM [64].

The extent to which these functional abnormalities are also linked to loss of β-cell mass is still a matter of discussion [65]. Assessment of β-cell mass is largely dependent on methodological approaches [66], but several reports claim that an apparent reduction in β-cell volume of up to 60% is present in individuals with prediabetes [18, 67, 68]. The decrease in β-cell mass is the result of a greater rate of apoptosis [18, 19, 66, 69, 70] and, to a lesser extent, autophagy [71]. An increase in β-cell death occurs without a compensatory increase in β-cell replication owing, at least in part, to the limited regenerative capacity of adult human β cells [72, 73]. It has been suggested that β-cell dedifferentiation, rather than cell death, may account for the loss of β cells in the pancreatic islet of an individual with diabetes [74, 75].

Insulin secretion progressively worsens after development of T2DM

Impaired insulin secretion and insulin secretory capacity are the major determinant in the development of T2DM. Neither hyperglycemia nor glucose intolerance develop in insulin-resistant individuals provided that sufficient insulin is secreted from β cells to compensate for the insulin resistance, which is the other characteristic pathogenic condition underlying the loss of glucose homeostasis. The β-cell dysfunction progresses over time and is well established by the time the plasma glucose level achieves the diabetic range and continues to worsen after diabetes has developed [24]. Multiple factors contribute to the progressive loss of β-cell function and β-cell mass, the most important being the direct consequences of an altered metabolic milieu characterizing T2DM.

Hyperglycemia

A large number of *in vivo* and *in vitro* studies have shown that elevation of glucose concentrations impairs β-cell function (and insulin action), a phenomenon known as "glucotoxicity." Conversely, improvement in glycemic control both under experimental conditions and in clinical studies has always been associated with improvement in β-cell function [76]. The

main mechanisms accounting for the negative effect of high glucose levels is activation of oxidative stress, the consequence of increased glucose oxidation in the mitochondria, mitochondrial dysfunction, and overproduction of reactive oxygen species (ROS) [77]. In T2DM, pancreatic islet markers of oxidative stress are significantly increased [77] compared with non-diabetic islets and inversely related to glucose-stimulated insulin secretion. In contrast, overexpression of antioxidant factors reduces the level of markers of oxidative stress and increases the β-cell response to insulin [77, 78]. The β cell is particularly susceptible to the negative effect of oxidative stress owing to an intrinsic low expression of antioxidant enzymes and reduced DNA repair capacity [79].

Increased glucose availability is also associated with activation of the glycolytic pathway in β cells and with excessive formation of fructose-6-phosphate with subsequent increased flux through the hexosamine pathway. *In vitro* studies have clearly shown how the activation of the hexosamine pathway interferes with the expression of genes involved in β-cell regeneration and differentiation [80] and triggers apoptosis [81].

Therefore, chronic exposure to hyperglycemia can affect both β-cell function and β-cell mass, although such an effect is likely to be more prominent when exerted on a predisposed β-cell, since in healthy individuals, 72 h of hyperglycemia does not impair β-cell function [82].

Hyperlipidemia

Obesity is a common condition in people with T2DM and it is considered one of the main causes of the progressive increase in the global prevalence of the disease [83]. Obesity, and concomitant insulin resistance, are often associated with dyslipidemia, increased circulating leptin concentrations, and chronic inflammation [84].

Leptin receptors are present in β cells, and their activation directly inhibits insulin secretion [85]. Moreover, leptin inhibits insulin gene expression and affects proliferation, apoptosis, and β-cell size [85]. Expansion of adipose tissue is associated with increased cytokine release [86]. TNF-α and interleukin-6 (IL-6) have been shown to affect both β-cell function and survival [87]. Moreover, apoptosis can stimulate the innate immune system with mobilization of T cells and macrophages [88]. Of interest, under stress conditions, such those generated by excessive stimulation by glucose and FFAs, the concentrations of proinflammatory factors are increased in the pancreatic islets [89, 90] where they can trigger Fas-dependent apoptosis through activation of nuclear factor kB (NFkB). Plasma FFA concentrations are commonly increased in persons with T2DM and they contribute to sustaining insulin resistance [91] as well as impaired β-cell function [92], a phenomenon also known as lipotoxicity. The effects of FFAs on β-cell function are complex as they also are physiological modulators of insulin secretion. Hence, under fasting conditions, an increase in plasma FFAs becomes essential for the maintenance of basal insulin levels and to ensure a normal insulin response to glucose [93]. Nonetheless, the toxic effect of FFAs can be easily demonstrated *in vitro*; even a short exposure of human pancreatic islets to an excessive FFA concentration is sufficient to impair glucose-stimulated insulin release [94]. High levels of FFAs can contribute to β-cell dysfunction through intracellular accumulation of triglycerides as a response to the activation of the sterol regulatory element binding proteins (SREBPs) [95], or by increased expression of uncoupling protein 2 (UCP-2), which regulates cellular ATP production [96]. The impact on β-cell function is paralleled by a cytostatic effect due to activation of caspase-mediated apoptosis [97]. FFAs also induce the expression of nitric oxide (NO) synthase, causing marked overproduction of NO. Of interest when NO production is limited by the use of inhibitors of inducible NO synthase, insulin secretion is significantly ameliorated [98]. NO also contributes to apoptosis through the activation of c-Jun N-terminal kinase (JNK), p38 mitogen-activated protein kinase (MAPK), and Akt inhibition [99].

In summary, similar to chronic hyperglycemia, lipotoxicity can accelerate the progressive loss of β-cell function and β-cell mass. However, such an effect seems to be more apparent when the two conditions coexist, as commonly occurs in individuals with T2DM. For this reason, it may be more appropriate to refer to the combination of these effects as "glucolipotoxicity" [100]. The adverse metabolic milieu may also affect gene expression through epigenetic mechanisms. For instance, increased methylation of the PGC1-α gene promoter has been reported in pancreatic islets from cadaveric donors with T2DM; the greater the degree of methylation, the lower is the expression of the protein and the lower the glucose-stimulated insulin release [101].

Chronic β-cell stimulation

Chronic hyperglycemia is associated with persistent β-cell stimulation and insulin biosynthesis. This process requires the activation of the endoplasmic reticulum (ER), which is responsible for the biosynthesis and folding of newly synthesized insulin [102]. Because of glucolipotoxicity, the ER folding capacity is impaired, causing accumulation and aggregation of unfolded proteins, a condition known as ER stress [103]. Up to a certain point, ER stress can be compensated via the so-called "unfolded protein response." This adaptive and protective pathway, however, can become ineffective if ER stress is persistent and may lead to the generation of proapoptotic signals. A number of studies have documented ER stress in *ex vivo* pancreatic islets of cadaveric donors with T2DM [104, 105]. In these islets, ER stress is marginally increased if they are incubated in the presence of normal glucose concentration. In contrast, exposure to higher glucose levels causes more ER stress than in islets from cadaveric donors without diabetes (Figure 12.6) [105]. These findings suggest a greater susceptibility to proapoptotic mechanisms in the diabetic β cell. In summary, increased and persistent insulin secretion can contribute to β-cell dysfunction and survival through insulin protein misfolding in the ER.

Chronic stimulation of β cells also results in an increase in the synthesis of islet amyloid polypeptide (IAPP). This peptide is

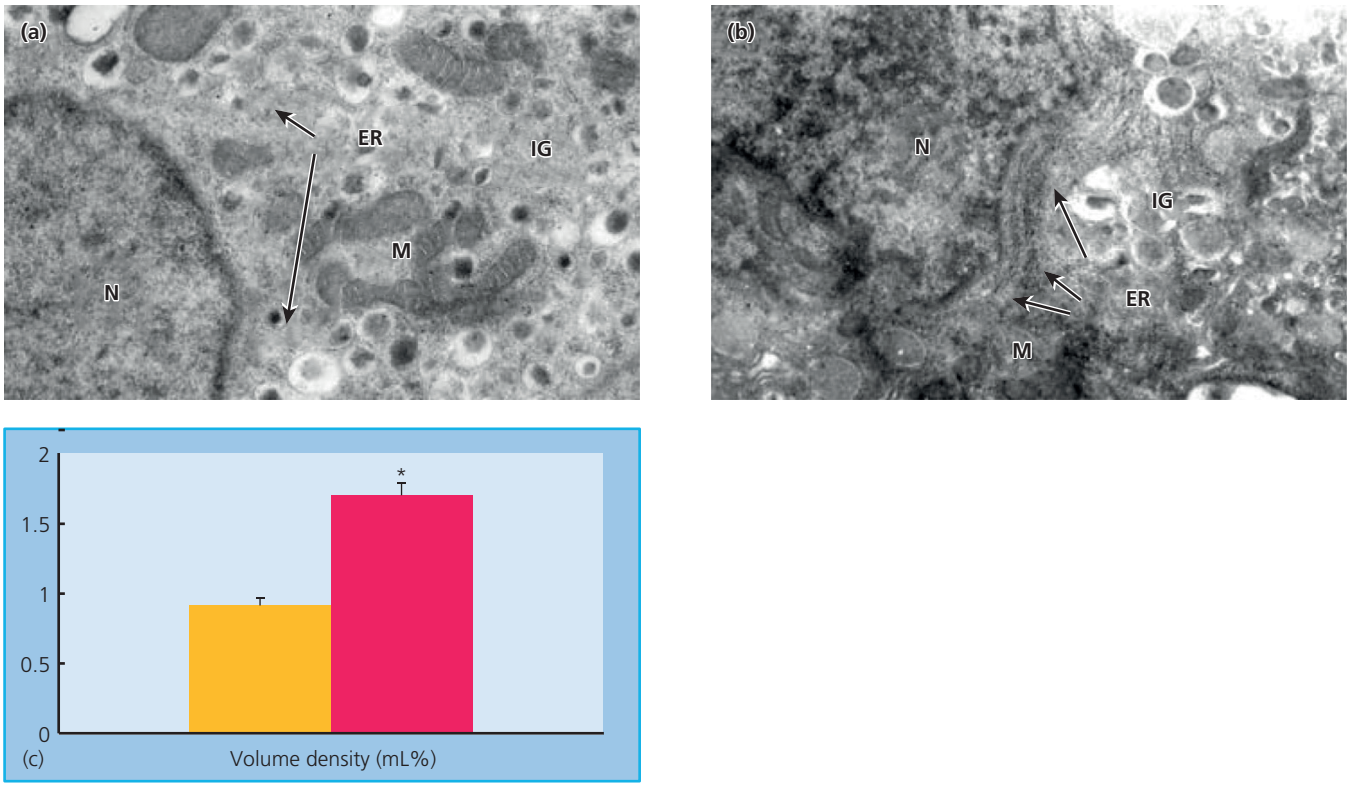

Figure 12.6 (a, b) Electron microscopy images showing the ER in (a) non-diabetic β cells and (b) T2DM β cells. The ER components (arrows) are scarcely visible in non-diabetic cells and more apparent in T2DM cells. Magnification ×10,000. IG, insulin granules; M, mitochondria; N, nucleus. (c) The ER density volume was significantly higher inT2DM β cells (red box) than non-diabetic β cells (yellow box). *p <0.05 (Student's t-test for unpaired data). Source: Marchetti et al. 2007 [105], Figure 3. Reproduced with permission of Springer.

co-localized with insulin secretory granules [106] and its production parallels that of proinsulin. IAPP can form aggregates and fibrils [107], leading to deposition of amyloid plaque that triggers an inflammatory response [108], recruitment of macrophages [109], and apoptosis [110]. The mechanism through which IAPP forms amyloid and results in β-cell damage is not completely understood. Amyloid deposition has been found in other hypersecretory conditions, such as non-diabetic obesity [111] and insulinoma [112], with no apparent negative impact on β-cell function. One possible explanation for this paradox is that the negative effect of amyloid may require concomitant glucolipotoxicity. In line with this hypothesis is the observation that pancreatic islet amyloid can be found in up to 90% of people with T2DM [113] and the degree of deposition correlates with the duration and severity of the disease [114].

Impaired incretin effect

GLP-1 and GIP are physiological factors involved in β-cell function and survival [115] and they are the main players in the incretin effect [12]. This effect is characteristically lost in T2DM, although it is still a matter of discussion whether this alteration is a primary defect or an acquired one [116]. In both cases, the loss of the incretin effect results in poor potentiation of the insulin release in response to the ingestion of a meal and excessive postprandial glucose excursion [117]. Whether this defect can also contribute to loss of β-cell mass in unclear, at least in humans, and preclinical studies have provided evidence for an effect of GLP-1 in reducing apoptosis and stimulating β-cell regeneration and differentiation in experimental murine models [118].

GLP-1 is mainly secreted by the L cells of the lower intestine. However, more recent data have provided evidence that GLP-1 can be synthesized by the α cells of the pancreatic islet [119, 120]. These cells also express dipeptidyl peptidase 4 (DPP-4), the peptidase responsible for GLP-1 inactivation [121]. GLP-1 production has been found to be increased [120] in pancreatic islets from cadaveric donors with T2DM, whereas DPP-4 activity is reduced [121]. The extent to which these mechanisms may ensure an *in vivo* increase in local GLP-1 levels is difficult to ascertain, but the increase in intra-islet GLP-1 availability could be seen as an attempt to protect the β cells [122].

Antihyperglycemic treatment

Improved glycemic control can relieve glucotoxicity and restore, to some extent, β-cell function [76]. However, there is some discussion on the potential direct effects that the currently available glucose-lowering agents may exert on the preservation of β cells. Potential protective effects have been claimed with the use of DPP-4 inhibitors [123, 124], GLP-1 receptor agonists [125, 126],

and pioglitazone [127]. Incubation of pancreatic islets of individuals with T2DM in the presence of therapeutic concentrations of metformin has been found to increase insulin content, to increase the number and density of mature insulin granules, to improve glucose-induced insulin release, and to reduce apoptosis along with normalization of several markers of oxidative stress [128]. In *ex vivo* studies, concern has been expressed with respect to the effects of sulfonylureas on the β cell. *In vitro* experiments have shown increased β-cell apoptosis [128], although some difference may exist among different sulfonylureas. In isolated human pancreatic islets, glibenclamide but not repaglinide was found to activate β-cell apoptosis [129]. Other observations have indicated a reduced insulin content in pancreatic islets incubated in the presence of glimepiride, glibenclamide, and chlorpropamide, although no change in insulin release in response to glucose was observed with glimepiride [130]. In cultured β-cell lines, no activation of apoptosis was found with gliclazide treatment along with some antioxidant effect noted in human pancreatic islets [131].

The real impact of these findings is still unclear. In the clinical setting, the durability of the glucose-lowering efficacy of sulfonylureas is claimed to be poorer than with other antihyperglycemic agents [132]. These findings may appear to be in agreement with animal studies showing that chronic glibenclamide treatment causes loss of insulin secretory capacity due to β-cell hyperexcitability [133]. However, the same studies also revealed rapid reversibility of this secretory failure, arguing against β-cell apoptosis or other cell death induced by sulfonylureas. In contrast, these findings support earlier observations showing *in vivo* restoration of β-cell response to sulfonylureas, once sustained therapy with sulfonylureas was discontinued [134].

In summary, upon development of overt hyperglycemia, a number of factors, including chronic hyperglycemia, obesity, increased FFA availability, persistent stimulation of β cells, and, potentially, the use of specific drugs, may contribute to the acceleration of the decline in insulin secretory capacity of individuals with T2DM and progression of the disease. These accelerating factors promote common damage mechanisms, including oxidative stress, ER stress, inflammation, and immune system activation (Figure 12.7) [135]. Because of these mechanisms, a vicious cycle develops by which the ability of the β cells to cope with hyperglycemia and insulin resistance becomes weaker and the impact of the accelerating factors becomes greater. These factors impair both the function and the survival of the β cells, although the relative contribution of the two remains to be established.

β-Cell dysfunction: exhaustion or insufficient mass?

At the time of diagnosis of T2DM, the β-cell mass is already reduced by 30–40% [18, 67–69]. However, the decreased number of cells is unlikely to account for the distinctive defect in insulin secretion that characterizes T2DM even before the time of diagnosis. Experimental data have shown that, at least in rodents, no disturbances in glucose homeostasis arise provided that the β-cell mass remains >20% [136]. In humans, diabetes has been shown to develop when the β-cell area declines by ~65% [137]. The suggestion that the reduction in β-cell mass may not be sufficient per se to result in glucose intolerance is supported by the simple observation that a large overlap exists between the β-cell mass of individuals with and without diabetes [138] (Figure 12.8). Moreover, hemi-pancreatectomy performed in normal individuals for the purpose of pancreas donation is not followed

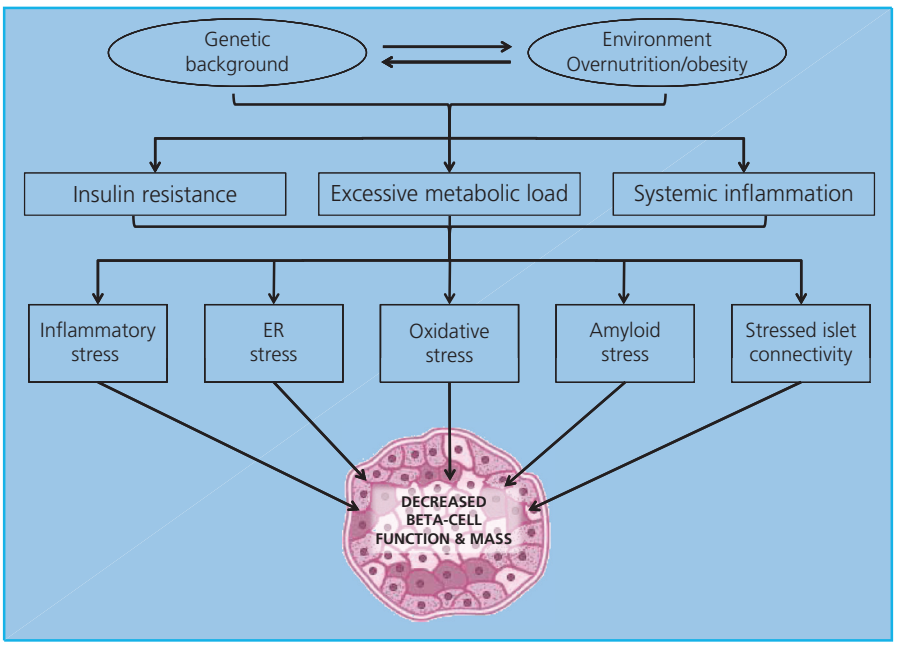

Figure 12.7 Mechanisms of β-cell damage in T2DM. Environmental factors and genetic backgrounds interact to activate stress processes that contribute to functional abnormalities and also progressive loss/dedifferentiation of β cells. Source: Adapted from Halban et al. 2014 [135].

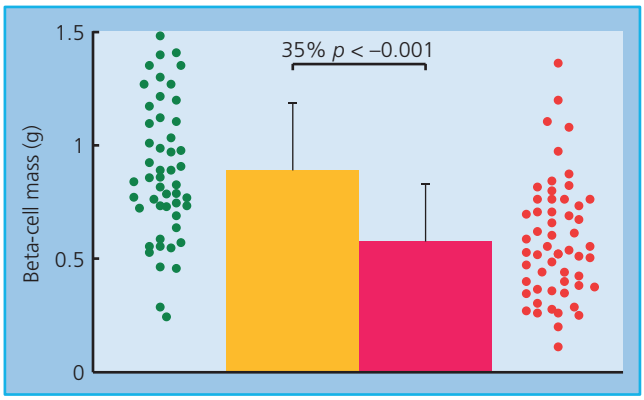

Figure 12.8 β-Cell mass in the pancreas of people without (left) and with T2DM (right). Data are presented for individual values as scatterplots and mean values ± SD as columns. Although on average the β-cell mass is about 40% less in people with T2DM, there is some degree of overlap between the two groups. Source: Rahier et al. 2008 [138], Figure 2B. Reproduced with permission of John Wiley & Sons.

by major disturbances in insulin secretion [139]. The β-cell mass may also be a misleading measurement as one may argue whether it is the number of β cells (or cell area) or the insulin content per cell (and therefore the total insulin content in the pancreas) that is of importance. Relevant to this issue is the finding that the β-cell mass declines with the duration of the disease, although the insulin content per cell tends to increase [138]. The progressive loss of β cells in diabetes is likely to be the consequence of even a mild elevation of plasma glucose levels and concomitant increased secretory demand sustained by insulin resistance, particularly if these mechanisms operate on a genetically predisposed β cell. Consistent with this view are animal experiments showing how a 60% pancreatectomy in dogs does not result in an alteration of insulin secretion unless the plasma glucose levels are modestly increased by intravenous glucose infusion [140]. These results are also in keeping with the few available human studies. In healthy people with no family history of diabetes, a 72-h glucose infusion resulting in constant elevation of post-absorptive plasma glucose levels just above 110 mg/dL was associated with a potentiation of both first- and second-phase insulin secretion rather than an impairment [82]. In contrast, when normo-tolerant first-degree relatives of individuals with T2DM were infused with fat emulsions to increase circulating FFA levels, a marked impairment of insulin secretion became apparent [141] (Figure 12.9).

Such a rapid worsening of insulin secretion is unlikely to be due to a sudden reduction in the number of β cells; rather, this is much more congruent with a further impairment of the mechanisms responsible for glucose sensing and insulin response. Finally, the results of bariatric surgery in people with diabetes provide stronger support to the primacy of impaired β-cell function rather than loss of β cells. Even in individuals with T2DM with long-standing duration of the disease, the surgical procedure is followed by an almost immediate improvement of β-cell function associated with simplification, if not withdrawal, of pharmacological glucose-lowering therapy [142–144]. β-Cell dysfunction may also be the result of the loss of islet organization. As mentioned, insulin secretion is pulsatile in nature, with a slow ultradian periodicity (<140 min) and a high-frequency periodicity [145]. These oscillations requires a sophisticated coordination of the secretory activity of the individual β cells dispersed through the ~1 million pancreatic islets present across the pancreatic tissue. Such connectivity recognizes a number of mechanisms operating in concert, including neural circuits, gap junctions, activity of primary cilia, and paracrine signaling [146]. Recently it has been suggested that lipotoxicity may disrupt the incretin effect on this connectivity [147], possibly through downregulation of connexin 36, a component of gap junctions [148].

In conclusion, the available evidence indicates that abnormalities of insulin secretion in T2DM are accounted for by β-cell dysfunction to a greater extent than can be account for by defects in β-cell mass. Alternatively, one can hypothesize an effect on β-cell differentiation and more efficient stocking and maturation of insulin granules. This view fits with the recent observation that β-cell dedifferentiation rather than β-cell death contributes to the reduction in β-cell mass [149, 150] and degranulation [151]. Further, experimental animal data suggest that insulin granules

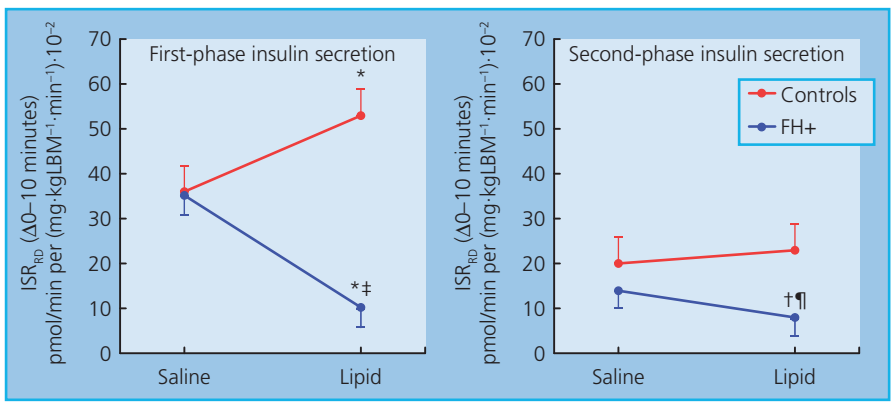

Figure 12.9 Insulin secretion rates (ISRs) during the hyperglycemic clamp studies related to the prevailing severity of insulin resistance (ISR_{Rd}). On comparing control participants with healthy participants with a strong family history of T2DM (FH+), the first-phase ISR_{Rd} is similar during the saline studies; with lipid infusion, the first-phase ISR_{Rd} deteriorates in FH+ participants, whereas it increases in control participants. The second-phase ISR_{Rd} is also reduced by lipid infusion in the FH+ group but is unchanged in healthy control. *p <0.01 vs. saline; †p <0.05 vs. saline; ‡p <0.001 vs. control participants; ¶p <0.05 vs. control participants. Source: Adapted from Kashyap et al. 2003 [141].

can be restored through a decrease in blood glucose [152] and insulin secretion recovered even in islets from individuals with T2DM [1198,153].

Conclusion

β-Cell dysfunction is an early feature in the natural course of T2DM and plays a critical role in the development of glucose intolerance and progression of the disease. This distinctive alteration recognizes a genetic background, with a number of genetic variants specifically associated with impaired β-cell function and survival. In people predisposed to diabetes and in those with prediabetes, both a reduction in β-cell mass and, to a greater extent, impaired insulin secretion are fully apparent. A minimal increase in fasting plasma glucose levels is already accompanied by a typical loss of first-phase insulin secretion. Obesity, development of hyperglycemia and dyslipidemia (in particular increased plasma FFA concentrations), and chronic overstimulation of insulin secretion can activate pathogenic mechanisms (glucolipotoxicity, oxidative stress, inflammation, ER stress, epigenetic modifications, amyloid deposition) that can accelerate the progression of β-cell impairment. The same mechanisms activate apoptosis and, to some extent, autophagy, which in the face of a lack of a compensatory increase in β-cell regeneration/differentiation can result in a decrease in β-cell mass. Based on this view, preservation of β-cell function is key to preventing deterioration of glucose tolerance and development of diabetes. Moreover, tight control of the accelerating factors may slow the progression of the disease and result in more durable glycemic control over the years.

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13 Insulin Resistance in Type 2 Diabetes

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Keypoints

- Insulin resistance is a major factor in the pathogenesis of type 2 diabetes, but it is also observed in type 1 diabetes.
- Impaired insulin-stimulated muscle glycogen synthesis, due to defects in glucose transport, is the major factor contributing to whole-body insulin resistance.
- Ectopic fat storage leads to increases in intracellular diacylglycerol and activates novel protein kinase isoforms (PKCθ in muscle and PKCε in liver), which inhibits insulin signaling at the level of the insulin receptor kinase.
- Reduced mitochondrial function is a predisposing factor for ectopic lipid deposition and insulin resistance.
- Macrophage-induced lipolysis promotes increased hepatic gluconeogenesis, hepatic insulin resistance, and fasting hyperglycemia in poorly controlled diabetes by increasing hepatic acetyl-CoA content which in turn activates pyruvate carboxylase activity and increased glycerol conversion to glucose.

Definition and measurement of insulin resistance in humans

The sensitivity to insulin results from its biological effects in the insulin-responsive tissues, predominantly skeletal muscle, liver, and adipose tissue. Impaired insulin sensitivity, also termed insulin resistance, is generally defined as reduced glucose clearance in skeletal muscle, impaired suppression of glucose production by the liver, and decreased rates of lipolysis in adipose tissue or by decreased combined action on whole-body glucose disposal (Figure 13.1).

In 1936, Himsworth [1] provided the first protocol for standardized *in vivo* determination of insulin sensitivity from the glycemic response upon intravenous insulin application. Decades later, the hyperinsulinemic–euglycemic clamp test [2–4] became the gold standard for measuring whole-body insulin sensitivity *in vivo* and for identifying insulin-resistant persons [5, 6]. This steady-state method relies on constant insulin and glucose concentrations, which disrupt the physiological feedback loop between blood glucose concentrations and insulin secretion. The glucose infusion rates required to maintain a defined level of glycemia will then reflect whole-body insulin sensitivity, given as the *M* value [3]. Combined with other techniques, including indirect calorimetry, isotopic tracer dilution, and nuclear magnetic resonance (NMR) spectroscopy of muscle, liver, and brain, the clamp allows the assessment of oxidative and non-oxidative glucose metabolism, systemic, and even tissue-specific fluxes of glucose and other metabolites under *in vivo* conditions (Figure 13.1). In contrast to the steady-state clamp test, other techniques such as the intravenous [7] or oral [8] glucose tolerance tests [5, 6] describe parameters of insulin action such as the S_i or OGIS (oral glucose insulin sensitivity) values from modeling of the dynamic changes of plasma glucose and insulin concentrations over time. These tests can also provide measures of insulin secretion and kinetics during the same experiment.

As these techniques are time consuming and laborious and require experienced personnel, simpler tests have been developed for assessing insulin sensitivity in epidemiological studies. The most common indices, the homeostasis model assessment (HOMA-R, HOMA-S) [9] and the QUICKI [10], are calculated from fasting plasma glucose and insulin or C-peptide concentrations [11]. The general limitation of this approach

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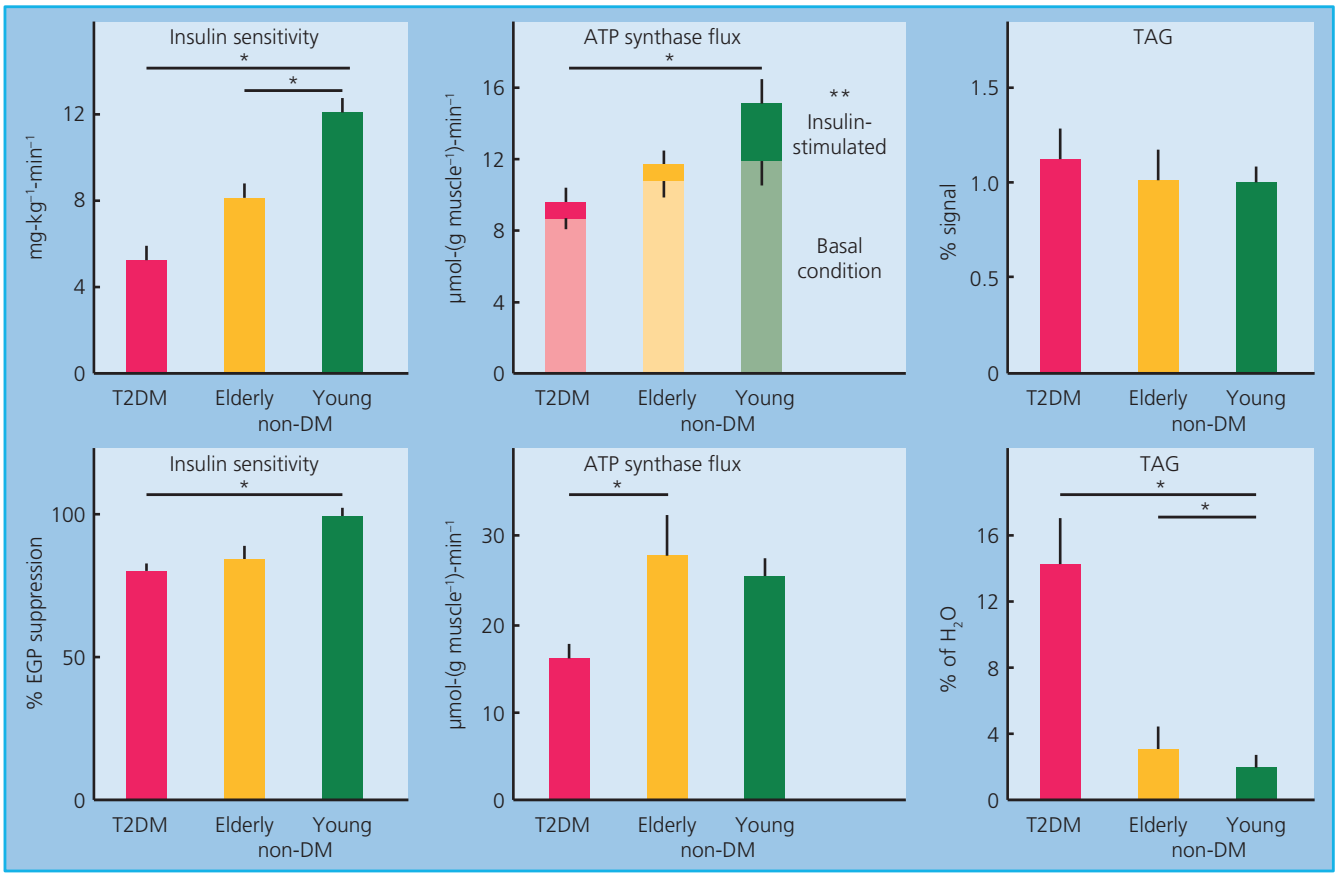

Figure 13.1 Basal and insulin-stimulated muscle and liver metabolism. In skeletal muscle (top left), insulin-stimulated glucose disposal is reduced in insulin-resistant non-obese elderly individuals and in those with type 2 diabetes mellitus (T2DM) compared with insulin-sensitive, lean, young individuals without diabetes. Both basal and insulin-stimulated ATP synthase flux show similar patterns (top middle), whereas intracellular triacylglycerols (TAGs) are frequently higher in insulin resistant persons (top right). In the liver, insulin-mediated suppression of glucose production is reduced in the insulin-resistant individuals (bottom left). ATP synthase flux is also lower only in persons with T2DM (bottom middle), whereas intracellular TAGs are markedly increased (bottom right). Source: data from Schmid et al. 2011 [138] and Szendroedi et al. 2007 [58] and 2009 [138].

results from the fact that the liver is responsible for providing fasting plasma glucose [12]. Under these conditions, glucose is utilized by 60% in non-insulin-dependent tissues, such as the brain, and to lesser extent in insulin-sensitive tissues, such as muscle and liver [13]. The insulin resistance indices obtained during fasting therefore do not correlate closely with clamp-derived glucose disposal [14, 15]. Finally, these indices are not valid for describing insulin sensitivity in states of overt diabetes, when the physiological relationship between circulating glucose and insulin is disrupted.

Insulin resistance as a risk factor for type 2 diabetes mellitus (T2DM)

Insulin resistance may occur independently of inadequate insulin secretion and be a prerequisite for incident T2DM [16–19]. The direct evidence for a time-dependent association between insulin sensitivity and deterioration of glucose tolerance preceding T2DM comes from comparison of population trajectories of fasting and post-glucose challenge plasma glucose concentrations with HOMA-S and insulin secretion (HOMA-B) in persons developing or remaining free of diabetes in the longitudinal Whitehall II study (Tabak et al., 2009) [20]. This study found that individuals had 29% lower HOMA-S but 13% greater HOMA-B values at 13 years before onset of diabetes. HOMA-S decreased linearly until 5 years before diagnosis and with an even steeper slope during the last 5 years prior to diagnosis. Thus, insulin resistance represents an early abnormality, which is compensated by augmented β-cell function for a long time before the insulin–glucose feedback loop fails. Insulin resistance not only predicts T2DM, but also correlates with cardiovascular disease and outcomes [21, 22].

The most important factors predicting T2DM are male sex, increasing age, overweight and obesity [23]. Insulin resistance is frequent in persons with the so-called metabolic syndrome, which, in addition to visceral obesity, comprises dyslipidemia, hypertension, and dysglycemia. Hyperuricemia, arteriosclerosis, microalbuminuria, platelet hyperaggregation and antifibrinolysis,

sleep apnea, and male hypogonadism have also been associated with this syndrome. The risk of T2DM is also markedly higher in first-degree relatives of individuals with T2DM and in women with a history of gestational diabetes mellitus (GDM) or polycystic ovary syndrome (PCOS), all of whom are mostly insulin resistant [14, 15, 24–27]. These associations raise the question of whether chronic insulin resistance represents an inherited or an acquired abnormality. Despite the fact that a family history of T2DM raises the risk of T2DM in the relatives, even the combination of all currently known genes associated with diabetes adds only little to the prediction of T2DM based on gender, age, and body mass index [23]. Interventions improving insulin resistance also markedly reduce the incidence of T2DM [28], which underscores the predominant role of lifestyle in the pathogenesis of insulin resistance.

As a result, several metabolic factors related to lifestyle associate or predict insulin resistance and T2DM. These factors are mainly related to lipid metabolism, such as plasma concentration of non-esterified or free fatty acids (FFAs) [29], serum triacylglyceride-to-serum high-density lipoprotein (TAG/HDL-C) [30, 31], and ectopic fat content in skeletal muscle (intramyocellular TAGs) [32–34] or in the liver (hepatocellular lipid content, HCL) [35, 36]. In addition, intake of red meat was among the best predictors of T2DM in a large epidemiological study [37] and plasma concentrations of amino acids also predict T2DM [38]. There is also evidence that altered secretion patterns of cytokines, mainly derived from adipose tissue, and elevation of circulating proinflammatory markers such as C-reactive protein may predict insulin resistance and T2DM [39, 40]. On the other hand, adiponectin is the only anti-inflammatory cytokine with lower circulating levels before the onset of T2DM [41], while concentrations of others such as interleukin-1 receptor antagonist (IL-1RA), transforming growth factor-β1 (TGF-β1) and growth differentiation factor-15 (GDF-15) are increased [42] and indicate the presence of a compensatory, but eventually futile, counter-regulation of proinflammatory stimuli. Although all metabolic and inflammation-related variables also circulate systemically and may cause effects in several tissues simultaneously, insulin resistance may sequentially affect certain insulin responsive tissues, such as skeletal muscle, liver, and adipose tissue.

Insulin resistance in skeletal muscle

^{13}C NMR spectroscopy permitted for the first time non-invasive, direct assessment of rates of insulin-stimulated muscle glycogen synthesis *in vivo*. Using this approach, it was found that muscle glycogen synthesis accounts for about 90% of insulin-stimulated whole-body glucose disposal and for virtually all of the non-oxidative glucose disposal in healthy insulin-sensitive humans [43]. Persons with T2DM exhibit a 60% reduction in insulin-stimulated muscle glycogen synthesis, which represent the main abnormality underlying their insulin resistance [43, 44]. Similarly, after ingestion of mixed meals, the increase in muscle glycogen synthesis was ~30% lower in persons with T2DM despite doubled serum insulin concentrations compared with insulin-sensitive individuals [45–47]. Applying combined ^{13}C/^{31}P NMR spectroscopy to measure directly the time course of intracellular concentrations of key metabolites in the pathway of muscle glycogen synthesis (intramyocellular glucose, glucose-6-phosphate [G-6-P] and glycogen) revealed diminished increases in G-6-P [48] and intramyocellular glucose concentrations [44] in skeletal muscle of T2DM during hyperinsulinemia (Figure 13.2). This indicates that an abnormality in insulin-stimulated glucose transport via glucose transporter 4 (GLUT-4) are the main abnormalities responsible for muscle insulin resistance in persons with T2DM and/or obesity and in insulin-resistant first-degree relatives of persons with T2DM [49]. Further studies to delineate the mechanism by which insulin resistance affects recruitment of GLUT-4 have indicated that upstream defects in the insulin signaling cascade are responsible for the impaired GLUT-4 translocation [50, 51].

It has been suggested previously that hyperglycemia may cause these abnormalities by a mechanism summarized as "glucose toxicity" [52, 53], which seems to be supported by similar impairments of insulin-stimulated glycogen synthesis and G-6-P increases in skeletal muscle in individuals with poorly controlled type 1 diabetes mellitus (T1DM) [54, 55]. However, since insulin-resistant but normoglycemic humans, such as lean relatives of obese or elderly persons with T2DM exhibit identical effects, mechanisms other than glucose toxicity have to explain the insulin resistance in the skeletal muscle of these groups [49, 56–58].

Most insulin-resistant but normoglycemic humans feature dyslipidemia with elevated very-low density lipoproteins (VLDLs), TAGs and/or FFAs, which also predict not only T2DM [29, 59–61] but also cardiovascular mortality [62]. Excess lipid storage in the form of obesity has long been associated with insulin resistance, but ^{1}H NMR studies provided evidence for an even stronger relationship between intramuscular [63] and intramyocellular TAG content and muscle insulin resistance than for body fat content [34, 63–65]. Intramyocellular TAG concentrations can be measured non-invasively by ^{1}H NMR spectroscopy and have also been termed ectopic lipid accumulation or metabolic obesity. The observation of augmented ectopic lipid deposition in insulin-resistant states infers that intracellular TAGs or lipid metabolites could mediate the effect of circulating lipids on insulin action (Figure 13.1a). From early preclinical studies, Randle explained the impaired glucose metabolism in T2DM by an interaction with FFAs, termed the "glucose–fatty acid cycle" [66]. This hypothesis postulated that FFA oxidation first raises the mitochondrial concentration ratio of acetyl-coenzyme A (acetyl-CoA)/CoA, which would inhibit the pyruvate dehydrogenase (PDH) complex. The subsequent rise in citrate would inhibit phosphofructokinase-1 and raise G-6-P, which would then inhibit hexokinase and finally increase intracellular glucose concentrations and reduce muscle glucose uptake. In contrast, short-term elevations of plasma TAGs and FFAs resulted in marked muscle insulin resistance but

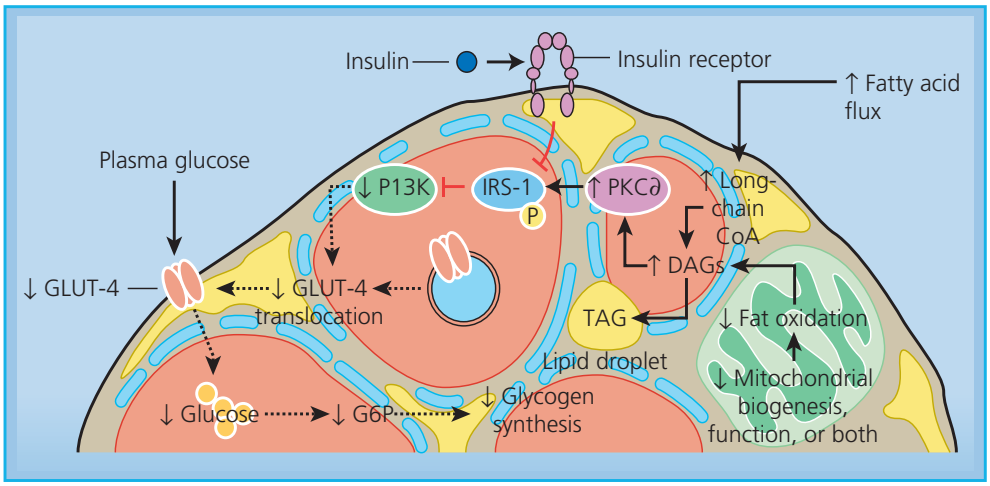

Figure 13.2 Cellular mechanism of insulin resistance in human skeletal muscle. Augmented lipid availability, mainly increased fatty acid flux, raises the intramyocellular pool of the long-chain fatty acyl (CoA) pool, which fuels mitochondrial oxidation or serves to synthesize diacylglycerols (DAGs) for storage as triglyceride (TAG) lipid droplets. When fatty acid delivery and uptake exceed the rates of mitochondrial long-chain fatty acyl-CoA oxidation and incorporation of DAGs into TAGs, the intramyocellular DAG content transiently or chronically increases. Specific, mainly C_{18}-containing, DAGs in the membrane and cytosol promote the activate novel protein kinase C (nPKC) isoforms. Translocation of the PKCθ isoform to the membrane leads to increased serine phosphorylation of insulin receptor substrate 1 (IRS-1) on critical sites (e.g. Ser 1101), which in turn blocks insulin-stimulated tyrosine phosphorylation of IRS-1 and the binding and activation of phosphatidylinositol 3-kinase (PI3K). This results in reduced recruitment of glucose transporter type 4 (GLUT-4) units to the membrane with impaired insulin-stimulated glucose uptake and phosphorylation to glucose-6-phosphate (G-6-P) and ultimately decreased insulin-stimulated glycogen synthesis. Source: Shulman 2014 [51]. Copyright © 2014 Massachusetts Medical Society. Reprinted with permission.

a blunted rise in intramyocellular glucose and G-6-P as measured using $^{13}C/^{31}P$ NMR spectroscopy during insulin stimulation in healthy humans. Lipid-induced muscle insulin resistance in humans thereby results from reduction of insulin-stimulated glucose transport into the muscle cells with subsequently impaired glucose phosphorylation and decreased insulin-stimulated glycogen synthesis [50, 67, 68] (Figure 13.2). Thus, lipids cause insulin resistance in humans via direct inhibition of glucose transport, but not via inhibition of the PDH complex [50, 69, 70]. Some studies [71, 72], but not others [73], suggest that lipid-induced insulin resistance may be more pronounced in men than in women, which would support the known greater diabetes risk for men.

Of note, intramyocellular TAGs are an even better predictor of insulin resistance in muscle and liver than circulating plasma FFAs [34]. Indeed, lipid-induced insulin resistance is reflected by impaired insulin signaling via reduction in tyrosine phosphorylation of insulin receptor substrate-1 (IRS-1) [50, 74], IRS-1-dependent phosphatidylinositol 3-kinase (PI3K) activation, and serine phosphorylation of Akt [75]. This could result from accumulation of intramyocellular long-chain fatty acyl-CoA (LCFA-CoA), diacylglycerols (DAGs), or ceramides [76] (Figure 13.2). Studies on transgenic and knockout animal models provide compelling evidence that FFA elevation increases intramyocellular LCFA-CoA, CoA, and DAGs, but not ceramide content, along with stimulation of TAG synthesis by DAG *O*-acyltransferase-1 (DGAT-1) and of novel protein kinase C (PKC) θ with subsequent serine phosphorylation of IRS-1 via the serine–threonine kinase cascade [77, 78]. However, studies employing other animal models showed that the ceramide pathway could also be involved in lipid-induced insulin resistance [79–81]. Several studies in humans reported conflicting results, likely due to differences in the design, cohorts, and analytical methods [72, 82, 83]. A recent study shed more light on the time course of events of lipid-induced insulin resistance by performing serial biopsies in humans during lipid infusion and comparing the results obtained from biopsies from insulin-resistant individuals with obesity or T2DM [73]. Lipid infusion resulted in a transient increase in intramyocellular DAGs, followed by activation of PKCθ and increased phosphorylation of the serine 1101 residues of IRS-1, with subsequent inhibition of insulin signaling and insulin-stimulated muscle glucose disposal (Figure 13.1). Similar increases in myocellular DAGs and PKCθ activation were found in obese individuals with T2DM without lipid infusion. Of note, DAG subspecies containing C_{18}-acyl residues correlated best with insulin resistance in all conditions of insulin resistance, whereas total ceramides and their subspecies were not affected either by lipid infusion or in common insulin resistance of obesity and T2DM [73].

In addition to lipids, dietary excess of protein has also been related to insulin resistance [84] and circulating branched-chain amino acids also predict T2DM [85]. In analogy with FFAs, short-term elevation of plasma amino acids indeed reduces insulin-stimulated G-6-P and glycogen synthesis [84] by activating the mammalian target of the rapamycin (mTOR)/p70 S60 kinase pathway with subsequent serine phosphorylation of IRS-1 [86, 87]. This pathway would further favor ectopic lipid storage [88]. In conclusion, the lipid-induced insulin resistance or lipotoxicity hypothesis proposes that in the absence of a balance between FFA delivery and muscle TAG synthesis via DGAT-1 as well as

oxidation in the mitochondria, lipotoxic species such as DAGs will accumulate and activate PKCθ in skeletal muscle. This in turn will activate a serine/threonine cascade, leading to impaired insulin signaling and impaired insulin-stimulated glucose uptake. Any mechanism by which lipid delivery to the muscle is reduced, lipid oxidation is increased, and/or TAG synthesis is stimulated will likely reduce LCFA-CoA and DAG concentrations and prevent lipid-induced muscle insulin resistance.

Consequently, decreases in muscle lipid oxidation could serve as another contributor to lipid accumulation in the skeletal muscle and thereby insulin resistance. Indeed, flux rates through muscle ATP synthase, reflecting basal mitochondrial phosphorylation, were found to be ~40% lower in lean insulin-resistant first-degree relatives of individuals with T2DM than in insulin-sensitive but otherwise matched people [89]. During insulin stimulation, muscle ATP synthase flux doubled in insulin-sensitive humans, but was almost abolished in the offspring of persons with T2DM [56]. Similarly, non-obese individuals with T2DM featured ~25% lower mitochondrial phosphorylation rates in the basal (fasting) state [58, 90] and no increase during insulin stimulation even in the presence of increased availability of glucose as a substrate [58, 90] (Figure 13.1a). This may be due to reduced capacities of the electron-transport chain and/or the phosphorylation system [90] and/or reduced insulin-stimulated phosphate transport into the myocytes.

Aging as one central risk factor of T2DM associates with impaired biogenesis and accelerated apoptosis of mitochondria [91]. Non-obese elderly humans are not only frequently insulin resistant but also feature higher intramyocellular TAG contents and ~30-40% lower rates of both muscle ATP synthase flux and tricarboxylic acid (TCA) cycle oxidation [92, 93]. Hence age-associated reductions in mitochondrial function may predispose elderly people to ectopic lipid accumulation and muscle insulin resistance [92], possibly owing to damage by accumulating reactive oxygen species (ROS). In line with this contention, similar reductions were reported for neural mitochondrial activity in healthy elderly individuals [94]. The hypothesis of age-associated ROS-induced reductions in mitochondrial function contributing to age-associated muscle insulin resistance was further supported by findings in transgenic mice with overexpression of human catalase targeted to the mitochondria (MCAT mice) [95]. These mice were protected from age-associated abnormalities in muscle mitochondrial function and DAG/PKCθ-induced muscle insulin resistance along with reduced mitochondrial oxidative damage, preserved muscle ATP synthesis, and adenosine 5′-monophosphate-activated protein kinase (AMPK)-induced mitochondrial biogenesis [96, 97]. Moreover, measurements of basal and insulin-stimulated rates of muscle pyruvate dehydrogenase (V_{PDH}) flux relative to citrate synthase flux (V_{CS}) employing [1-^{13}C]glucose incorporation into glutamate relative to alanine in muscle biopsies from healthy, lean, elderly and young humans revealed a blunted rise of insulin-stimulated V_{PDH}/V_{CS} fluxes in the elderly along with 25% lower muscle glucose uptake and 70% higher accumulation of intramyocellular TAGs [98]. These findings indicate a marked inability of mitochondria to switch from lipid to glucose oxidation during insulin stimulation. Taken together, combined acquired and age-associated reductions in features of mitochondrial function may promote intramyocellular lipid accumulation and insulin resistance in T2DM.

In addition to aging per se, other metabolic factors such as hyperglycemia and dyslipidemia may impair mitochondrial function and thereby contribute to muscle insulin resistance. In this context, insulin-resistant individuals with type 1 diabetes have lower insulin-stimulated ATP synthase flux, which negatively relates to glucometabolic control [55]. Short-term lipid infusion also leads to lower muscle ATP synthase flux, but only upon the onset of insulin resistance in healthy humans [99]. Of note, the reduced rates of insulin-stimulated ATP synthase flux were associated with impaired insulin-stimulated increases in muscle G-6-P concentrations due to lower insulin-stimulated glucose uptake [99, 100]. Also, lipid lowering via inhibition of lipoprotein lipase (LPL) by acipimox improves insulin resistance independently of changes in oxidative capacity in T2DM [101]. These findings suggest that glucose- and lipid-induced abnormalities in muscle mitochondrial function are not primary events in the development of insulin resistance in common T2DM.

A series of studies addressed the role of mitochondrial function independently of age and metabolic control [89, 102]. Young, lean, but severely insulin-resistant first-degree relatives of persons with T2DM were identified with 30% lower basal rates of muscle ATP synthase and TCA cycle fluxes compared with to age- and body mass-matched insulin-sensitive individuals [89]. This abnormality of mitochondrial oxidative phosphorylation was found in the presence of 38% lower mitochondrial density, indicating that the reduction in mitochondrial function may be attributed to lower muscle mitochondrial content [103]. In contrast to previous reports on skeletal muscle of persons with T2DM [104, 105], this was not explained by reduced expression of the peroxisome proliferator-activated receptor (PPAR) γ-coactivator 1α (PGC1α) [103], a key regulator of mitochondrial biogenesis. Likewise, in another cohort of first-degree relatives of individuals with T2DM, the stimulatory effect of exercise training on insulin sensitivity and ATP synthesis did not depend on common single-nucleotide polymorphisms (SNPs) of PGC1α, but was modified by a G/G-SNP of the gene encoding NADH dehydrogenase (ubiquinone) 1β subcomplex (NDUFB6), a component of complex I of the mitochondrial respiratory chain [55]. The finding that the insulin resistance in relatives of T2DM is related to lower fasting and insulin-stimulated rates of muscle ATP synthesis in a similar fashion as in persons with overt T2DM strongly underlines the role of inherited factors in the pathogenesis of insulin resistance and T2DM [58, 106]. Taken together, at least in this cohort of insulin-resistant first-degree relatives of individuals with T2DM, it is likely that a reduction in mitochondrial content, due to reduced mitochondrial biogenesis, is responsible for the reduced mitochondrial oxidative and phosphorylation activity and may be an acquired abnormality [107, 108]. Nevertheless, given the key role of mitochondrial activity in the regulation of fat metabolism in

muscle cells [109–113], these data suggest that the reduced mitochondrial function may be an important predisposing factor that promotes DAG accumulation in muscle cells and insulin resistance in muscle among persons with insulin resistance whose parents have T2DM.

Insulin resistance in the liver

The liver plays a key role in the transition from the fasted to the fed state by its unique ability to switch rapidly from a glucose-producing organ to a glucose-storing organ. After ingestion of a mixed meal, the liver suppresses glucose production and takes up glucose for storage in the form of glycogen [114, 115]. In insulin-resistant individuals with T2DM, the excessive postprandial hyperglycemia results from impaired suppression of glucose production along with ~45% lower hepatic glycogen accumulation than in healthy people [46]. This cannot be explained simply by the impaired prandial insulin secretion, but rather results from other mechanisms such as defective insulin-stimulated flux through glycogen synthase, because this abnormality persists during hyperinsulinemic–hyperglycemic clamps, which maximally favor glycogen synthesis [46]. Insulin-mediated hepatic glycogen synthesis correlates inversely with ectopic lipid content in the liver not only in persons with T2DM but also in those without, in line with a close link between hepatic lipid content and hepatic insulin resistance [46, 93] (Figure 13.1). Hepatic lipid accumulation, previously termed steatosis, is another form of ectopic lipid accumulation and is now included in the definition of non-alcoholic fatty liver disease (NAFLD). Steatosis relates closely to whole-body insulin resistance and is present in obesity, the metabolic syndrome, and women with a history of GDM or with T2DM [116, 117]. Although it has been discussed that NAFLD develops in the setting of or secondary to prevailing insulin resistance [118, 119], increased lipid availability per se could also induce hepatic triglyceride storage and insulin resistance [35]. This hypothesis is supported by studies in humans where short-term lipid infusions caused hepatic insulin resistance as reflected by impaired insulin-mediated suppression of glucose production [120]. Recent reviews have summarized the data from animal models that indicate that lipid intermediates such as DAGs also inhibit insulin signaling and stimulate triglyceride accumulation in the liver, similarly to the mechanism of lipid-induced insulin resistance in skeletal muscle [51, 77, 83] (Figure 13.3). In particular, one study in rats inducing selective hepatic steatosis by a 3-day high-fat diet found that hepatic insulin resistance corresponds to impaired tyrosine phosphorylation of IRS-2 and increased activities of PKCε and c-Jun N-terminal kinase (JNK) 1, which act as serine/threonine kinases and can phosphorylate serine residues of IRS-2 [121]. One study of human liver biopsies detected increases in some PKC isoforms (ε, α, and ζ) in obese persons with T2DM [122]. Human fatty livers also contain more stearoyl-CoA desaturase 1 (SCD1) activity and DAGs but not ceramide, which positively relate to hepatic fat content [123]. Recent intraoperative liver biopsy studies provided evidence that increases in hepatic DAG content [124, 125] and PKCε activity [124] correlate negatively with hepatic insulin sensitivity in obese individuals with NAFLD, thereby underlining a critical role of the DAG/nPKC pathway also in hepatic insulin resistance in humans (Figure 13.3).

Although NAFLD is most often associated with obesity, there are important exceptions where NAFLD and hepatic insulin resistance coexist in lean individuals [126, 127]. Healthy, young, lean Asian Indian men have a markedly greater risk of hepatic steatosis associated with hepatic insulin resistance than men of other

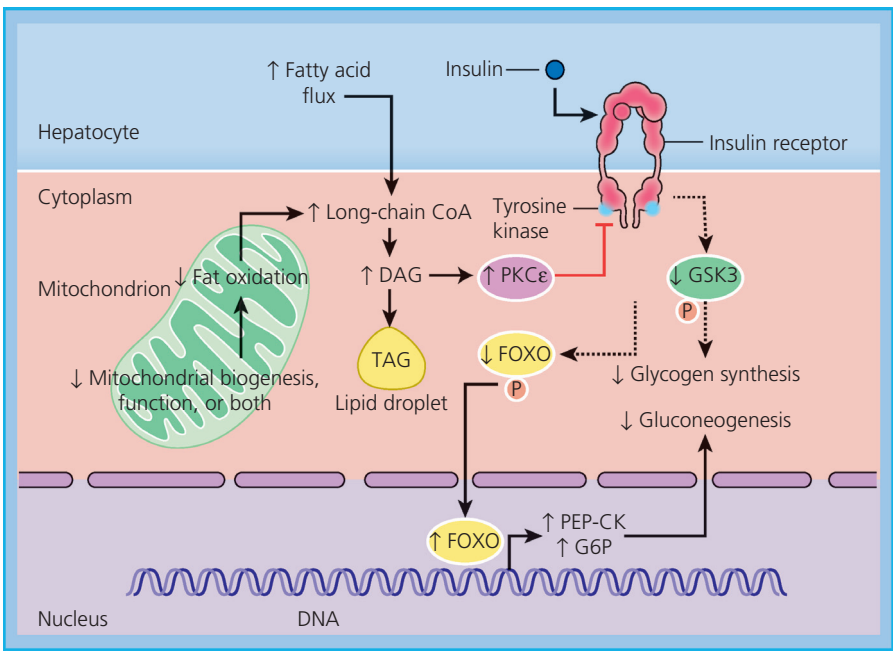

Figure 13.3 Cellular mechanism of insulin resistance in human liver. An imbalance of intrahepatocellular fluxes gives rise to hepatocellular diacylglycerols (DAGs), particularly when DAG synthesis, from both fatty acid re-esterification and *de novo* lipogenesis, exceeds the rates of mitochondrial oxidation of long-chain fatty acyl-coenzyme A (CoA) and/or the rates of DAG incorporation as triglycerides (TAGs) into lipid droplets. This activates the epsilon isoform of protein kinase C (PKCε), which likely phosphorylates the insulin receptor tyrosine kinase. In turn, phosphorylation of glycogen synthase kinase 3 (GSK3) phosphorylation increases, while that of forkhead box subgroup O (FOXO) decreases. This results in inhibition of glycogen synthase activity and thereby lower insulin-stimulated glycogen storage and in FOXO-mediated gene transcription of the gluconeogenic enzymes (e.g. phosphoenolpyruvate carboxykinase [PEP-CK] and G6P), with decreased insulin suppression of hepatic gluconeogenesis. Source: Shulman 2014 [51]. Copyright © 2014 Massachusetts Medical Society. Reprinted with permission.

ethnic groups. Two polymorphisms (rs2854116 and rs2854117) in the apolipoprotein C3 (ApoC3) gene seem to predispose these individuals and lean men of Asian ethnic backgrounds to NAFLD and insulin resistance [128]. In these carriers of the APOC3 variant alleles (C-482T, T-455C, or both), higher fasting plasma apolipoprotein C3 and plasma TAG concentrations are 30% and 60% higher, respectively, than in wild-type homozygous humans [128, 129]. These findings can be explained in part by the inhibitory effect of apolipoprotein C3 on LPL activity resulting in reduced plasma triglyceride clearance, leading to increases in postprandial hypertriglyceridemia and increased postprandial chylomicron remnants. This mechanism was validated genetically in transgenic mice with hepatic overexpression of human ApoC3, which were more prone to develop hepatic steatosis than their wild-type littermate counterparts when fed a high-fat diet [130]. Of note, this ApoC3 gene–environment interaction has only been observed in male individuals, likely reflecting a protective effect of estradiol on inhibition of LPL activity [131]. Furthermore, this ApoC3 gene–environment interaction is not observed in obese individuals in whom this relatively subtle gene–environment effect to promote hepatic steatosis in lean individuals is masked by the dominant effect of obesity and insulin resistance to promote NAFLD [132].

A genome-wide association study identified a missense mutation I148M within a patatin-like phospholipase domain containing 3 (PNPLA3/adiponutrin) that is more prevalent in Hispanic individuals and associates with NAFLD [133]. The rs738409 polymorphism PNPLA3 also leads to impaired TAG hydrolysis [134]. Although the association between this polymorphism and hepatic steatosis has been reproduced in other populations, there is no association with insulin resistance with the limitation of these studies that all the participants were obese and likely insulin resistant [135]. Finally, alterations in other genes that regulate lipogenesis leading to lipodystrophy (e.g. AGPAT2, PPARγ) [136] or lipolysis (e.g. perilipin, ATGL, CGI-58) [137] may also lead to ectopic lipid deposition and insulin resistance. Hence there is growing evidence that gene–environment interactions can predispose even lean individuals to hepatic insulin resistance, NAFLD, and T2DM. Of note, there are few exceptions in which ectopic lipid content dissociates from insulin resistance. A mutation in the *ABHD5* gene with consecutive deficiency in the protein comparative gene identification 58 (CGI-58) leads to Chanarin–Dorfman syndrome [92, 94, 95], which is characterized by excessive lipid deposition in the liver, muscle weakness, and central nervous symptoms in the absence of insulin resistance. In this condition, DAGs are restricted to storage in lipid droplets and thereby cannot promote PKCε translocation to the plasma membrane, which is required for its binding to the insulin receptor and inhibition of insulin signaling in the liver.

Similarly to skeletal muscle, non-obese persons with T2DM also show reductions in hepatocellular ATP concentrations as measured with non-invasive ^{31}P NMR methods [138] compared with age-matched and young persons without diabetes [139] (Figure 13.1). Even with adjustments for liver fat content, hepatic ATP concentrations correlated closely with hepatic insulin sensitivity but not with whole-body insulin sensitivity. Non-obese persons with T2DM also had 40% lower flux rates through hepatic ATP synthase, which relate to both peripheral and hepatic insulin sensitivity but negatively with body fat content [140]. Nevertheless, other features of hepatic mitochondrial function are not uniformly impaired in insulin-resistant humans [141–143]. Using high-resolution respirometry to quantify directly mitochondrial respiration in liver biopsies, it was found that despite similar mitochondrial contents, obese persons with or without steatosis had 4.3–5.0-fold higher maximal respiration rates in isolated mitochondria than lean persons, whereas persons with non-alcoholic steatohepatitis (NASH) featured 30–40% lower maximal respiration associated with greater hepatic insulin resistance [144] (Figure 13.4). These individuals also had higher degrees of mitochondrial uncoupling and leaking activity together with augmented hepatic oxidative stress paralleled by reduced antioxidant defense capacity and increased inflammatory response. These findings suggest an adaptation of the liver at early stages of obesity-related insulin resistance, which is subsequently lost during progression of NAFLD and insulin resistance. In line with this hypothesis, obese insulin-resistant individuals with steatosis had a sixfold greater increase in hepatic ATP concentrations than in lean insulin-sensitive individuals after ingestion of a single mixed meal [145].

Taken together, these findings suggest that loss of adaptation of hepatic energy metabolism to increased lipid flux from large visceral adipose tissue depots and/or adaptation-related hepatic oxidative stress could cause hepatic lipid accumulation and subsequent hepatic insulin resistance in the context of T2DM.

Insulin resistance in adipose tissue

Adipose tissue is highly sensitive to the action of insulin on lipolysis in healthy humans, but not in states of insulin resistance and T2DM [146–148], which are also characterized by elevations in plasma concentrations of TAGs and FFAs. These alterations will contribute to lipid-mediated effects on insulin sensitivity in other organs such as liver and skeletal muscle. On the other hand, obesity and the metabolic syndrome have been linked to a state of so-called "subclinical inflammation" arising from adipose tissue and leading to an imbalance of the secretion of adipocytokines with anti-inflammatory and insulin-sensitizing properties such as adiponectin and proinflammatory cytokines such as leptin, tumor necrosis factor-α and interleukin-6 (IL-6), and many others [149] (Figure 13.5). The latter adipocytokines may cause insulin resistance in liver and muscle by stimulating increased serine phosphorylation of IRS1 by activation of JNK1 and activation of Iκ kinase β (IKKβ)–nuclear factor-κB (NF-κB) kinase β, both of which are involved in chronic insulin resistance. Anti-inflammatory treatment either acutely with acetyl salicylate or chronically with salsalate promotes a modest improvement in glycemic control and insulin resistance in obese persons with

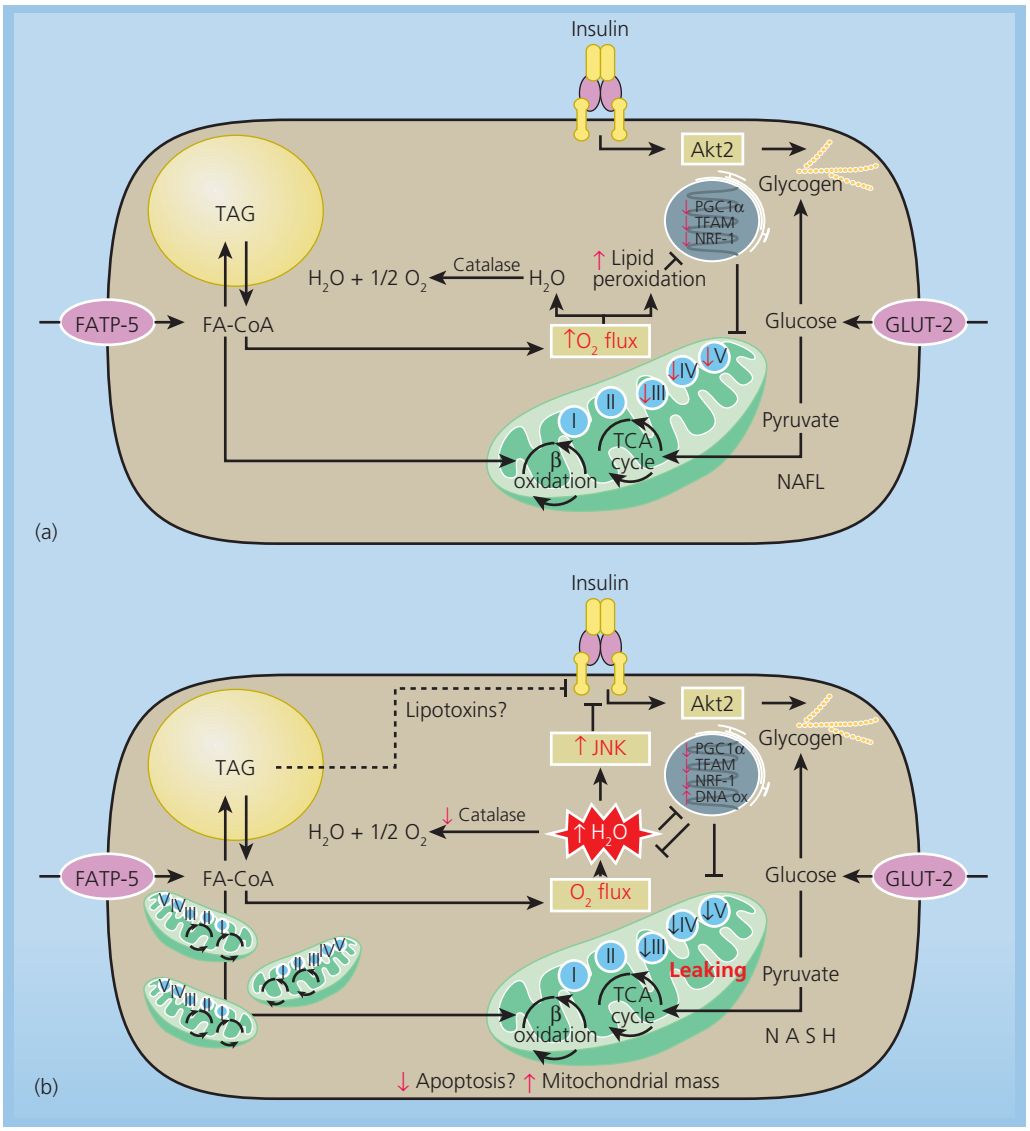

Figure 13.4 Hypothesis of adaptation of hepatic energy metabolism in the pathogenesis of non-alcoholic fatty liver disease and progression of hepatic insulin resistance. (a) In states of obesity, increased fatty acid delivery upregulates hepatic mitochondrial oxidative capacity, which prevents excessive storage of triacylglycerols (TAGs) but promotes the accumulation of reactive oxygen species and lipid peroxides, which are scavenged by hepatic catalase activity. (b) During the development of non-alcoholic fatty liver disease (NAFLD), the efficiency of mitochondrial coupling fails, which accelerates the generation of hydrogen peroxide (H_2O_2) in the face of decreasing catalase activity. Finally, oxidative stress decreases mitochondrial biogenesis, but increases leakage of mitochondria and activates c-Jun N-terminal kinase (JNK), which drives cellular inflammation and progression to steatohepatitis (NASH). Source: Koliaki et al. 2015 [144]. Copyright 2015 Elsevier.

T2DM [150, 151], indicating that activation of inflammatory pathways can contribute to obesity-associated insulin resistance and hyperglycemia in T2DM. Endoplasmic reticulum stress may serve as another cause of cellular inflammation and insulin resistance via JNK activation [152, 153]. In humans, weight loss following bariatric surgery improves insulin sensitivity [150, 154], which has been further associated with altered gut microbiota or hormone secretion [155] and also with reductions in endoplasmic reticulum stress. These hypotheses are currently under further investigation. Finally, chronically increased lipid availability may also cause mitochondrial and endoplasmic reticulum stress with release of reactive oxygen species, which in turn activate proinflammatory NF-κB [23]. Under these conditions, intracellular lipid metabolites (DAGs, ceramides, acyl-CoA) or even incomplete β-oxidation raising acylcarnitines can also contribute to the resulting insulin resistance [70, 156, 157].

Syndromes of lipodystrophy or lipoatrophy made it possible to study the roles of peripheral or visceral adipose tissues for insulin resistance and ectopic lipid deposition [126, 158–160]. Both inherited and acquired forms of generalized lipodystrophy are

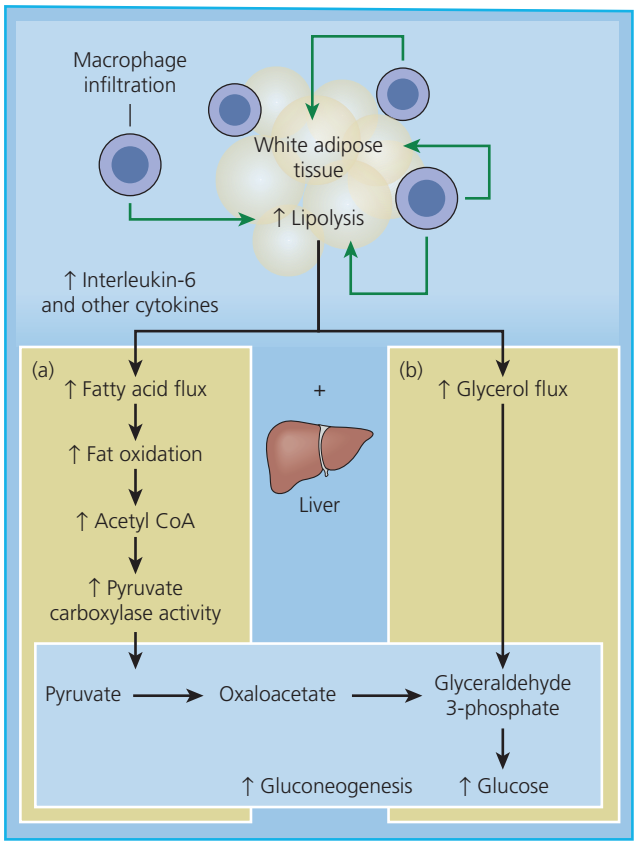

Figure 13.5 Hypothesis of macrophage-induced lipolysis in the pathogenesis of fasting hyperglycemia and insulin resistance. During the development of obesity, macrophage infiltration of white adipose tissue results in increased lipolysis by release of macrophage-derived cytokines such as interleukin-6. Increased rates of lipolysis lead to accelerated rates of hepatic gluconeogenesis by two mechanisms. (a) First, increased fatty acid delivery to the liver gives rise to hepatic acetyl-CoA levels, when its production through fat oxidation exceeds its rates of oxidation in the TCA cycle. This leads to increased pyruvate carboxylase activity. (b) Second, increased delivery of glycerol promotes its conversion to dihydroxyacetone (glyceraldehyde) 3-phosphate, which serves as precursor of glucose. Source: Shulman 2014 [51]. Copyright © 2014 Massachusetts Medical Society. Reprinted with permission.

devoid of relevant amounts of adipose tissue and develop excessive hypertriglyceridemia and ectopic fat deposition owing to fat overflow from the negligible triglyceride storage in adipocytes. Furthermore, these individuals have lower levels of inflammatory cytokines and leptin, resulting in hyperphagia [127]. Individuals with severe, generalized lipodystrophy have severe steatosis along with hepatic and muscle insulin resistance or even overt T2DM, which completely resolves after 3–8 months of leptin replacement therapy, as demonstrated previously in rodent models of lipodystrophy [77, 83]. Thus, visceral lipid may be a marker of hepatic steatosis rather than a causal player in the development of insulin resistance [127].

Although these findings also demonstrate that the important role of lipid-induced alterations at the onset of insulin resistance can be dissociated from inflammation, they do not exclude the operation of other mechanisms promoting the progression to impaired glucose tolerance and fasting hyperglycemia. According to the canonical view, impaired pancreatic β- and α-cell function first leads to reduced hepatic activation of Akt and exclusion of forkhead box (FOXO1) from the nucleus of the hepatocyte, with consequent transcription-mediated hepatic gluconeogenesis [161]. Second, subclinical inflammation would diminish insulin action through secreted (adipo)cytokines, which subsequently interfere with insulin signaling and increase hepatic gluconeogenic protein transcription by activating the NF-κB/JNK/ceramide pathways. Recently, an alternative mechanism has been proposed, by which macrophage-induced lipolysis may regulate hepatic gluconeogenesis independently of canonical insulin receptor signaling and thereby link subclinical inflammation to the onset of fasting hyperglycemia [51, 162] (Figure 13.5). Using a novel *in vivo* metabolomics approach in rodent models, it was demonstrated that IL6, released from macrophages within adipose tissue, inhibits insulin-mediated lipolysis in white adipose tissue (WAT) with augmented delivery of FFAs and to a lesser extent of glycerol to the liver [163]. This resulted in increased hepatic acetyl-CoA concentrations, due to increased fatty acid β-oxidation, which stimulated hepatic gluconeogenesis through allosteric activation of pyruvate carboxylase. In line with these studies in rodents, insulin-resistant obese adolescents displayed increased circulating IL6 concentrations and a more marked, 50% rise in IL-6 concentration in WAT along with impaired insulin-mediated suppression of lipolysis and endogenous glucose production compared with age- and body mass-matched insulin-sensitive humans. These studies collectively support the concept of an indirect action of insulin on hepatic glucose production via adipocytes [164, 165]. Some further observations underline that transcriptional control of hepatic gluconeogenesis cannot be due simply to direct insulin action on the liver to suppress glucose release. Insulin-mediated reduction in endogenous glucose production occurs rapidly, within minutes, even in individuals withT2DM [34], and there is a lack of any relationship between hepatic expression of gluconeogenic protein and fasting hyperglycemia in obese humans with and without T2DM [124].

Stepwise development of tissue-specific insulin resistance

The close association between obesity, ectopic fat accumulation, and insulin resistance makes it difficult to identify skeletal muscle, liver, or adipose tissue as the primary cause of insulin resistance. Nevertheless, the earliest development of insulin resistance occurs most likely in skeletal muscle, particularly in cohorts with inherited risk of insulin resistance or T2DM [89, 166] (Figure 13.6). The observation of rapid reversibility of hepatic but not muscle insulin resistance with moderate weight loss in individuals with NAFLD, and leptin replacement in generalized lipodystrophy [127] and T2DM [126], is in agreement with this contention. As detailed

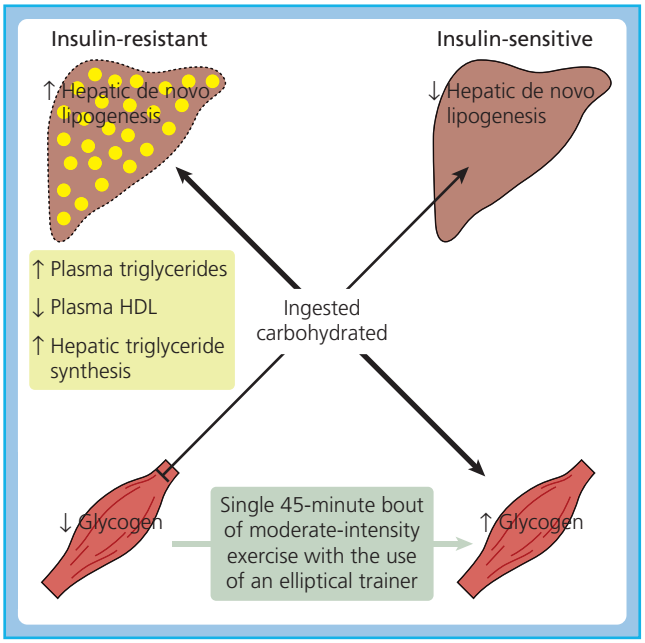

Figure 13.6 Concept of the stepwise development of insulin resistance from skeletal muscle to atherogenic dyslipidemia and non-alcoholic fatty liver disease. In healthy, young, lean persons, selective insulin resistance in skeletal muscle results in diversion of ingested carbohydrates from muscle glycogen synthesis to the liver. Combined with compensatory hyperinsulinemia, this stimulates hepatic de novo lipogenesis, synthesis of triglycerides and secretion of very low-density lipoproteins (VLDL) resulting in hypertriglyceridemia and reduced plasma high-density lipoprotein (HDL) levels. Of note, even one bout of exercising is able to restore the abnormal pattern of energy storage after carbohydrate ingestion by stimulating glucose uptake and glycogen synthesis in muscle through insulin-independent adenosine 5′-monophosphate-activated protein kinase (AMPK) activation of glucose transporter 5 (GLUT-4) recruitment. Source: Shulman 2014 [51]. Copyright © 2014 Massachusetts Medical Society. Reprinted with permission.

above, the principal mechanism involves tissue-specific accumulation of lipid species such as specific membrane and cytosolic but not droplet-bound DAGs, which occurs owing to an imbalance between substrate influx and oxidation (mitochondrial activity) and/or synthesis of TAGs in insulin-responsive tissues. Accordingly, any situation that will disrupt the balance between delivery and removal of DAG species to the muscle and the liver will lead to the accumulation of these lipid species, resulting in insulin resistance. This likely explains the high prevalence of obesity-associated insulin resistance, where lipid delivery exceeds storage and oxidation, the impaired adipocyte storage capacity in lipodystrophy, and the decreased substrate oxidation in certain forms of inherited insulin resistance such as lean, insulin-resistant relatives of individuals with T2DM or in acquired insulin resistance occurring during aging [135].

Evidence for the specific role of inefficient substrate oxidation during the onset of insulin resistance comes from the human model of lean, young, severely insulin-resistant relatives of persons with T2DM, who are devoid of any other confounding factors such as obesity, hyperglycemia, or subclinical inflammation. In these individuals, inherited abnormalities in muscle mitochondrial biogenesis and/or function can cause or at least contribute to muscle insulin resistance due to decreased substrate oxidation and subsequent accumulation of intracellular lipid metabolites with diminished insulin signaling [103, 167]. The impaired adaptation of insulin sensitivity to exercise training in carriers of the rs540467 polymorphism of the *NDUFB6* gene in such relatives of persons with T2DM is in line with this hypothesis [168]. Likewise, the rs2267668 A/G SNP in *PPARD* gene and the Gly482Ser SNP in the *PGC1A* gene also have independent and additive effects on the effectiveness of aerobic exercise training to increase physical fitness and insulin sensitivity in humans at risk for T2DM [169]. Impaired mitochondrial function as assessed from ATP synthesis was also found in other non-obese groups at increased risk for T2DM such as individuals with previous acromegaly [170] or gestational diabetes [117]. All these alterations in skeletal muscle metabolism would lead to lower rates of insulin-stimulated glucose disposal and accelerated rates of anaerobic glycolysis with release of lactate and alanine as substrates of hepatic gluconeogenesis.

Chronic overnutrition will increase the size of WAT and recruit macrophages to adipose tissue. As described above, local inflammation of adipose tissue leads to macrophage-induced lipolysis with release of TAGs and FFAs, which in turn elevates the WAT-derived hepatic acetyl-CoA pool and drives hepatic gluconeogenesis. This mechanism could potentiate the transition from whole-body insulin resistance to impaired glucose tolerance and T2DM. Chronic increases in hepatic gluconeogenesis would then impair insulin secretion by the pancreatic β cells and inappropriate glucagon secretion by the α cells due to glucose toxicity and ultimately exacerbate both fasting and postprandial hyperglycemia in the context of overt T2DM.

Finally, excessive flux of FFAs to the liver will promote NAFLD through increased hepatic esterification, which occurs in a mostly insulin-independent manner [171]. Hepatic mitochondria may transiently adapt to the increased substrate availability by upregulating their oxidative capacity at the expense of decreased coupling efficiency until NAFLD develops [143]. Ongoing substrate overloading will blunt the liver's antioxidant capacity and increase hepatic oxidative stress, with subsequent leakage of mitochondria and decreased mitochondrial biogenesis resulting in NASH and aggravated insulin resistance.

Recent studies provided experimental support for the concept of the stepwise development of insulin resistance in humans (Figure 13.6). Monitoring energy distribution employing $^{13}C/^{1}H$ NMR spectroscopy and hepatic *de novo* lipogenesis after ingestion of a high-carbohydrate meal revealed that postprandial muscle glycogen synthesis was reduced by ~60% in insulin-resistant compared with insulin-sensitive young, lean individuals [171]. On the other hand, liver TAG content and hepatic *de novo* lipogenesis were doubled in the insulin-resistant group. This was accompanied by 60% higher plasma TAG and uric acid contents and 20% lower fasting HDL-C but with no changes in circulating adipocytokines. These data confirmed that muscle insulin resistance per

se shifts the distribution of postprandial energy storage away from muscle glycogen and leads to upregulation of hepatic lipid synthesis and hepatic lipid storage and export of VLDL, thereby contributing to the development of atherogenic dyslipidemia; these are features of the metabolic syndrome independently of visceral obesity or subclinical inflammation. Meal-dependent increases in liver glycogen synthesis were comparable in insulin-resistant and insulin-sensitive individuals, which is in accordance with the low amount of liver lipids and normal hepatic insulin sensitivity in these individuals with muscle insulin resistance [90, 172]. Noteworthy, a single bout of moderate-intensity exercise abrogated the abnormal pattern of energy storage, which promoted muscle glycogen synthesis after carbohydrate ingestion through increased glucose transport activity [166, 173] (Figure 13.6). Moreover, non-obese insulin-resistant women with a history of GDM also feature doubled fasting liver TAGs without NAFLD, which correlates with insulin resistance and fat mass [117]. Of note, hepatic, but not visceral, fat mass relates to hepatic insulin resistance and increased TAG release [174]. Obese humans can further be identified as insulin resistant on the basis of liver and muscle lipid content, but not subcutaneous or visceral obesity [175].

Conclusion

Insulin resistance is likely the initial event preceding T2DM by decades before the onset of any relevant insulinopenia. Skeletal muscle insulin resistance results from accumulation of specific lipid intermediates, such as DAGs, which accumulate due an imbalance between delivery and removal by oxidation and TAG storage. Excess delivery of substrates is currently the most common reason for muscle insulin resistance. The impaired muscle insulin action distributes postprandial energy away from muscle glycogen storage towards hepatic *de novo* lipogenesis, NAFLD, the metabolic syndrome, and T2DM. During the onset of obesity, macrophage-induced lipolysis in the WAT-derived hepatic acetyl-CoA pool enhances hepatic gluconeogenesis and causes a transition from insulin resistance to impaired glucose tolerance and T2DM. Finally, loss of adaptation of hepatic mitochondria to excessive substrate delivery may accelerate steatosis and promote the progression of NAFLD, which is a major and independent predictor of cardiovascular morbidity and mortality in the context of T2DM [176].

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14 Genetic Architecture of Type 2 Diabetes

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Keypoints

- Diabetes can be considered as a spectrum of disorders with type 1 diabetes mellitus (T1DM) and type 2 diabetes mellitus (T2DM) as two ends of the spectrum, and maturity-onset diabetes of the young (MODY), latent autoimmune diabetes in adults (LADA) and other types being intermediates.
- T2DM is a complex disease characterized by impaired insulin secretion, insulin resistance, or both, and is caused by the intricate interplay between genetic, epigenetic, and environmental factors.
- The genetic architecture of a complex phenotype is defined by the number, frequencies, and effect sizes of causal alleles. The current understanding of the genetic architecture of T2DM points towards a combination of common single-nucleotide polymorphisms (SNPs), protective and rare variants, parent-of-origin effects, structural polymorphisms, and microRNAs, which can further be complicated by gene–gene and gene–environment interactions and also epigenetics.
- The technical revolution in the field of genetics such as genome-wide association studies (GWAS) and next-generation sequencing has allowed identification of >100 genetic variants in risk and protection of T2DM and many more with diabetes-related traits.
- Reported associations of SNPs significantly associated with T2DM account for <20% of the heritability of T2DM. There may be several reasons for these shortcomings: too simple assumptions have been made about the genetic architecture of the disease, ignoring additive and intrauterine effects, and restricting the analysis to only SNPs associated at 5×10^{-8}.
- The *CAPN10* gene on chromosome 10 encoding calpain 10 was the first T2DM susceptibility gene to be identified through linkage studies. The greatest success in linkage studies relates to the discovery of variants in the TCF7L2 as being associated with T2DM, but not the cause of linkage.
- The first candidate gene reproducibly associated with T2DM was *PPARG*, encoding the nuclear receptor PPAR-γ. The PPAR-γ receptor is a molecular target for thiazolidinediones, a class of insulin-sensitizing drugs used to treat T2DM, making it a very compelling candidate gene.
- In 2007, several GWAS on T2DM were published. Uniquely, for the first time most of them reported associations to the same SNPs and genes such as *TCF7L2*, *FTO*, *CDKAL1*, *HHEX*, *SLC30A8*, *IGF2BP2*, and *CDKN2A/2B*. These discoveries were therefore denoted Breakthrough of the Year 2007 by *Science*. Most of these variants have very modest risks. An exception was published recently from Greenland, where a common variant in the *TCFCB4* gene was strongly (odds ratio close to 10) associated with glucose tolerance as measured from an oral glucose tolerance test.
- Most T2DM-associated risk variants seem to influence β-cell function (e.g. *TCF7L2*, *CDKAL*, *SLC30A8*).
- Whereas monogenic forms of diabetes (MODY) have been successfully ascribed to highly penetrant mutations in more than 10 genes, only a few rare variants have been associated with T2DM, among them rare variants in the *PAM* and *PDX1* genes.
- A few variants protecting against T2DM have also been reported, including variants in the *SLC30A8* and *TCF2* genes. Mimicking how these variants protect against T2DM represents an ideal scenario for the development of new drugs.
- To describe the full genetic architecture of T2DM, a systems genetic approach will be needed, combining GWAS, DNA methylation and histone modifications, and expression profiling including mRNA, proteins, and metabolites.

The diabetes epidemic

Diabetes refers to a group of metabolic diseases characterized by hyperglycemia resulting from defects in insulin secretion, insulin action, or both [1]. The chronic hyperglycemia of diabetes is associated with long-term damage, dysfunction, and failure of different organs, especially the eyes, kidneys, nerves, heart, and blood vessels. Diabetes is currently the fastest growing epidemic. Worldwide prevalence figures estimate that there were 415 million people living with diabetes in 2015 and that by 2040 this number will have risen to 642 million [2]. India and China have the highest reported prevalences of diabetes, with 69.2 and 109.6 million in 2015, respectively, more than 90% of which is considered as type 2

Textbook of Diabetes, Fifth Edition. Edited by R. Holt, C. Cockram, A. Flyvbjerg and B. Goldstein.

diabetes mellitus (T2DM). In Europe, ~8% of the population is affected by diabetes, 90% of which is accounted for by T2DM, making T2DM the fastest increasing disease in Europe and worldwide [2, 3].

The T2DM epidemic can largely be ascribed to the worldwide increase in obesity during the last 30 years; for instance, more than 60% of individuals older than 15 years in the United Kingdom and United States are overweight (body mass index [BMI] >25 Kg/m^2) [4]. This has been attributed to a collision between genes and the environment. The social determinants of environmental factors tend to vary across populations and have changed rapidly over recent decades. A high energy-consuming lifestyle has been replaced by a Western sedentary one, with little or no exercise and energy-dense diet consumption. Meanwhile, genetic factors evolve at a slower rate across generations, and tend to favor the selection of "energy-saving thrifty genotypes," which might have been beneficial for individuals living in times of unstable food supply by storing energy in times of surplus [5]. While this hypothesis provides an appealing explanation of the obesity and T2DM epidemic, formal proof of this hypothesis is still lacking.

The diabetes spectrum

Diabetes encompasses a range of heterogeneous metabolic disorders characterized by the inability of the body to assimilate glucose and maintain glucose homeostasis. Diabetes has been traditionally subdivided into T2DM and type 1 diabetes mellitus (T1DM). However, this is a gross oversimplification of a rather complex situation. The concept of diabetes has grown over recent decades to the understanding that several different overlapping contributions from genetics and the environment can lead to manifestations of varying forms of disease. Contrary to being dichotomously distinct disorders, T1DM and T2DM can be considered rather as the two ends of a diabetes spectrum, with intermediates comprising of maturity-onset diabetes of the young (MODY), latent autoimmune diabetes in adults (LADA), and other subtypes.

T1DM, previously known as juvenile diabetes or insulin-dependent diabetes, is a chronic condition which is due to autoimmune destruction of pancreatic β cells and is characterized by (nearly) complete absence of insulin secretion, and the presence of autoantibodies including glutamic acid decarboxylase (GAD) antibodies, leading to dependence on insulin injections. It is most often diagnosed in children, adolescents, or young adults less than 35 years old. The incidence of T1DM varies based upon geography, age, gender, and family history [2]. Interestingly, the risk in offspring of an affected mother is 2–4% whereas the risk in those of an affected father is as high as 5–8% [6, 7]. The sibling relative risk of T1DM is estimated at 15 [8–10]. T1DM results from an interplay between genetic, epigenetic, and environmental factors [11]. Genetic studies have been able to explain 80% of the heritability of T1DM [12]. The main susceptibility genes currently accepted for T1DM are the HLA class II alleles, which account for up to 50% of genetic T1DM risk, and non-HLA loci including the insulin gene, *CTLA4*, *PTPN22*, interleukin 2 receptor a (*IL2RA*), and others [13]. Environmental factors suggested so far include enterovirus infections such as viruses of the picorna family, as they are seen more often among individuals with newly diagnosed T1DM than in the general population, and they precede the appearance of autoantibodies. Furthermore environmental pollutants, gut flora variations, and vitamin D exposure has all been implicated (See Chapter 10) [14–16].

LADA is a common subgroup of diabetes accounting for about 7% of all persons with diabetes in Europe. LADA is usually defined as GAD antibody-positive diabetes with onset at greater than 35 years of age and no insulin requirement during the first 6 months after diagnosis [17–19]. LADA with high antibody titers are found to the left of the spectrum close to T1DM, whereas LADA with lower titers are to the right of the spectrum close to T2DM [20]. A family history of any form of diabetes is a strong risk factor for the development of LADA [21]. Further discussion of clinical disorders with a type 1 phenotype can be found in Chapter 11.

MODY refers to monogenic forms of diabetes with well-defined high penetrance mutations in more than 10 different genes, and this number is still increasing (See Chapter 18). The disease is characterized by autosomal dominant transmission of early-onset (<25 years) diabetes and varying degree of β-cell dysfunction [22]. It was long debated whether the MODY genes would harbor common, less penetrant variants increasing the risk for T2DM; now, this seems to be the case for most of them, including *HNF1A*, *HNF4A*, *HNF1B*, *GCK*, and *PDX1* [23–25]. MODY shows extreme allelic heterogeneity, meaning that most MODY mutations are unique; to date, more than 200 mutations have been described in the *GCK* (MODY2) and *HNF1A* (MODY3) genes [26, 27]. The appropriate diagnosis of MODY requires sequencing. With the advent of next-generation sequencing technologies, accurate MODY diagnoses are much more feasible today.

Maternally inherited diabetes and deafness (MIDD) is due to the A3242G mutation in mitochondrial DNA (mtDNA) [26, 28]. As mtDNA is only transmitted from the mother, MIDD shows maternal transmission. In addition to hearing loss, many individuals also display neurological problems similar to those in persons with the MELAS syndrome (mitochondrial myopathy, encephalopathy, lactic acidosis, and stroke), which is also caused by the same mutation in mtDNA.

Neonatal diabetes is defined as diabetes with onset at birth or during the first 6 months of life with both transient and permanent forms [26]. Mutations in several genes have been shown to cause neonatal diabetes (*KCJN11*, *SUR1*, *GCK*, *INS*, etc.), and an appropriate genetic diagnosis is a prerequisite for optimal treatment. Individuals with mutations in the *KCJN11* gene have not only severe diabetes but also developmental defects (e.g. developmental delay, epilepsy, and neonatal diabetes [DEND]). These conditions are improved after switching from insulin treatment to treatment with large doses of sulfonylureas [29].

Diabetes can also develop secondary to pancreatic disease (See Chapter 21) or other endocrine disorders (See Chapter 20) and is referred to as *secondary diabetes*.

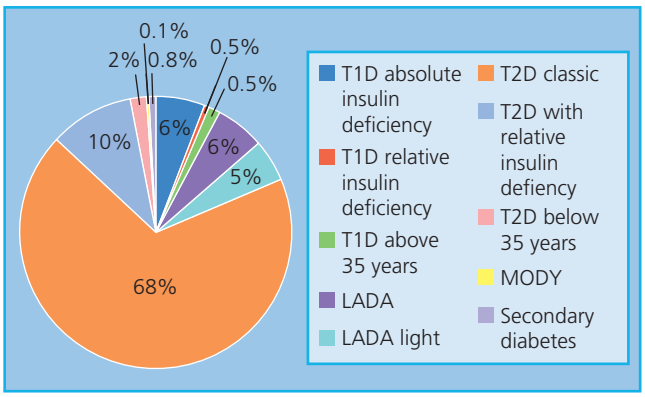

Figure 14.1 The spectrum of diabetes subgroups. The data are from the ANDIS project (All New Diabetics in Scania) (http://andis.ludc.med.lu.se) in April 2012, which at that time included 5800 individuals aged 0–100 years with newly diagnosed diabetes. The criteria used for diagnosis are as follows. T1DM: age at onset <35 years, C-peptide <0.2 nmol/L, and GAD antibodies >20; T1DM with relative insulin deficiency if C-peptide 0.2–0.6 nmol/L. T2DM: age at onset >35 years, C-peptide >0.6 nmol/L, GAD antibodies <10; T2DM with relative insulin deficiency C-peptide 0.2–0.6 nmol/L. LADA: age at onset >35 years, GAD antibodies >20; LADA light if GAD antibodies 10–20. The data clearly illustrate the difficulty in classifying persons with diabetes at diagnosis, with 19% unclassifiable. Source: Prasad RB, Groop L. Genetics of type 2 diabetes—Pitfalls and possibilities. *Genes* 2015; **6**:87–123 (this is an open-access article distributed under the Creative Commons Attribution License [CC BY]).

Type 2 diabetes is the most prevailing form, constituting 80–90% of all reported diabetes cases. T2DM is the result of a complex interplay between genetic, epigenetic, and environmental factors. T2DM develops when pancreatic β cells can no longer produce enough insulin to compensate for the insulin resistance. There is no formal definition of T2DM; individuals who do not fulfill criteria of T1DM, LADA, secondary diabetes, or monogenic forms of diabetes are considered to have T2DM. T2DM is more often associated with increased age, the age of onset usually being over 35 years [12]. However, it is increasingly reported in adolescents in high-risk countries such as India and China [3]. Heritability of T2DM is discussed below.

All these forms of diabetes represent a range of genetic etiologies from the monogenic MODY variants to T2DM, which is a complex heterogeneous polygenic disease with a strong environmental component. The ANDIS (All New Diabetics in Scania) project in southern Sweden represents a new attempt to reclassify diabetes into subgroups based upon genetic markers and biomarkers (Figure 14.1). A similar project has been initiated in Uppsala, Sweden, with the same goal (ANDIU: All New Diabetics in Uppsala).

Heritability of T2DM

T2DM clusters in families and it is well established that the risk of developing T2DM depends on both genetic and environmental factors. Heritability parameters facilitate understanding the genetic architecture of complex traits such as T2DM. However, heritability estimates have varied between 25 and 80% in different studies; the highest estimates are seen in those studies with longest follow-up period. The lifetime risk of developing T2DM is 40% for individuals who have one parent with T2DM and almost 70% if both parents are affected [30]. Further, the concordance rate of T2DM in monozygotic twins is about 70%, whereas that in dizygotic twins is only 20–30%. The proband-wise concordance rates (number of affected twins having a co-twin with diabetes) for monozygotic twins vary between 34 and 100% [31–34].The relative risk for first-degree relatives, i.e. the risk for developing T2DM if the person has an affected parent or sibling compared with the general population, is ~3, and ~6 if both parents are affected [35]. However, these figures vary depending on the cohort and population studied.

The prevalence of T2DM varies widely among populations, from a few percent among white Europeans to as high as 50% among Pima Indians in Arizona [36]. While part of the observed ethnic variability could be attributed to environmental and cultural factors, some of the variation seems to depend on genetic differences.

In spite of these reservations, there is no doubt that the risk of T2DM is partly determined by genetic factors, many of which have already been identified, and although each identified variant explains only a very small proportion of the risk of T2DM in the human population, they have contributed to our understanding of disease pathogenesis. One should also keep in mind that the variance explained by a risk allele in a population is not necessarily an indicator of its importance in specific persons, nor is it proportional to the affected pathway's importance or potential as a therapeutic target.

The >80 loci identified (see Tables 14.1–14.3 for lists of loci) explain less than 20% of the heritability of T2DM. There are many possible explanations for the missing heritability, including assumptions made about the genetic architecture of the disease and the definitions of heritability. The estimations of heritability explained assume that only additive affects determine disease risk and that the risk follows the liability threshold model, i.e. that the genetic and environmental effects sum up to form a normal distribution of liability and that disease arises in individuals surpassing a certain threshold in the distribution [86]. If these assumptions are not true, the estimate of heritability explained will not be correct.

Intrauterine effects can also affect heritability estimates because monozygotic twins are often monochorionic, which results in growth retardation compared with dizygotic twins and low birth weight is associated with increased risk of T2DM later in life. Furthermore, there could be other explanations to the "missing heritability" problem. However, one should keep in mind that heritability can only be estimated from the most recent generations for which information on affected status is available, whereas most of the variants studied thus far are ancestral variants hundreds of generations old. We do not know whether these ancestral variants (that have modest effects and have escaped purifying selection)

can really explain the diabetes epidemic that we see in the most recent generations or whether this can be ascribed to rare variants with stronger effects.

Moreover, heritability estimates are based on "top" SNPs from GWAS associations; novel methods have been proposed that take into account the (i) 0–1 scale as opposed to liability, (ii) ascertainment bias, and (iii) quality control of the GWAS SNPs. Estimating the proportion of variance explained by all SNPs in GWAS as opposed to only the most significantly associated SNPs could result in a more detailed estimate of heritability [87]. Applying an approach that considers all SNPs on the chip could in fact explain a much larger proportion of the "narrow-sense" heritability (>50%) supporting the existence of numerous yet unidentified loci with smaller effects [23, 88, 89].

The genetic architecture of T2DM

The genetic architecture of a complex phenotype is defined by the number, frequencies, and effect sizes of causal alleles. Many hypotheses have been proposed to define the genetic architecture of T2DM; one suggested that the unexplained heritability lies in a large number of common variants with low additive effects and that the disease represents the extremes of a normal distribution [69]. Another proposed that rare alleles might be responsible for effects observed with common variants (synthetic associations) and explain a majority of the heritability [59, 70, 71]. One argument against common and, more so, against rare variants is that they would have been removed from the population by natural selection [36]; however, this is not a valid argument for a disease such as T2DM where the penetrance of the genetic effect depends strongly on interactions with the environment, especially since this environment has changed in recent years and the genetic risk variants could have been neutral or even beneficial before the introduction of the westernized lifestyle.

Although extreme models are excluded by the present data based on epidemiological, linkage, and GWAS, models in which rare variants explain a little (<25%) or a lot (>80%) of the heritability remain consistent [72]. It is hoped that large next-generation sequencing studies in families will answer the questions about the role of rare variants in complex diseases. There is already substantial evidence for parent-of-origin effects on T2DM risk, and studies are ongoing to explore this further. Structural polymorphisms and microRNAs add a further layer of complexity and have not yet been exhaustively studied.

The genetic architecture could also be influenced by gene–gene interactions (epistasis) where rare variants with high penetrance could act jointly with common alleles to increase the risk of disease. The extent of allelic heterogeneity seems to be less pronounced for the common form of T2DM than for monogenic forms such as MODY. Moreover, there could be differences in the genetic predisposition to T2DM due to phenotypic heterogeneity within T2DM cases. For instance, lean people with T2DM are likely to carry a disproportionately high load of T2DM risk alleles [73].

Linkage studies

The *CAPN10* gene on chromosome 10 encoding calpain 10, a cysteine protease with largely unknown functions in glucose metabolism, was the first T2DM susceptibility gene to be identified through linkage studies. Unfortunately, this locus has been difficult to replicate in subsequent studies. The greatest success in linkage studies relates to the discovery of variants in the *TCF7L2* gene that are associated with T2DM. The DeCode team observed a rather modest linkage at a 10.5 Mb region on chromosome 10q, but decided to pursue and fine map it, thereby identifying the variant showing the strongest association with T2DM at the time. This was an intronic variant (rs7903146) in the *TCF7L2* gene that contributed to, but did not fully explain, the original linkage [37–39]. This association has since been confirmed in African, Asian, and European populations, rendering it the most consistently replicated genetic association with T2DM to date, conferring a relative risk of ~1.4 [40].

Candidate genes for T2DM

The first candidate gene reproducibly associated with T2DM was *PPARG*, encoding the nuclear receptor PPAR-γ [41]. The PPAR-γ receptor is a molecular target for thiazolidinediones, a class of insulin-sensitizing drugs used to treat T2DM, making it a very compelling candidate gene. The transcript expressed in adipose tissue has an extra exon B and a substitution of a proline for alanine at position 12 of this protein, which is seen in about 15% of the European population. This variant has been shown to be associated with increased transcriptional activity, increased insulin sensitivity, and protection against T2DM [41].

T2DM-risk variants in *KCJN11* were also discovered through candidate association studies [42, 43]. *KCNJ11* codes for four subunits of the ATP-sensitive potassium (K-ATP) channel, the other four coded by another gene (*ABCC8*). The E23K polymorphisms in *KCNJ11* and P12A in *PPARG* putatively acted in an additive manner to increase T2DM risk [44]. In pancreatic β cells, K-ATP channels are crucial for the regulation of glucose-stimulated insulin secretion and are the target for the sulfonylureas which are oral antidiabetes agents widely used in the treatment of T2DM, and for diazoxide, a potassium channel opener. Activating mutations in this gene also caused neonatal diabetes. Additionally, loss-of-function mutations in *KCNJ11* and *ABCC8* caused hyperinsulinemia in infancy [45].

Genome-wide association studies (GWAS) identify common variants associated with disease

The development of new genotyping technologies and the realization that we inherit stretches of the genome together as haplotypes facilitated the cataloguing of common variants (HAPMAP, 1000

genomes) and allowed for new possibilities of applying unbiased global approaches to screen millions of common variants for association with complex diseases. Several GWAS for diabetes were published in 2007, coined "Breakthrough of the Year" by *Science* magazine. The first was a GWAS on early-onset T2DM reporting two new diabetes loci: *HHEX* and *SLC30A8* [46]. The ultimate proof of the value of GWAS for T2DM came from three GWAS published back-to-back in *Science* in 2007; for the first time in the genetics of T2DM, three different studies reported the same top findings! [47–49].

The first wave of GWAS was followed by a second wave combining existing or new GWAS into meta-analyses of >50,000 individuals [23]. A prerequisite for this was that many research groups could work together in consortia such as DIAGRAM (DIAbetes Genetics Replication And Meta-analysis consortium) and MAGIC (Meta-Analyses of Glucose-and Insulin-related traits Consortium). GWAS do not inevitably lead to the identification of a gene or genes in a given locus associated with disease. Since the most strongly associated SNPs are often only markers for the functional variant responsible for the observed genetic effect and most associated regions harbor several genes, additional fine mapping of the loci in even larger sample sets is often necessary. To do this cost-efficiently, a custom-designed chip, the so-called CardioMetabochip (Illumina), was been developed for metabolic/cardiovascular gene mapping. This chip contains ~200,000 polymorphisms selected to cover association signals from a wide range of metabolic disorders (T2DM, lipid disorders, obesity, and cardiovascular disease), and was designed to perform both deep replication of major disease signals and fine mapping of established loci. Meta-analysis of previous GWAS by the DIAGRAM consortium with an additional 22,669 individuals with T2DM and 58,119 controls genotyped using the CardioMetabochip has recently added a further eight new loci associated with T2DM in the European population and two novel loci not previously reported in populations of European descent [50].

Recently, a number of GWAS and meta-analysis studies have also been performed with non-European cohorts, adding several new loci to the list of genome-wide significant associations [51–58]. Interestingly it seems that most associations found in one ethnic group also show some evidence of association in populations with other ethnicities. In total, GWAS have provided ~153 variants for T2DM mapping to >120 loci (Table 14.1, Figures 14.2 and 14.3) and also numerous loci for glucose- or insulin-related traits (Table 14.2), and more are likely to come.

Most studies to date have been limited to SNPs, leaving structural polymorphisms relatively unexplored. However, since common structural variants are likely to be tagged by surrounding SNPs, they are unlikely to explain a large proportion of missing heritability. A recent study identified a common copy number variant (CNV), CNVR5583.1 (*TSPAN8*), as associated with T2DM [65]. This association could be convincingly replicated by previously typed SNPs that tag the CNV [66].

Rare variants with stronger effects are often rare

Rare variants are more recent and therefore more likely to be those that arose recently in an extended pedigree. Of course, natural selection removes the more deleterious variants before they reach a high frequency, so risk alleles for diseases should be enriched at lower frequencies. The idea that there are unique rare variant combinations in families that play a role in disease etiology is referred to as "clan genomics" [59]. Recent data suggest that combined effects of rare and common variants contribute to varying extents to disease causation, not least linkage, and rare alleles may, in fact, explain the majority of heritability [60]. Next-generation sequencing provides an even denser coverage of genetic variation, rendering the detection of causal rare variants more feasible. Whole-genome sequencing (WGS) of 2630 Icelanders and imputation into 11,114 Icelandic individuals and 267,140 controls followed by testing in Danish and Iranian samples revealed variants in *PAM* and *PDX1* in risk of T2DM [61] (Table 14.3). Array-based genotyping and exome sequencing on a small founder population from Greenland revealed a nonsense p.Arg684Ter variant (allele frequency of 17%) in *TBC1D4* associated with higher concentrations of 2-hour glucose and serum insulin [62]. Whole exome sequencing in a Latino population revealed that a rare missense variant in *HNF1A* (c.1522G>A [p.E508K]) was associated with type 2 diabetes prevalence [63]. Additionally, rare variants associated with glycemic traits were discovered through exome sequencing of 9717 individuals from the METSIM study in Finland [64] (Table 14.3).

Protective variants

The average T2DM risk variant frequency in the general population is 54%, which raises the question of whether T2DM is the default condition. If so, then does carrying protective variants makes a difference in the disease susceptibility? Studies have been performed to address this question by including people without diabetes who, despite having clustering of risk factors for T2DM, have escaped the disease. A rare (0.66%) loss of function mutation (R138X) was detected in the *SLC30A8* gene in the Botnia region of Finland and subsequently replicated in a massive effort applying the Exome chip to >150,000 individuals in other European countries. Also, the DeCode group had identified another loss of function mutation, a frameshift mutation that was also enriched in the non-diabetic Icelandic population. The *SLC30A8* gene encodes the islet zinc transporter 8 with a putative effect on insulin secretion. Notably, a common variant in the same gene increases susceptibility to T2DM whereas autoantibodies to T1DM predispose to T1DM.

Collectively, carriers of these protein-truncating mutations have a 65% lower risk of T2DM [67]. Other studies based on Icelandic, Danish and Iranian populations identified a low-frequency variant in *CCND2* that reduced T2DM risk by half [61]. Moreover, variants in *TCF2* were found to be protective against T2DM [68]. It is also likely that more recent such variants that are only a few generations old segregate in families and could be detected though sequencing in families (Table 14.3).

Table 14.1 Genetic loci associated with risk of T2DM.

No.	T2DM risk SNP	Gene/nearest gene	Gene location	Chromosome	Risk allele	Other allele	Odds ratio	Trait	Ref.
1	rs17106184	*FAF1*	Intron	1	G	A	1.10	T2DM	[58]
2	rs2296172	*MACF1*	Coding – missense	1	G	A	1.10	T2DM	[131]
3	rs10923931	*NOTCH2*	Intron	1	T	G	1.13	T2DM	[4, 66]
4	rs340874	*PROX1*	Intergenic	1	C	T	1.07	Fasting glucose/ HOMA B/T2DM	[132]
5	rs243021	*BCL11A*	Intergenic	2	A	G	1.08	T2DM	[23]
6	rs243088	*BCL11A*	Intergenic	2	T	A	1.07	T2DM	[133]
7	rs2975760	*CAPN10*	Intron	2	C	T	1.17	T2DM	[134, 135]
8	rs3792267	*CAPN10*	Intron	2	G	A	1.17	T2DM	[134, 135]
9	rs7607980	*COBLL1*	Coding – missense	2	T	C	1.14	T2DM	[131]
10	rs560887	*G6PC2/ ABCB11*	Intron	2	T	C	1,03	Fasting glucose/ T2DM/HOMA B	[132]
11	rs780094	*GCKR*	Intron	2	C	T	1.06	T2DM/Fasting glucose/β-cell function/ triglycerides/ fasting insulin	[132]
12	rs3923113	*GRB14*	Intergenic	2	A	C	1.07	T2DM	[133, 136]
13	rs13389219	*GRB14*	Intergenic	2	C	T	1.07	T2DM	[133]
14	rs2943641	*IRS1*	Intergenic	2	C	T	1.19	Fasting glucose/ T2DM/HOMAB, HOMA IR/AUC ins./AUC ratio/ISI	[77]
15	rs7578326	*KIAA1486/ IRS1*	Intron of uncharac-terized LOC646736	2	A	G	1.11	T2DM	[23]
16	rs7593730	*RBMS1/ITGB6*	Intronic	2	C	T	1.11	T2DM	[137]
17	rs7560163	*RND3*	Intergenic	2	G	C	1.33	T2DM	[55]
18	rs7578597	*THADA*	Coding – missense	2	T	C	1.15	T2DM	[4, 66]
19	rs10200833	*THADA*	Intron	2	G	C	1,06	T2DM	[66, 138]
20	rs6723108	*TMEM163*	Intergenic	2	T	G	1.31	Decreased fasting plasma insulin/ HOMA-IR/T2DM	[139]
21	rs998451	*TMEM163*	Intron	2	G	A	1.56	Decreased fasting plasma insulin/HOMA-IR/T2DM	[139]
22	rs4607103	*ADAMTS9-AS2*	Intron	3	C	T	1.09	T2DM	[4, 66]
23	rs6795735	*ADAMTS9-AS2*	Intron	3	C	T	1,09	T2DM	[4, 66]
24	rs11708067	*ADCY5*	Intron	3	A	G	1.12	T2DM/2-h glucose/HOMA B	[80, 132]
25	rs2877716	*ADCY5*	Intron	3	C	T	1.12	2-h insulin adjusted for 2-h glucose/2-h glucose/T2DM	[80, 132]
26	rs11071657	*FAM148B*	Intergenic	3	A	G	1.03	Fasting glucose/ T2DM/HOMA B	[132]

Table 14.1 (*Continued*)

No.	T2DM risk SNP	Gene/nearest gene	Gene location	Chromosome	Risk allele	Other allele	Odds ratio	Trait	Ref.
27	rs4402960	*IGF2BP2*	Intron	3	T	G	1.11	T2DM	[47]
28	rs1470579	*IGF2BP2*	Intron	3	C	A	1.15	T2DM	[24, 47, 140, 141]
29	rs6808574	*LPP*	Intergenic	3	C	T	1.07	T2DM	[58]
30	rs1801282	*PPARG*	Coding – missense	3	C	G	1.09	T2DM	[47]
31	rs13081389	*PPARG*	Intergenic	3	A	G	1.24	T2DM	[23, 41, 140, 142]
32	rs17036160	*PPARG*	Intron	3	C	T	1.11	T2DM	[138]
33	rs1797912	*PPARG*	Intron	3	A	C	1.06	T2DM	[138]
34	rs831571	*PSMD6*	Intergenic	3	C	T	1.09	T2DM	[51]
35	rs7647305	*SFRS10*	Intergenic	3	C	T	1.08	BMI/obesity T2DM	[143]
36	rs16861329	*ST6GAL1*	Intron	3	G	A	1.09	T2DM	[136]
37	rs6780569	*UBE2E2*	Intergenic	3	G	A	1.21	T2DM	[144]
38	rs6815464	*MAEA*	Intron	4	C	G	1.13	T2DM	[51]
39	rs7656416	*MAEA*	Intron	4	C	T	1.15	T2DM	[51, 52]
40	rs6813195	*TMEM154*	Intergenic	4	C	T	1.08	T2DM	[58]
41	rs10010131	*WFS1*	Intron	4	G	A	1.14	T2DM	[4, 145]
42	rs4689388	*WFS1*	Neargene-5	4	T	C	1.16	T2DM	[77]
43	rs6446482	*WFS1*	Intron	4	G	C	1.11	T2DM	[23, 145, 146]
44	rs1801214	*WFS1*	Coding – missense	4	T	C	1.13	T2DM	[23, 145, 146]
45	rs459193	*ANKRD55*	Intergenic	5	G	A	1.08	T2DM	[133]
46	rs702634	*ARL15*	Intron	5	A	G	1.06	T2DM	[58]
47	rs4457053	*ZBED3*	Intron of ZBED3-AS1	5	G	A	1.08	T2DM	[23]
48	rs1048886	*C6orf57*	Coding – missense	6	G	A	1.54	T2DM	[147]
49	rs7754840	*CDKAL1*	Intron	6	C	G	1.17	T2DM	[23, 25, 47, 48, 54, 73, 144, 148]
50	rs7756992	*CDKAL1*	Intron	6	G	A	1.20	T2DM	[25]
51	rs2206734	*CDKAL1*	Intron	6	T	C	1.20	T2DM	[23, 25, 47, 48, 54, 73, 144, 148]
52	rs4712523	*CDKAL1*	Intron	6	G	A	1.27	T2DM	[23, 25, 47, 48, 54, 73, 77, 144, 148]
53	rs10946398	*CDKAL1*	Intron	6	C	A	1.12	T2DM	[23, 25, 47, 48, 54, 73, 144, 148]
54	rs7766070	*CDKAL1*	Intron	6	A	C	1.23	T2DM	[23, 25, 47, 48, 54, 73, 144, 148]
55	rs2244020 (rs9266650)	*HLA-B*	Intergenic	6	G	A	1.09	T2DM	[149]
56	rs1535500	*KCNK16*	Coding – missense	6	T	G	1.08	T2DM	[51]
57	rs3130501	*POU5F1-TCF19*	Neargene-5	6	G	A	1.07	T2DM	[58]
58	rs9505118	*SSR1-RREB1*	Intron	6	A	G	1.06	T2DM	[58]
59	rs9470794	*ZFAND3*	Intron	6	C	T	1.12	T2DM	[51]
60	rs17168486	*DGKB*	Intergenic	7	T	C	1.15	T2DM	[50]
61	rs2191349	*DGKB/TMEM195*	Intergenic	7	T	G	1.06	Fasting glucose, HOMA B/T2DM	[132]
62	rs6467136	*GCC1-PAX4*	Intergenic	7	G	A	1.11	T2DM	[51]
63	rs4607517	*GCK*	Intergenic	7	A	G	1.07	Fasting glucose/ T2DM/HOMA B	[132]
64	rs864745	*JAZF1*	Intron	7	T	C	1.10	T2DM	[4, 66]

(*continued*)

Table 14.1 (*Continued*)

No.	T2DM risk SNP	Gene/nearest gene	Gene location	Chromosome	Risk allele	Other allele	Odds ratio	Trait	Ref.
65	rs849134	*JAZF1*	Intron	7	A	G	1.13	T2DM	[23, 66]
66	rs12113122	*JAZF1*	Intron	7	G	C	1.55	T2DM	[138]
67	rs972283	*KLF14*	Intergenic	7	G	A	1.07	Reduced insulin sensitivity T2DM	[23]
68	rs516946	*ANK1*	Intron	8	C	T	1.09	T2DM	[50]
69	rs515071	*ANK1*	Intron	8	G	A	1.18	T2DM Reduced β-cell function	[50, 52]
70	rs13266634	*SLC30A8*	Coding – missense	8	C	T	1.19	T2DM	[46]
71	rs11558471	*SLC30A8*	Utr-3	8	A	G	1.15	Fasting glucose, HOMA B T2DM	[23, 46, 47, 73, 132, 140, 148]
72	rs3802177	*SLC30A8*	Utr-3	8	G	A	1.26	T2DM	[23, 46, 47, 73, 132, 140, 148]
73	rs896854	*TP53INP1*	Intron	8	T	C	1.06	T2DM	[23]
74	rs10965250	*CDKN2A/2B*	Intergenic	9	G	A	1.20	T2DM	[25, 48, 54, 142, 144, 148, 150, 151]
75	rs2383208	*CDKN2A/2B*	Intergenic	9	A	G	1.19	T2DM	[25, 48, 54, 142, 144, 148, 150, 151]
76	rs7018475	*CDKN2A/2B*	Intergenic	9	G	T	1.35	T2DM	[25, 48, 54, 142, 144, 148, 150, 151]
77	rs564398	*CDKN2A/2B*	Intergenic	9	T	C	1.12	T2DM	[25, 48, 54, 142, 144, 148, 150, 151]
78	rs10757282	*CDKN2A/2B*	Intergenic	9	C	T	1.14	T2DM	[25, 48, 54, 142, 144, 148, 150, 151]
79	rs10811661	*CDKN2B*	Intergenic	9	T	C	1.20	T2DM	[23, 47, 48, 54, 56, 66, 140, 142, 148]
80	rs7034200	*GLIS3*	Intron	9	A	C	1.03	Fasting glucose/ T2DM/HOMA B	[132]
81	rs7041847	*GLIS3*	Intron	9	A	G	1.10	T2DM	[51, 54]
82	rs10814916	*GLIS3*	Intron	9	C	A	1.11	T2DM	[51, 54, 132]
83	rs17584499	*PTPRD*	Intron	9	T	C	1.57	T2DM	[152]
84	rs2796441	*TLE1*	Intergenic	9	G	A	1.07	T2DM	[50]
85	rs13292136	*TLE4 (CHCHD9)*	Intergenic	9	C	T	1.11	T2DM	[23]
86	rs553668	*ADRA2A*	Utr-3	10	A	G	1.42	T2DM	[153]
87	rs10885122	*ADRA2A*	Intergenic	10	G	T	1.04	Fasting glucose/ HOMA B/T2DM	[132]
88	rs12779790	*CDC123, CAMK1D*	Intergenic	10	G	A	1.11	T2DM	[4, 66]
89	rs11257655	*CDC123/ CAMK1D*	Intergenic	10	C	T	1.15	T2DM	[54, 57, 66]
90	rs10906115	*CDC123/ CAMK1D*	Intergenic	10	A	G	1.13	T2DM	[54, 57, 66]
91	rs10886471	*GRK5*	Intron	10	C	T	1.12	T2DM	[54]
92	rs5015480	*HHEX*	Intergenic	10	C	T	1.13	T2DM	[23, 46, 142, 148, 151]
93	rs1111875	*HHEX/IDE*	Intergenic	10	C	T	1.13	T2DM	[47]
94	rs7903146	*TCF7L2*	Intronic/ promoter	10	T	C	1.35	T2DM, fasting glucose, 2-h glucose	[39]
95	rs4506565	*TCF7L2*	Intron	10	T	A	1.34	Fasting glucose, HOMA B T2DM	[23, 25, 39, 46, 48, 49, 66, 140, 142, 148, 151, 154–156]

Table 14.1 (*Continued*)

No.	T2DM risk SNP	Gene/nearest gene	Gene location	Chromosome	Risk allele	Other allele	Odds ratio	Trait	Ref.
96	rs7901695	*TCF7L2*	Intron	10	C	T	1.37	T2DM	[23, 25, 39, 46, 48, 49, 66, 140, 142, 148, 151, 154–156]
97	rs1802295	*VPS26A*	Utr-3	10	A	G	1.08	T2DM	[136]
98	rs12571751	*ZMIZ1*	Intron	10	A	G	1.08	T2DM	[50]
99	rs11603334	*ARAP1*	Utr-5	11	G	A	1.13	T2DM fasting proinsulin levels/fasting glucose	[157]
100	rs1552224	*CENTD2*	Intergenic	11	A	C	1.14	T2DM	[23]
101	rs11605924	*CRY2*	Intron	11	A	C	1.04	Fasting glucose/ HOMA B/T2DM	[132]
102	rs174550	*FADS1*	Intron	11	T	C	1.04	Fasting glucose/ T2DM/HOMA B	[132]
103	rs2334499	*HCCA2*	Intergenic	11	T	C	1.35	T2DM	[158]
104	rs3842770	*INS-IGF2*	Intron	11	A	G	1.18	T2DM, African American	[149]
105	rs5219	*KCNJ11*	Coding – missense	11	T	C	1.14	T2DM	[42, 47, 48, 140, 156]
106	rs5215	*KCNJ11*	Coding – missense	11	C	T	1.14	T2DM	[42, 47, 48, 140, 156]
107	rs2237895	*KCNQ1*	Intron	11	C	T	1.45	T2DM	[159]
108	rs231362	*KCNQ1*	Intron	11	G	A	1.08	T2DM	[23]
109	rs163184	*KCNQ1*	Intron	11	G	T	1.22	T2DM	[133, 159]
110	rs2237892	*KCNQ1*	Intron	11	C	T	1.25	Reduced β-cell function T2DM	[23, 141, 148, 152, 159]
111	rs10501320	*MADD*	Intron	11	G	C	1.01	T2DM fasting proinsulin levels/fasting glucose	[157]
112	rs10830963	*MTNR1B*	Intron	11	G	C	1.09	T2DM	[76]
113	rs1387153	*MTNR1B*	Intergenic	11	T	C	1.09	Reduced β-cell function T2DM	[23, 76, 152]
114	rs7138803	*BCDIN3D/ FAIM2*	Intergenic	12	A	G	1.11	BMI/obesity T2DM	[143, 160]
115	rs11063069	*CCND2*	Intergenic	12	G	A	1.12	T2DM	[50]
116	rs1153188	*DCD*	Intergenic	12	A	T	1.08	T2DM	[66]
117	rs1531343	*HMGA2*	Intron of pseudogene	12	C	G	1.10	T2DM	[23]
118	rs9668162	*HMGA2*	Intron	12	G	C	1.26	T2DM	[138]
119	rs7305618	*HNF1A*	Intergenic	12	C	T	1.14	T2DM	[23, 56]
120	rs35767	*IGF1*	Neargene-5	12	G	A	1.04	Fasting insulin/ T2DM/HOMA IR	[132]
121	rs10842994	*KLHDC5*	Intergenic	12	C	T	1.10	T2DM	[50]
122	rs4275659	*MPHOSPH9*	Intron	12	C	T	1.06	T2DM	[58]
123	rs7957197	*OASL/TCF1/ HNF1A*	Intron of OASL	12	T	A	1.07	T2DM	[23]
124	rs7961581	*TSPAN8,LGR5*	Intergenic	12	C	T	1.09	T2DM	[4, 66]
125	rs9552911	*SGCG*	Intron	13	G	A	1.63	T2DM	[161]
126	rs1359790	*SPRY2*	Intergenic	13	G	A	1.15	T2DM	[57]
127	rs2028299	*AP3S2*	Utr-3	15	C	A	1.10	T2DM	[136]

(*continued*)

Table 14.1 (*Continued*)

No.	T2DM risk SNP	Gene/nearest gene	Gene location	Chromosome	Risk allele	Other allele	Odds ratio	Trait	Ref.
128	rs7172432	*C2CD4A/B*	Intergenic	15	A	G	1.14	Reduced β-cell function, T2DM	[144]
129	rs7178572	*HMG20A*	Intergenic	15	A	G	1.09	Lean T2DM	[73, 136]
130	rs7177055	*HMG20A*	Intergenic	15	A	G	1.08	T2DM	[50]
131	rs8042680	*PRC1*	Intron	15	A	C	1.07	T2DM	[23]
132	rs7403531	*RASGRP1*	Intron	15	T	C	1.10	T2DM	[54]
133	rs4502156	*VPS13C/ C2CD4A/B*	Intergenic	15	T	C	1.07	Fasting proinsulin levels T2DM	[157]
134	rs11634397	*ZFAND6*	Intergenic	15	G	A	1.06	T2DM	[23]
135	rs7202877	*BCAR1*	Intergenic	16	T	G	1.12	T2DM	[50]
136	rs8050136	*FTO*	Intron	16	A	C	1.17	Increased BMI, reduced insulin sensitivity, T2DM	[23, 48, 49, 66, 73, 140, 156, 162]
137	rs9939609	*FTO*	Intron	16	A	T	1.25	T2DM (obese)	[23, 48, 49, 66, 73, 140, 156, 162]
138	rs11642841	*FTO*	Intron	16	A	C	1.13	T2DM	[23, 48, 49, 66, 73, 140, 156, 162]
139	rs4430796	*HNF1B*	Intron	17	G	A	1.19	Reduced β-cell function T2DM	[54, 68, 163, 164]
140	rs7501939	*HNF1B*	Intron	17	T	C	1.09	T2DM	[68]
141	rs391300	*SRR*	Intron	17	G	A	1.28	T2DM	[152]
142	rs4523957	*SRR*	Neargene-5	17	T		1.27	T2DM	[152]
143	rs8090011	*LAMA1*	Intron	18	G	C	1.13	Lean T2DM	[73]
144	rs17782313	*MC4R*	Intergenic	18	C	T	1.06	BMI/T2DM	[143, 160]
145	rs12970134	*MC4R*	Intergenic	18	A	G	1.08	T2DM/BMI/waist circumference/insulin resistance	[133, 165]
146	rs3794991	*GATAD2A/ CILP2*	Intron, intergenic	19	T	C	1.12	T2DM	[133, 138]
147	rs8108269	*GIPR*	Intergenic	19	G	T	1.05	T2DM	[133]
148	rs3786897	*PEPD*	Intron	19	A	G	1.10	T2DM	[166]
149	rs10401969	*SUGP1/CILP2*	Intron	19	C	T	1.13	T2DM	[133, 138]
150	rs6017317	*FITM2-R3HDML-HNF4A*	Intergenic	20	G	T	1.09	T2DM	[51]
151	rs4812829	*HNF4A*	Intron	20	A	G	1.09	T2DM	[136]
152	rs5945326	*DUSP9*	Intergenic	X	A	G	1.27	T2DM	[23]
153	rs12010175	*FAM58A*	Intron	X	G	A	1.21	T2DM	[54]

Gene–gene and gene–environment interactions

Gene–gene interactions, or epistasis, have been suggested as a possible explanation for difficulties in replicating genetic association in complex diseases [106]. The standard statistical methods used in association studies are usually limited to the analysis of single marker effects and thereby do not account for interactions between markers. Previous attempts to study epistasis in complex diseases have focused on interactions between candidate regions [107, 108]. However, the recent abundance of GWAS data has made a comprehensive search across the genome more feasible. Some studies have attempted to account for epistasis in GWAS using a two-step approach in which significant SNPs are tested against each other or against all other SNPs in the study, with variable results [109, 110]. The main problem when studying epistasis is power, since interaction between loci with modest effects is difficult to detect without extremely large sample sizes. However, some studies have pointed at novel tests to increase power [111]. Thorough studies in diabetes addressing epistasis using this approach are lacking. Further, a recent paper by Lander and co-workers provided compelling evidence that gene–gene

Table 14.2 Genetic loci associated with glycemic traits.

No.	SNPs	Gene/nearest gene	Gene location	Chromosome	Effect allele	Other allele	Effect	Trait	Ref.
1	rs9727115	*SNX7*	Intron	1	G	A	0.0133	Fasting proinsulin levels adjusted for fasting glucose	[157]
2	rs2785980	*LYPLAL1*	Intergenic	1	T	C	0.017	Fasting insulin	[167]
3	rs4675095	*IRS1*	Intron	2	A	T	–0.006/–002	Fasting glucose/HOMA-IR	[132]
4	rs2943634	*IRS1*	Intergenic	2	C	A	0.025	Fasting insulin, CAD	[167]
5	rs1371614	*DPYSL5*	Intron	2	T	C	0.022	Fasting glucose	[167]
6	rs11920090	*SLC2A2*	Intron	3	T	A	0.02	Fasting glucose/HOMA B/HBA_{1C}	[132]
7	rs17046216	*MSMO1*	Intron	4	A	T	0.18; 0.19	Fasting insulin; insulin resistance	[168]
8	rs4691380	*PDGFC*	Intron	4	C	T	0.021	Fasting insulin	[167]
9	rs6235	*PCSK1*	Coding – missense	5	G	C	0.0394/–0.014	Fasting proinsulin levels/fasting glucose	[157]
10	rs13179048	*PCSK1*	Intergenic	5	C	A	0.018	Fasting glucose	[167]
11	rs4646949	*TAF11*	Neargene-3	6	T	G	0.020	Fasting insulin	[167]
12	rs6943153	*GRB10*	Intron	7	C	T	0.0154	Fasting glucose, fasting insulin	[24]
13	rs4841132	*PPP1R3B*	Intergenic	8	A	G	0.030	Fasting glucose	[167]
14	rs7077836	*TCERG1L*	Intergenic	10	T	C	0.28; 0.34	Fasting insulin; insulin resistance	[168]
15	rs7944584	*MADD*	Intron	11	A	T	0.021	Fasting proinsulin/fasting glucose/HOMA B	[132]
16	rs10838687	*MADD*	Intron	11	T	G	0.0253	Fasting proinsulin levels	[157]
17	rs1483121	*OR4S1*	Intergenic	11	G	A	0.015	Fasting glucose	[167]
18	rs2074356	*HECTD4/C12orf51*	Intron	12				1-h plasma glucose	[169]
19	rs2293941	*PDX1 – AS1*	Intron	13	A	G	0.016	Fasting glucose	[167]
20	rs17271305	*VPS13C*	Intron	15	G	A	0.07	2-h glucose /2-h insulin, adjusted for 2-h glucose	[80]
21	rs1549318	*LARP6*	Intergenic	15	T	C	0.0192	Fasting proinsulin levels	[157]
22	rs4790333	*SGSM2*	Intron	17	T	C	0.0154	Fasting proinsulin levels	[157]
23	rs10423928	*GIPR*	Intron	19	A	T		2-h glucose/insulinogenic index/AUC ins./glucose/2-h insulin, adjusted for 2-h glucose/T2DM	[80]
24	rs6048205	*FOXA2/LINC00261*	Intergenic/ neargene-5	20	A	G	0.029	Fasting glucose	[167]

interactions can also contribute to missing heritability by causing "phantom heritability" that inflates the estimated narrow sense heritability of the trait [112].

Gene–environment interactions are equally difficult to study but are likely to play an important role in T2DM development. The epidemic of T2DM dates back only 50 years, and it is obvious that during this period only the environment, not the genes, has changed. However, the genetic architecture determines our response to the environment. Genetic variants could affect specific metabolic processes to make an individual more susceptible to the harmful effects of a poor diet but also personality traits that make an individual more or less likely to over-consume and live a sedentary lifestyle. It will be a formidable task, however, to identify the environmental triggers for most of the genetic variants increasing susceptibility to diabetes, as this will require very large studies with precise information on diet, exercise, energy expenditure, etc.

Parent-of-origin effects

The risk of T2DM in offspring is greater if the mother has T2DM than if the father is affected, in contrast to T1DM, where the risk of T1DM in offspring is greater if the father is affected [90, 91]. Sex-specific parental effects have been reported for insulin response to the oral glucose load, with male offspring of mothers with diabetes showing the lowest insulin values, and also influencing HDL concentrations [90]. One potential explanation for this could be preferential parental specific transmissions of risk alleles to offspring, which is often associated with DNA methylation and imprinting. Epigenetic modifications have the potential to be stable and heritable across cell divisions [92, 93] and manifest as parent-of-origin effects. Insulin was the first gene reported to show parent-of-origin effects. The paternally transmitted class III alleles of the variable number tandem repeat (VNTR) region upstream of the insulin gene (*INS*-VNTR) showed association with T2DM [94]. Interestingly, class III alleles

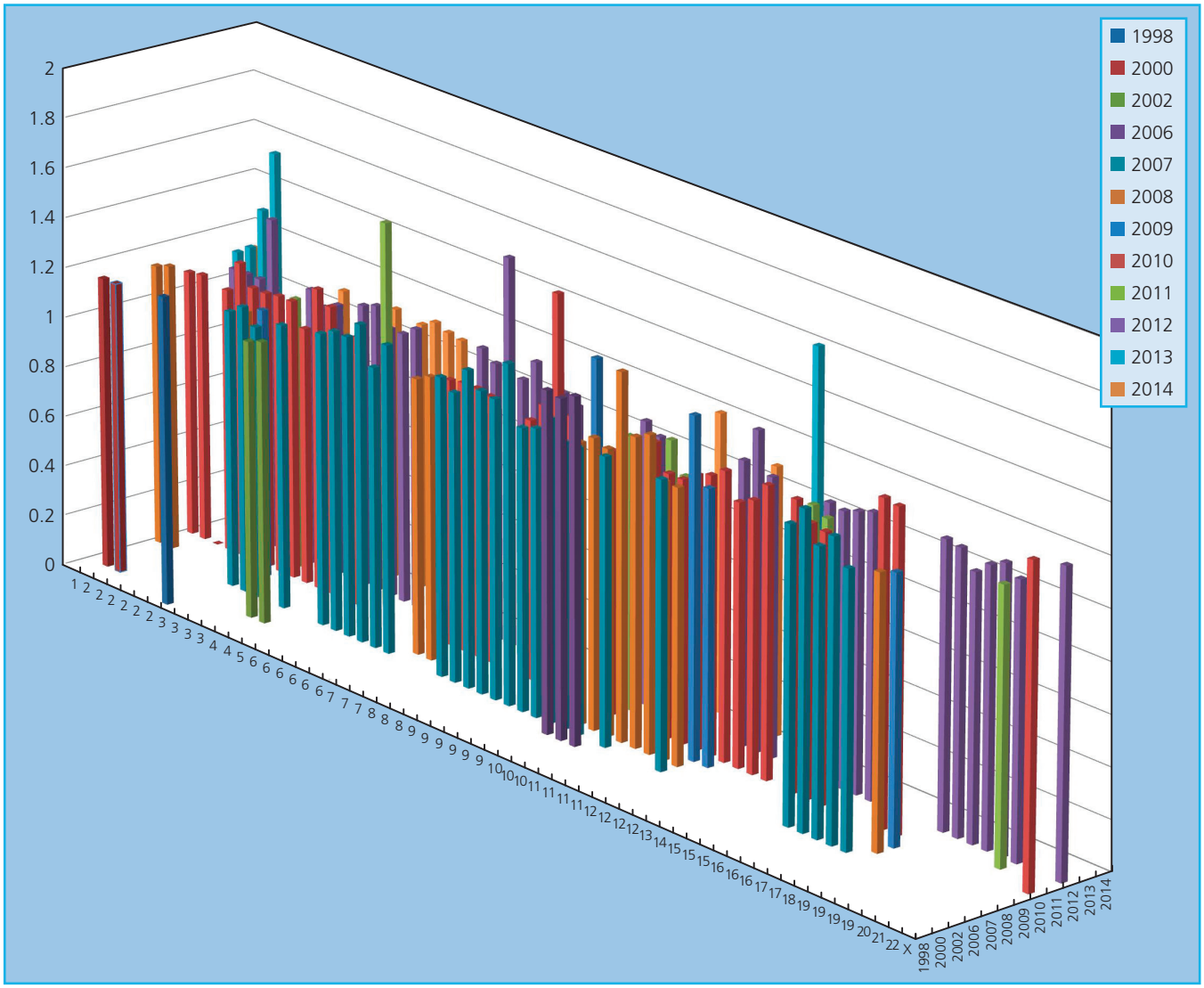

Figure 14.2 T2DM risk variants. The *x*-axis shows the chromosomal location, the *y*-axis shows the effect sizes, and the *z*-axis shows the year of discovery. One risk variant was reported in 1998, two in 2002, to a total of 153 T2DM variants that we have today. Source: Prasad RB, Groop L. Genetics of type 2 diabetes—Pitfalls and possibilities. *Genes* 2015; **6**:87–123 (this is an open-access article distributed under the Creative Commons Attribution License [CC BY]).

(one of the two main classes of *INS*-VNTR allele length, with 141–209 repeats) were also associated with increased length and weight at birth [95] and were protective against type 1 diabetes compared with type I alleles [96]. A large-scale family-based study on an Icelandic population determined that variants in *KCNQ1* and *KLF14* show stronger effects on T2DM when the risk allele is transmitted from the mother than from the father [97, 98] and this was replicated in later studies [99], including our own.

The conflict hypothesis suggests that imprinting arose due to a genomic tug-of-war between mothers and fathers over the use of maternal resources in the fetus. The paternal imprinting maximizes the utilization of intrauterine resources to the offspring which would increase their evolutionary fitness whereas the maternal imprinting tries to minimize this in order to conserve it for her future offspring [100]. Conversely, the co-adaptation hypothesis suggests that imprinted genes coevolve to optimize parental care of offspring. Although there is insufficient evidence to support either theory, nevertheless, the significant role of imprinting in defining paternal and maternal effects has been consistently established [101].

The intrauterine environment plays a significant role in determining fetal programming. It has been shown that poor nutrition can affect fetal growth, can produce permanent changes in glucose–insulin metabolism, and often results in low birth weight [102] This can induce permanent changes in metabolism and affect chronic disease susceptibility as proposed by the Developmental Origin of Health and Disease hypothesis [103]. If this intrauterine programming results in a reduced β-cell mass, it could predispose to diabetes later in life when the insulin requirements increase as a consequence of obesity resulting

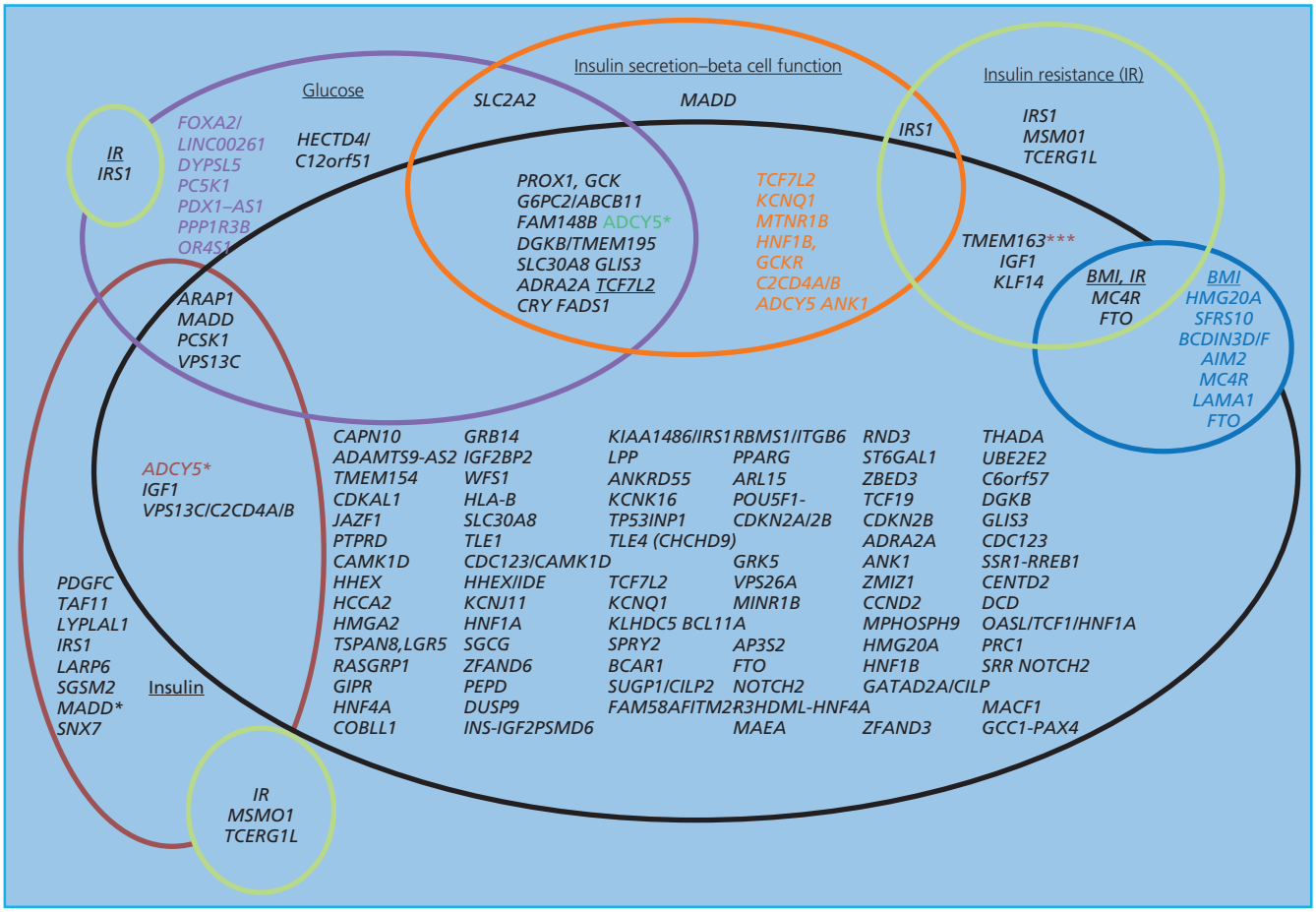

Figure 14.3 T2DM and glycemic trait-associated variants. The variants are represented by gene names here, which could indicate that the location is present either in the gene or in the vicinity of the gene. The black circle represents T2DM, and the gene names in black in this represent variants associated only with T2DM. The overlapping circles indicate additional reporting associations for that variant; for instance, *TCF7L2*, *KCNQ1*, *MTNR1B*, etc., are associated with T2DM and also with β-cell dysfunction. An ADCY5 variant is associated with 2-h insulin adjusted for 2-h glucose, 2-h glucose/T2DM (in brown) ***Variants in TMEM163 are also associated with fasting insulin, *TCF7L2*, associated with fasting and 2-h glucose, and *MADD* variants, associated with fasting proinsulin, fasting glucose and HOMA-B. Source: Prasad RB, Groop L. Genetics of type 2 diabetes—Pitfalls and possibilities. *Genes* 2015; **6**:87–123 (this is an open-access article distributed under the Creative Commons Attribution License [CC BY]).

in insulin resistance. *KCNQ1* could represent an example of fetal programming wherein the maternally expressed gene was monoallelically expressed in fetal tissues and biallelically expressed in adult tissues [104].

Dissection of genetic parent-of-origin effects requires genotype data from families and only heterozygous parents are informative, yielding reduced power for relatively rare variants. However, long-range phasing and imputation methods allow the prediction of genotypes with a great likelihood, thus making this a valuable method for finding "surrogate" parents even if DNA exists from only a few family members. When the paternal and maternal alleles have effects in opposite directions, for instance a situation where the maternal allele could confer risk whereas the paternal allele could be protective, such an association would be almost impossible to detect in a traditional case–control GWAS. However, novel parent-of-origin detection methods allow the detection of imprinting effects from differences in the phenotypic variance of heterozygotes in very large case–control studies [105]. Parent-of-origin effects could explain a large proportion of the missing heritability and must be taken into consideration in investigations of genetic T2DM susceptibility.

Epigenetics

The environment can also influence the expression of the genome, and ultimately the phenotype, via the epigenome. Even though the DNA sequence is not changed, the phenotype is altered by epigenetic modifications of gene expression by mechanisms including methylation of DNA, post-translational modification of histones, or activation of microRNAs. Changes to the phenotype can be at the level of the cell, tissue, or whole organism.

It is tempting to speculate that environmental factors such as diet and exercise can change the level of DNA methylation and thereby cause changes in gene expression, but evidence that DNA methylation contributes to the increase in T2DM is still

Table 14.3 Rare risk and protective loci associated with T2DM and glycemic traits.

No.	SNPs	Gene/nearest gene	Gene location	Chromosome	Ref.
1	rs35658696	*PAM*	Coding – missense	5	[64]
2	rs78408340	*PAM*	Coding – missense	5	[64]
3	rs36046591	*PPIP5K2*	Coding – missense	5	[64]
4	p.Lys34Serfs*50	*SLC30A8*	Coding – missense	8	[67]
5	p.Arg138*	*SLC30A8*	Coding – missense	8	[67]
6	rs3824420	*KANK1*	Coding – missense	9	[64]
7	rs505922	*ABO*	Intronic	9	[64]
8	rs60980157	*GPSM1*	Coding – missense	9	[64]
9	p.Leu5Val (20)	*ATG13*	Coding – missense	11	[64]
10	p.Ile131Val (1)	*ATG13*	Coding – missense	11	[64]
11	p.Gln249Pro (3)	*ATG13*	Coding – missense	11	[64]
12	p.Arg392Trp (1)	*ATG13*	Coding – missense	11	[64]
13	p.Leu427Gln (3)	*ATG13*	Coding – missense	11	[64]
14	p.Gly434Arg (488)	*ATG13*	Coding – missense	11	[64]
15	p.X406Gly (200)	*ATG13*	Coding – missense	11	[64]
16	rs35233100	*MADD*	Coding – missense	11	[64]
17	p.Arg279Cys (324)	*TBC1D30*	Coding – missense	12	[64]
18	p.Pro746Leu (427)	*TBC1D30*	Coding – missense	12	[64]
19	c.1522G>A [p.E508K]	*HNF1A*	Coding – missense	12	[63]
20	rs76895963	*CCND2*	Intergenic	12	[61]
21	rs75615236	*CCND2*	Intergenic	12	[61]
22	rs150781447	*TBC1D30*	Coding – missense	12	[64]
23	rs2650000	*HNF1A*	Intergenic	12	[64]
24	Chr. 13: g.27396636delT	*PDX1*	Coding – missense	13	[67]
25	p.Tyr416Cys (78)	*SGSM2*	Coding – missense	17	[64]
26	p.Thr789Pro (3),	*SGSM2*	Coding – missense	17	[64]
27	p.Val996Ile (236)	*SGSM2*	Coding – missense	17	[64]
28	rs61741902	*SGSM2*	Coding – missense	17	[64]

lacking. Epigenetic mechanisms may, however, play a role in progression of the disease by inducing glucotoxicity in islets and predispose to diabetic complications [113]. Elevated glucose is a prerequisite to this condition and it is well established that cells can memorize changes in glucose concentrations. For example, two large studies, the UKPDS and DCCT studies, showed that initial good metabolic control was associated with reduced frequency of diabetic complications decades later. The advanced "metabolic memory" hypothesis suggests that this is because glucose can induce histone modifications in endothelial cells that can be remembered long after [114].

Non-coding RNAs – microRNAs and lincRNAs

Non-coding RNAs have recently emerged as important regulators of gene expression and function. MicroRNAs (miRNAs) naturally regulate programs of gene expression. Altered miRNA function has been shown to contribute to human disease, and manipulation of specific miRNAs is now being explored as a novel therapeutic modality [115]. The efficiency of miRNAs binding to target transcripts depends on both the sequence and the intramolecular structure of the transcript. SNPs can contribute to alterations in the structure of regions flanking them, thereby influencing the accessibility for miRNA binding. Several studies have implicated miRNAs in diabetes and inflammation and common SNPs change the target sequence of miRNAs in several T2DM susceptibility loci (http://omictools.com/dbsmr-tool) [116, 117]. Other forms of non-coding RNAs, such as piRNAs (PIWI-interacting RNAs), snoRNAs (small nucleolar RNAs), lincRNAs (long intergenic non-coding RNAs), and lncRNAs (long non-coding RNAs), might also contribute to the development of diabetes. For example, the *CDKN2A/B* region on chromosome 9 is associated with T2DM, and also in cardiovascular disease and a number of other disorders. This region harbors a lincRNA, *ANRIL* (non-protein coding *CDKN2B-AS1 CDKN2B* antisense RNA 1), which can potentially modify and explain some of these associations [118].

Difficulties in assigning functions to associated genes

Most identified diabetes loci have not been tied mechanistically to the disease. While loci are commonly referred to by the names of genes located close to them, only a few are close to strong biological candidates, e.g. the melatonin receptor (*MTNR1B*) and the insulin receptor substrate-1 (*IRS1*). For others, such as *TCF7L2* and *GIPR*, the evidence is fairly strong that an intronic

SNP is the causal SNP. Melatonin receptor 1B (*MTNR1B*) has been associated with both fasting glucose and T2DM risk [74–76]. Melatonin works as a chronobiotic factor, adjusting the timing of the biological clock. Its receptors are present in the pancreas and melatonin is proposed to contribute to the nocturnal lowering of insulin in humans. The *MTNR1B* risk genotype is associated with impaired early insulin release to both oral and intravenous glucose and insulin secretion deteriorates over time in the risk allele carriers [74]. The proposed mechanism by which *MTNR1B* polymorphism could predispose to T2DM involves altered expression of *MTNR1B* in pancreatic β cells, leading to decreased cAMP/cGMP concentrations via G-proteins and, thereby, impaired insulin secretion.

The insulin receptor substrate 1 (*IRS1*) gene encodes a protein that mediates insulin's control of various cellular processes by transmitting signals from the insulin receptor to intracellular signaling pathways. The C allele of rs2943641 has been shown to be associated with insulin resistance and increased risk of diabetes. The genetic variant causes reduced basal levels of IRS1 protein and decreased insulin induction of IRS1-associated phosphatidylinositol-3-hydroxykinase activity in human skeletal muscle biopsies [77].

TCF7L2 is a transcription factor playing an important role in the Wnt signaling pathway. The risk allele is associated with decreased insulinogenic index and lower disposition index, suggesting a reduced capacity for insulin secretion in relation to insulin sensitivity. Since it was identified as a diabetes gene, it has been shown to be important for several vital functions in the pancreatic islet, including pancreas development, determination of β-cell mass, maintenance of the secretory function of mature β cells, and regulation of insulin production and processing [78, 79].

The incretin hormone GIP (glucose-dependent insulinotropic polypeptide) promotes pancreatic β-cell function by potentiating insulin secretion and β-cell proliferation. The GIP receptor (*GIPR*) locus showed association to postprandial insulin levels in a meta-analysis performed by the MAGIC consortium but was surprisingly not associated with risk of diabetes in the DIAGRAM+ study [23, 80]. The reason seems to be that the same variant results in decreased BMI, which neutralizes the effect of the SNP on risk of T2DM. GIP influences expression of the inflammatory cytokine OPN in islets, which in turn has protective effects on β-cell proliferation and potentially apoptosis [81].

Many of the other identified loci can be subgrouped based on their association with other phenotypes with a key role in T2DM etiology. Exploration of the effects of T2DM-associated variants on glucose and insulin traits in non-diabetic populations has shown that most of the known loci act through an effect on insulin secretion rather than insulin resistance (Table 14.1) [23, 82–84].

Fasting glucose-raising alleles of the *MADD*, *GIPR*, *GCK*, *FADS*, *DGKB*, *PROX1*, *TCF7L2*, *SLC30A8*, and *C2CD4B* loci have all been associated with either abnormal insulin processing or secretion, whereas *GCKR* and *IGF1* are associated with OGTT-based disposition indices and β-cell function [83]. The DIAGRAM+ consortium observed that three loci (*TCF7L2*, *ARAP1*, and *CDKAL1*) were associated with reduced fasting insulin, also suggestive of β-cell dysfunction, whereas the T2DM risk alleles at *PPARG*, *FTO*, *IRS1*, and *KLF14* were associated with higher fasting insulin, indicating a primary effect on insulin action [23].

Genotype-based treatment

The *ADRA2A* (adrenergic receptor alpha 2) locus was recently identified as a T2DM risk locus after first having been positionally mapped in congenic GK rats, where it was associated with impaired insulin granule docking and reduced β-cell exocytosis [82]. Human carriers of the *ADRA2A* risk variant (rs553668) have reduced fasting insulin and decreased insulin secretion as a consequence of increased expression of the ADRA2 receptor in pancreatic islets. It is well known that excess epinephrine can suppress insulin secretion and cause diabetes. The α_{2A}AR antagonist yohimbine enhances insulin release *in vitro* in islets from organ donors carrying the risk allele to levels similar to those in non-risk carriers. A randomized clinical study was performed blocking α_{2A}AR pharmacologically to increase insulin secretion in individuals with T2DM with the rs553668 risk allele. Yohimbine administration enhanced 30-min insulin, corrected insulin response, and disposition index in the risk group, making secretion similar to that in persons carrying the low-risk allele. Insulin secretion defect in individuals carrying the *ADRA2A* risk genotype could be corrected by α_{2A}AR antagonism [85]. This demonstrated the potential application of genetic risk variants to guide therapeutic interventions that target the underlying pathophysiology, one step closer to individualized medicine.

Little common genetic basis for T1DM and T2DM

T1DM and T2DM can be considered two extremes of the diabetes spectrum and share a few similarities in manifestation of underlying physiology, including hyperglycemia, insulin deficiency, and development of complications. However, the genetics of T1DM and T2DM differ greatly, with very few T2DM susceptibility loci showing an association with T1DM. Notable exceptions include the *PPARG* Pro12Ala variant, *MTNR1B*, *HNF1A*, *GLIS3*, 6q22.32, and novel loci near the major histocompatibility complex (MHC), which harbor the HLA class II genes associated with about half of the T1DM risk [58, 119–121]. Based on these studies, the mechanisms underlying T1DM and T2DM appear to be intrinsically distinct. The distribution of T2DM risk SNPs should be more random in a person with T1DM; however, this does not seem to be the case. The strongest T2DM SNP in the *TCF7L2* gene almost seems to protect against T1DM. T1DM risk variants for *BCAR1*, *GLIS3*, and *RAD51L1* were protective for T2DM whereas for those in *C6orf173*, *COBL*, and *C10orf59*, the effects were concordant [50]. Also, it has been reported that *APOC3* haplotypes increase the risk of T1DM, but the same variants increase the risk of T2DM in lean carriers while having a protective effect

in overweight carriers [122]. Common variants in *SLC30A8* are associated with an increased risk of T2DM, and rare variants with a protective effect [46, 67]. Puzzlingly, SLC30A8 was also found to be a major autoantigen, eliciting 60–80% autoantibodies in individuals with new-onset T1DM [123].

Curiously, gene variants associated with T1DM underwent recent positive selection and have been increasing in prevalence. There is more selection in alleles increasing, rather than decreasing, susceptibility to T1DM. This is indicative of an evolutionary benefit, wherein these variants were possibly protective against viruses and bacterial infections. However, no such link has been reported for T2DM risk variants, as could be expected from the thrifty genotype hypothesis [124]. In terms of genetics, T2DM seems to have more in common with cancer rather than T1DM [125]. It has been suggested there may rather be a specific yin–yang relationship between cancer and T2DM, with too much cell proliferation resulting in cancer and insufficient proliferation of pancreatic islets resulting in T2DM [125].

LADA is considered an intermediate form between T1DM and T2DM, and is also referred to as type 1.5 diabetes. There is much less information available on the genetic basis of LADA compared with T1DM and T2DM. One way to understand this would be to assess the extent LADA to which shares genetic similarities with T1DM and T2DM. The HLA locus, conferring 50% of the genetic susceptibility of T1DM, also shows similar associations with LADA, with a few differences. The T1DM variant *PTPN22* shows a weak association with LADA. Data on the *INS* class I VNTRs have been inconclusive and associations reported with both T1DM and T2DM wherein the short tandem repeat was associated with T1DM and the long repeat with T2DM. Although previously several T1DM-associated variants could be tested for association with LADA, it was not until the discovery that the common variant in the *TCF7L2* gene was strongly associated with T2DM that the genetic contribution of T2DM to LADA could really be tested. This variant is clearly associated with LADA and T2DM but not with T1DM. This indicates that LADA is indeed a genetic admixture of T1DM and T2DM.

There are more lessons to be learned from differences between T1DM and T2DM rather than similarities. Elucidating the genetic heterogeneity of the spectrum of diabetes disorders will help us in understanding the mechanisms underlying the phenotypic heterogeneity of diabetes and would be a step towards individualized therapy.

A holistic view – systems genetics

A restricted focus on the genome through GWAS provides limited insights into the molecular mechanisms driving disease and is akin to a snapshot of the genetics of the disease. To obtain an understanding of disease pathogenesis, it is important to analyze the GWAS data in the context of complementary follow-up analyses, including DNA methylation and histone modifications, expression profiling under conditions relevant for the disease, related protein analysis, and analysis of genotype–phenotype associations. Global transcriptome profiling in relevant tissues such as the pancreas has facilitated identification and cataloguing of a wide array of transcription based events in the pathogenesis of T2DM [126]. For example, by combining GWAS information with metabolomics, it has been possible to identify strong associations between SNPs and metabolic reactions that otherwise would have been missed [127]. Network- or pathway-based approaches, including enrichment in predefined pathways by, for example, KEGG [128] (http://www.genome.jp) and Gene Ontology (GO) (http://www.geneontology.org), have also been used to identify disease genes for various diseases. Thus, an integrative approach with several data types is likely to discover disease genes that would not be identified by the use of classical GWAS approaches alone. This was also illustrated in recent studies of human islets identifying novel candidate genes for T2DM based upon expression differences and coexpression with known T2DM genes and also protein–protein interaction analyses [129, 130]. Integration of GWAS data with such data could thus facilitate a systems-based understanding of the pathogenic mechanisms.

Conclusions

Advances in genomic technology have initiated a myriad of novel genetic discoveries including more than 100 common variants contributing to risk of complex disease. This has led to a deeper understanding of the underlying biology and pathogenesis of these diseases. The genetic landscape of T2DM susceptibility is as yet incomplete, so far explaining only a small proportion of the total heritability of diabetes. Many possibilities for dissecting the architecture of T2DM etiology have emerged in the form of large-scale genetic studies, meta-analyses and sequencing in families. This work has already contributed greatly to our understanding of disease mechanisms by identifying pathways that could not be linked to diabetes by existing hypothetical models, even though many genetic findings are very recent and have yet to make their contribution to our knowledge about diabetes pathogenesis. However, one must bear in mind that diabetes is probably a much more diverse disease than the current subdivision into T1DM and T2DM implies, and a more precise subdivision into subgroups may both facilitate the investigation of T2DM genetics and pave the way for more individualized treatment. A holistic systems biology approach will also be required to obtain a complete picture of how genetic variation leads to diabetes. The rapid technology development during recent years holds promise that this will be possible in the not too distant future.

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15 Metabolic Disturbances in Diabetes

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Key points

- Type 1 diabetes mellitus (T1DM), or immune-mediated diabetes, is characterized by evidence of immune-mediated destruction of the insulin-secreting β cells in the islets of Langerhans.
- In type 2 diabetes mellitus (T2DM), although the endocrine pancreas can produce insulin, secretion and circulating concentrations of insulin are inappropriate for the prevailing glucose concentrations.
- Glucose disposal depends on insulin secretion, insulin action, suppression of glucagon, and the ability of glucose itself to stimulate glucose uptake and suppress glucose release.

Introduction

Hyperglycemia, for better or for worse [1], is the metabolic abnormality that has been used to define the presence of, and characterize, diabetes. Diabetes comprises a heterogeneous group of disorders characterized by fasting and/or postprandial hyperglycemia. The underlying abnormalities that lead to the development of hyperglycemia, however, differ amongst subgroups. Conventionally, diabetes has been categorized into two subgroups that, from a metabolic standpoint, differ in the degree of insulin deficiency present. This broad dichotomy is simplistic as a given individual may exhibit metabolic abnormalities previously considered unique to each category [2].

Type 1 diabetes mellitus (T1DM), or immune-mediated diabetes, is characterized by evidence of immune-mediated destruction of the insulin-secreting β cells in the islets of Langerhans. Usually this leads to absolute insulin deficiency, which is insufficient to prevent unrestrained lipolysis during systemic illness or severe physical stress. In type 2 diabetes mellitus (T2DM), however, although the endocrine pancreas can produce insulin, secretion and circulating concentrations of insulin are inappropriate for the prevailing glucose concentrations. T2DM has traditionally been considered a disorder of insulin signaling (exacerbated by poor diet, obesity, and lack of physical activity) rather than a deficiency of insulin.

It is important to remember that obese individuals with T1DM can behave in a fashion similar to those with long-standing T2DM and that metabolic differences between the two categories may be more imagined than real.

Carbohydrate metabolism

In the fasting state, glucose appearance is determined by the rate of endogenous glucose release from the liver and to a lesser extent the kidney. This is collectively referred to as endogenous glucose production. Glucose concentrations increase when glucose appearance exceeds glucose disappearance and continues to increase until these rates are equal. In humans without diabetes, glucose concentrations average 4.5–5.5 mmol/L following a 6–12-h overnight fast.

Gluconeogenesis is responsible for ~50–60% of endogenous glucose production following an overnight fast, with the proportion increasing with increasing duration of the fast [3]. Gluconeogenesis utilizes three-carbon precursors such as lactate, alanine, and glycerol to synthesize glucose molecules.

Following an overnight fast, ~80% of glucose disposal is insulin independent and occurs in the brain, splanchnic tissues, and erythrocytes [4]. The majority of insulin-mediated glucose disposal occurs in muscle [5]. Because insulin levels are low in the postabsorptive state, muscle tissue predominantly uses free fatty acids (FFAs) for fuel [6]. In the presence of low insulin concentrations, glucose taken up by tissues predominantly is oxidized or undergoes glycolysis to release alanine and lactate, which can be reutilized by the liver for gluconeogenesis [7].

Sensitivity to insulin varies amongst tissues. Low concentrations of insulin limit lipolysis and prevent unrestrained breakdown of fat. The insulin concentrations sufficient to prevent lipolysis are insufficient to stimulate significant muscle glucose uptake. Whereas maximal suppression of endogenous glucose production

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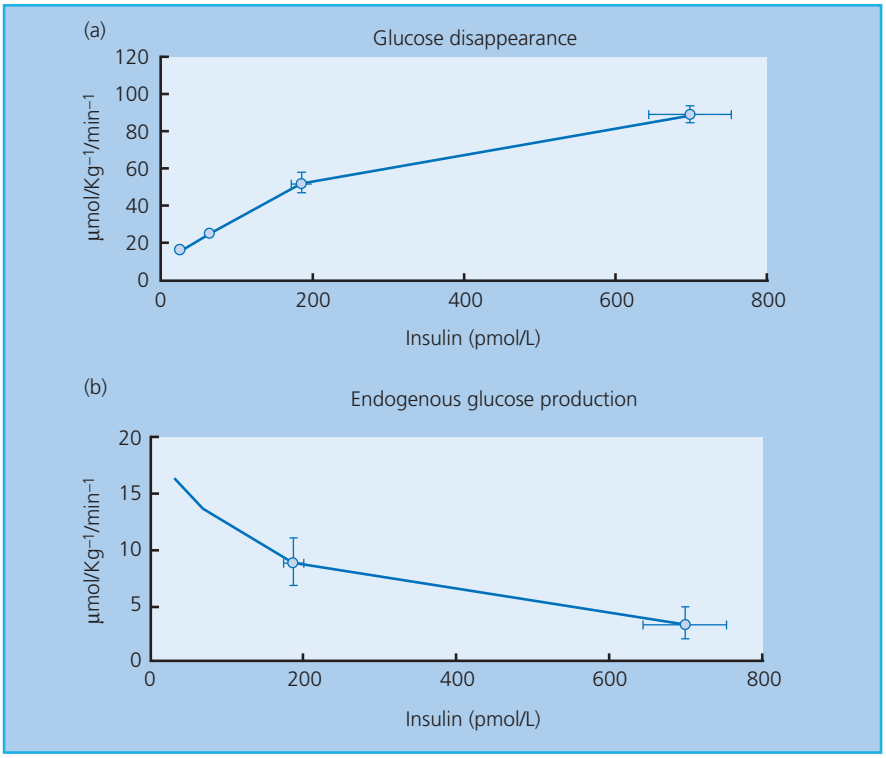

Figure 15.1 Insulin dose–response curves for glucose production and utilization in individuals without diabetes. Source: Adapted from Vella A. *Diabetologia* 2002; **45**:1410–1415. Reproduced with permission from Springer-Verlag.

occurs at insulin concentrations of ~250 pmol/L, these concentrations result in only half maximal stimulation of glucose uptake (Figure 15.1) [8].

Increases in plasma glucose, which occur within 5–10 min after eating, stimulate insulin secretion and suppress glucagon secretion. The reciprocal changes in hepatic sinusoidal insulin and glucagon concentrations in concert with the elevated glucose concentrations enhance hepatic glucose uptake and suppress hepatic glucose production [9, 10]. The splanchnic tissues initially extract 10–25% of ingested glucose and eventually dispose of ~40% of ingested glucose, with muscle accounting for most of the remainder [11]. It is important to note the significant variability in the reported splanchnic extraction of glucose, a significant proportion of which is explained by limitations of the tracer methodology used [12]. These coordinated changes in hepatic and extrahepatic glucose metabolism generally limit the postprandial rise in glucose to 7–8 mmol/L. Late postprandial hypoglycemia is avoided by a smooth increase in hepatic glucose output to rates that closely approximate glucose uptake.

In the transition from normal glucose metabolism to overt diabetes, the relative contribution of alterations in glucose disappearance or appearance is uncertain. Most [13–16] but not all [17] epidemiological studies that have attempted to elucidate the pathogenesis of impaired fasting glucose (IFG) (defined as a fasting glucose of 5.8–6.9 mmol/L) have reported that insulin action is decreased in individuals with IFG. Weyer et al. [16] reported that fasting endogenous glucose production was increased in people with IFG. Bock et al. [18] subsequently established that insulin-induced suppression of endogenous glucose production and gluconeogenesis are impaired in people with IFG, indicating hepatic insulin resistance. Epidemiological studies have shown that 20–30% of people with IFG will develop frank diabetes within 5–10 years [19, 20]. Indeed, individuals with a fasting glucose between 5.3 and 5.7 mmol/L have an 8% risk of developing diabetes within the next 10 years.

Regulation of glucose concentrations after meal ingestion is more complex. The pattern of change of postprandial plasma glucose concentrations is determined by the extent to which glucose entering the systemic circulation (equal to the sum of endogenous glucose production and the systemic appearance of ingested glucose) exceeds or is exceeded by the rate at which glucose leaves the systemic circulation (glucose disappearance). Therefore, differences in postprandial glucose concentrations could theoretically arise because of differences, alone or in combination, in rates of meal glucose appearance, suppression of endogenous glucose production, or stimulation of glucose uptake [21, 22].

Postprandial hyperglycemia is primarily caused by reduced postprandial glucose disappearance because suppression of endogenous glucose production and the rate of appearance of ingested glucose do not differ in people with IFG and normal fasting glucose [18]. The insulin secretion in response to higher postprandial glucose concentrations is impaired in people with IFG with accompanying defects in glucose disappearance and consequent postprandial hyperglycemia. A further reduction in insulin secretion eventually results in overt T2DM [18].

Endogenous glucose production is regulated (inhibited) by insulin, which increases hepatic glucose uptake by stimulating glucokinase activity and decreases hepatic glucose release by

decreasing the conversion of glucose-6-phosphate to glucose. The latter step is regulated by glucose-6-phosphatase. Insulin can also stimulate glycogen synthesis, inhibit glycogen breakdown, and suppress gluconeogenesis. Postprandial hyperglycemia and hyperinsulinemia stimulate hepatic glycogen synthesis, thereby replenishing hepatic glycogen stores. Hepatic glycogen synthesis occurs via both the direct (i.e. glycogen synthesis utilizing glucose-6-phosphate derived directly from extracellular glucose) and indirect pathway (i.e. glycogen synthesis utilizing glucose-6-phosphate derived from gluconeogenesis). The relative contribution of these two pathways appears to be determined by multiple factors, including the duration of fast, composition of the meal, and the prevailing insulin and glucagon concentrations [23, 24].

In the presence of euglycemia, rising hepatic sinusoidal concentrations of insulin suppress endogenous glucose production by decreasing glycogenolysis. Insulin concentrations within the physiological range in healthy humans do not appreciably suppress gluconeogenesis and direct glucose-6-phosphate (derived from gluconeogenesis) into glycogen [25].

Carbohydrate metabolism in type 1 diabetes

T1DM is characterized by insulin deficiency as a result of autoimmune destruction of the pancreatic β cells. Fasting hyperglycemia does not develop until most (>80%) of the β cells are lost to the underlying autoimmune process. Defects in insulin secretion, however, are evident years before the development of diabetes in asymptomatic affected individuals. For example, siblings of people with T1DM who are islet antibody positive (a group at high risk for the development of T1DM) frequently exhibit a decreased first phase of insulin secretion in response to intravenous glucose injection [26, 27]. This usually occurs at a time when the response to other stimuli such as oral glucose or mixed meal ingestion is intact, suggesting that incretins and other secretagogues are capable of compensating for decreased islet cell mass.

Impaired insulin secretion is frequently accompanied by impaired insulin action [28, 29]. The severity of insulin resistance is related to the degree of glycemic control. People with poorly controlled T1DM may exhibit the same degree of insulin resistance as people with T2DM [29, 30]. In people with T1DM, the defect in insulin action is tissue specific; for example, glucose uptake in cardiac muscle, as opposed to skeletal muscle, is normal [31]. Glucose oxidation and non-oxidative storage in people with T1DM are decreased in proportion to glucose uptake, suggesting that glucose transport and/or phosphorylation (after transport across the membrane) are the sites of defective insulin action [32]. In contrast, insulin-induced suppression of glucose production is not impaired and may in fact be increased in people with T1DM [33, 34].

Insulin binding and action have been reported to be decreased in adipocytes [35, 36] but normal in fibroblasts [37, 38] of people with T1DM. This may be explained by the fact that insulin binding in adipocytes is measured immediately after biopsy whereas insulin binding to fibroblasts is measured following several days of culture. Decreased insulin binding in the former but not the latter suggests an effect of abnormal metabolic milieu rather than an intrinsic defect of insulin action. This is supported by several observations that improved chronic glycemic control is accompanied by improved whole-body insulin action [39, 40]. It should be noted that when insulin action is measured by means of a hyperglycemic hyperinsulinemic clamp, hyperglycemia may compensate for small defects in insulin action by means of its ability (glucose) to stimulate its own uptake and suppress its own release (glucose effectiveness) [34].

Because insulin is typically delivered via the subcutaneous rather than the intraportal route, treatment with insulin leads to systemic hyperinsulinemia, which has been shown to impair insulin action in humans without diabetes [41]. The improved insulin action observed in people with T1DM following treatment with insulin, however, suggests that any negative effects of systemic hyperinsulinemia on insulin action are more than offset by the lowering of glucose concentrations and the reversal of glucose toxicity.

In the absence of insulin-stimulated muscle glucose uptake, substantial glucose disappearance in insulin-deficient people with T1DM occurs by glucose excretion in the urine and by glucose uptake via non-insulin-mediated pathways [42]. Food ingestion does not result in a rise in insulin or a reciprocal decrease in glucagon concentration [43]. Because of this, the increase in splanchnic glucose uptake and the decrease in endogenous glucose production are not appropriate for the prevailing glucose concentration. Postprandial glycogen synthesis is markedly decreased, with most of the glycogen being synthesized by the indirect gluconeogenic pathway [44, 45].

Consequently, because of abnormal hepatic glucose handling, excessive amounts of glucose reach the systemic circulation. The excessive rise in postprandial glucose concentrations is compounded by the low insulin concentrations and defective insulin action present in people with poorly controlled T1DM [42, 46]. In contrast, the ability of glucose to stimulate its own uptake and suppress its own release (glucose effectiveness) is normal in T1DM and most postprandial glucose disposal occurs predominantly via non-insulin-mediated pathways and by glucose excretion in the urine [47].

Postprandial glucose metabolism in the splanchnic and extrasplanchnic tissues can be almost completely normalized by insulin administration, which increases circulating insulin concentrations and prevents the excessive rise in counter-regulatory hormones that accompanies insulin deficiency. Insulin administration also restores postprandial suppression of glucose production and stimulation of glucose uptake to rates similar to those observed in persons without diabetes [42, 48].

Animal studies have shown diabetes to be associated with hypertrophy of the intestinal mucosa and increased intestinal glucose transport [49, 50]. By contrast, when glucose, insulin, and glucagon concentrations are matched in individuals with

T1DM and age- and weight-matched controls, initial splanchnic glucose extraction and uridine diphosphate (UDP)–glucose flux (an index of hepatic glycogen synthesis) do not differ between groups. This demonstrates that relative insulin deficiency, glucagon excess, or both, rather than an intrinsic defect in splanchnic glucose metabolism, are the primary causes of postprandial hyperglycemia in people with poorly controlled T1DM [34].

Carbohydrate metabolism in type 2 diabetes

People with T2DM have elevated fasting glucose levels and excessive glycemic excursions following carbohydrate ingestion. Insulin secretion in those with T2DM is typically decreased and delayed following food ingestion [9, 22]. Defects in insulin secretion are observed early in the evolution of T2DM. In fact, alterations in both the timing and amount of insulin secreted have been reported in relatives of persons with T2DM prior to the development of hyperglycemia [51, 52].

Chronic hyperglycemia alone or in combination with elevated FFA impairs insulin secretion. Abnormalities in glucose sensing, insulin processing, or intracellular signaling can alter insulin secretion [53]. In addition, β-cell mass decreases with increasing duration of diabetes [54, 55]. Alterations in β-cell morphology occur in most people with T2DM, with extensive intra-islet deposition of amylin commonly being observed [56, 57].

Prolonged elevations in glucose concentration following ingestion of a carbohydrate-containing meal occur because postprandial glucose appearance exceeds disappearance. The more significant the defects in insulin secretion and action, the higher glucose concentrations have to rise to balance glucose appearance and disappearance [58]. Glucose appearance is elevated owing to failure to suppress hepatic glucose production because the systemic rate of appearance of ingested glucose does not differ from that observed in individuals without diabetes [9, 11, 18, 59]. Although glucose disappearance is commonly higher in people with diabetes than in those without diabetes following a meal, in large part this is accounted for by elevated rates of urinary glucose excretion. Furthermore, although elevated, the rates of glucose disappearance are not appropriate for the prevailing glucose concentrations [60, 61].

Defects in insulin secretion and action both contribute to postprandial hyperglycemia. A delay in the early rise in insulin concentrations causes a delay in suppression of glucose production, which in turn results in an excessive glycemic excursion. In contrast, a decrease in insulin action results in sustained hyperglycemia but has a minimal effect on peak glucose concentrations. Whereas an isolated alteration in either hepatic or extrahepatic insulin action impairs glucose tolerance, a defect in both results in severe hyperglycemia [58].

Glucose is also an important regulator of its own metabolism. In the presence of basal insulin concentrations, an increase in plasma glucose stimulates glucose uptake and suppresses glucose production. The ability of glucose to regulate its own metabolism is impaired in T2DM. This is commonly referred to as a defect in "glucose effectiveness." Whereas intravenous infusion of 35 g of glucose in individuals without diabetes whose insulin concentrations are clamped at basal levels produces only a modest rise in plasma glucose concentration, infusion of the same amount of glucose results in severe hyperglycemia in people with T2DM [62]. The excessive rise in glucose is caused by impaired glucose-induced stimulation of glucose uptake because glucose-induced suppression of glucose production is normal [62, 63].

Inhibition of glucagon secretion lowers both fasting glucose and postprandial glucose concentrations. Failure to suppress glucagon secretion appropriately, however, has minimal effects on glucose production and glucose tolerance when insulin secretion is intact [64, 65]. In contrast, it causes marked hyperglycemia when insulin secretion is decreased and delayed, as is typical in T2DM. Taken together, these data suggest that agents that simultaneously improve insulin secretion, insulin action, glucose effectiveness, and glucagon secretion are likely to have a profound effect on glucose metabolism in people with T2DM (Figure 15.2) [65, 66].

Amylin is a 37 amino acid polypeptide that is co-secreted with insulin by the pancreatic β cells in response to nutrient stimuli and other secretagogues. Human studies have shown that the plasma concentrations of amylin and insulin rise and fall in parallel in both the fasted and fed states [67]. Because amylin is potentially toxic to β cells, it has been suggested that excessive amylin secretion may contribute to β-cell destruction in T2DM [68, 69].

The secretion of incretins such as glucagon-like peptide 1 (GLP-1) in response to meal ingestion is decreased in T2DM [70–72]. Supraphysiological concentrations of GLP-1, achieved by either intravenous infusion or subcutaneous injection, lower both fasting and postprandial glucose concentrations in people with T2DM. GLP-1 does so by increasing insulin secretion, inhibiting glucagon secretion, and delaying gastric emptying [73–76]. By contrast, GLP-1 does not appear to alter insulin action or glucose effectiveness in T2DM [77].

In addition to defects in insulin secretion, people with T2DM commonly exhibit defects in insulin action. Numerous studies have shown that insulin-induced stimulation of glucose uptake in muscle and adipose tissues and also insulin-induced suppression of glucose production are impaired in T2DM [78, 79]. The severity of insulin resistance is influenced by multiple factors, including exercise, obesity, and diet, and also genetic factors. Insulin resistance increases with increasing severity of diabetes and improves but is not normalized by improved glycemic control [80]. Defects in the ability of insulin to regulate muscle and fat glucose metabolism are evident in normoglycemic relatives of people with T2DM, strongly implying a genetic basis for at least some degree of insulin resistance [51, 81].

Both glucose production and the contribution of gluconeogenesis to glucose production are increased in people with "mild" in addition to "severe" T2DM [82]. The increase in glucose production is correlated with the severity of hyperglycemia [22, 59, 83].

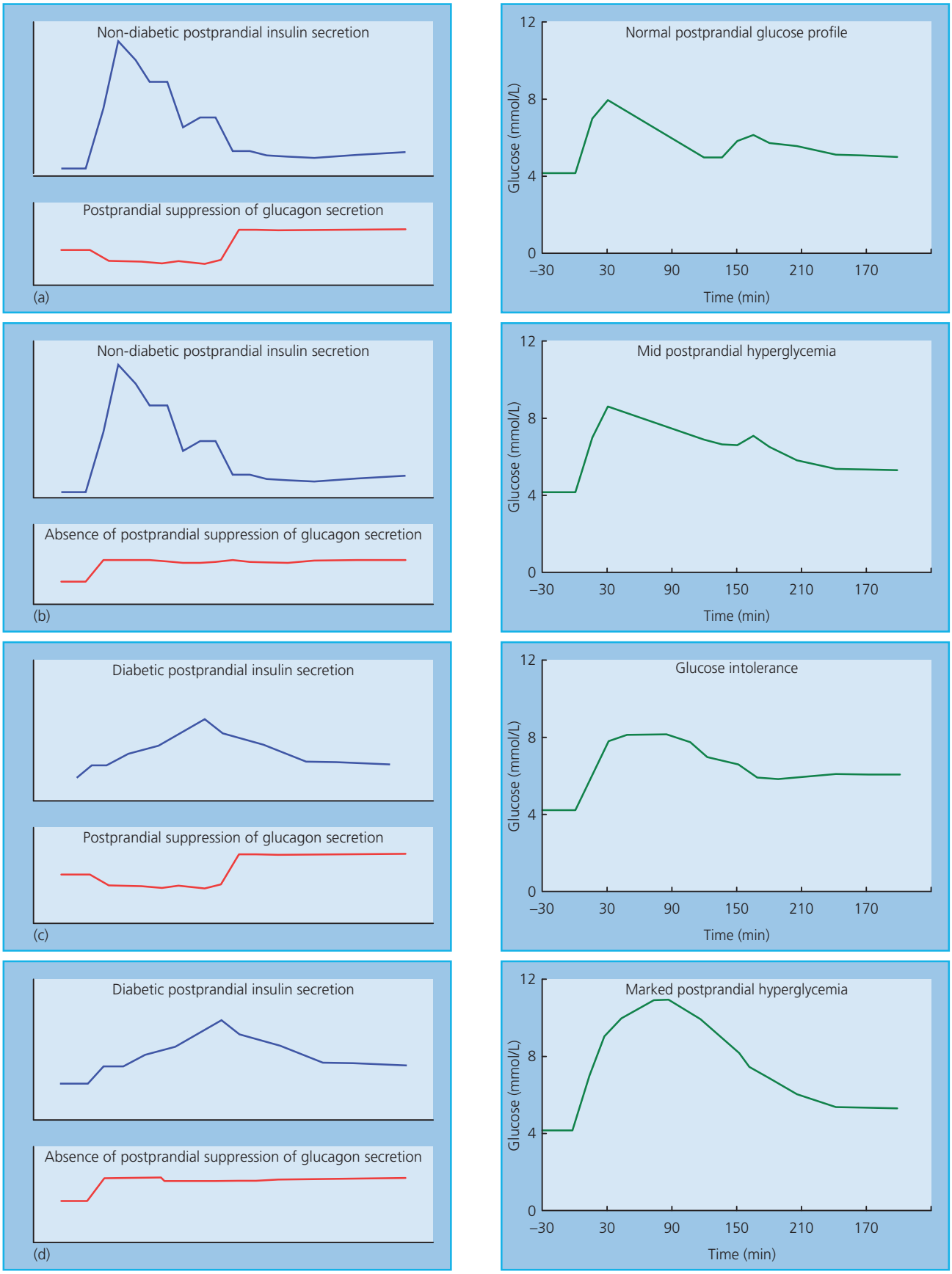

Figure 15.2 In an experiment in otherwise healthy volunteers, a non-diabetic postprandial insulin profile coupled with postprandial glucagon suppression results in a normal postprandial glucose profile (a). In the same individuals, absent postprandial glucagon suppression in the presence of a non-diabetic postprandial insulin profile resulted in a minimal increase in postprandial glucose (b). On the other hand, a diabetic insulin profile produced glucose intolerance (c), which was markedly worsened by the absence of postprandial glucagon suppression (d).

Insulin-induced stimulation of splanchnic (and therefore presumably hepatic) glucose uptake is also impaired in T2DM. The lower rates of hepatic uptake in people with diabetes are almost entirely accounted for by decreased uptake of extracellular glucose, suggesting lower glucokinase activity [84, 85].

Lipid metabolism in type 1 and type 2 diabetes

Dietary fat is an essential component of the human diet. However, excessive consumption of fat can have deleterious consequences on overall health. Part of the problem is that fat is a calorically dense macronutrient and excess caloric intake promotes obesity, with its attendant metabolic consequences. Dietary fat regulates *de novo* lipogenesis through nutrient control of transcription factors regulating expression of enzymes, including fatty acid synthase (FAS) and acetyl-CoA carboxylase (ACC) [86]. Elevated *de novo* lipogenesis and esterification of FFAs into triglycerides contribute to triglyceride elevation in the diabetic and prediabetic states.

Triglycerides are an important source and storage form of energy and are mobilized as FFAs. Plasma FFA concentrations represent a balance between release and disposal. FFAs are taken up by and re-esterified in adipose and hepatic tissues, or oxidized in muscle (cardiac and skeletal) or the liver. They are released by intravascular lipolysis of triglyceride-rich lipoproteins and intra-adipocyte lipolysis of triglyceride stores. In the fasting state, FFA concentrations are determined largely by the rate of entry into the circulation whereas in the postprandial period the rate of uptake by adipose and hepatic tissue is also a major determinant in FFA concentrations [87].

Hormone-sensitive lipase is the principal regulator of FFA release from adipose and is exquisitely sensitive to insulin. Insulin is the main hormonal regulator of lipolysis. Increasing plasma glucose concentration (e.g. after a meal) normally leads to increased insulin secretion, which inhibits lipolysis [88]. Rising insulin concentrations suppress lipolysis, leading to a fall in FFA concentration. This insulin-induced suppression of FFA concentration enhances insulin-dependent glucose disposal and insulin-induced suppression of endogenous glucose production [89].

Conversely, in individuals without diabetes, falling blood glucose concentrations increase lipolysis because of suppression of insulin secretion [90]. The resulting rise in FFA concentration will stabilize or raise glucose concentrations. Hypoglycemia caused by exogenous hyperinsulinism will also suppress lipolysis and impair counter-regulation.

Absolute or relative insulin deficiency is responsible for most of the excess FFAs available for oxidation in T1DM. Elevated FFA concentrations directly impair peripheral glucose uptake [91] and, at least acutely, stimulate endogenous glucose production [92]. Another consequence of elevated FFA flux is increased ketogenesis, a precursor to ketoacidosis [93]. Insulin is able to counteract the lipolytic effects of other hormones so that growth hormone or cortisol has little effect on lipolysis unless insulin availability is reduced [94]. Similarly, the lipolytic effect of catecholamines is blunted by hyperinsulinemia and accentuated by hypoinsulinemia [95]. Although glucagon has no effect on systemic FFA availability, increased concentrations, as seen in uncontrolled diabetes, may drive hepatic metabolism towards ketogenesis [93].

Moderate-intensity exercise is normally accompanied by a fall in insulin and a rise in catecholamine concentrations, which increases FFA availability and fatty acid oxidation [96]. Plasma insulin concentrations do not decrease with exercise in T1DM and, depending on the timing of exercise in relation to insulin administration, may not allow the normal increase in FFA concentration that accompanies exercise [97]. In these instances, people with T1DM become dependent on the catecholamine response to exercise to mobilize FFAs, a response that may be impaired in individuals with long-standing diabetes [98]. In people with fasting hyperglycemia, low insulin concentrations, and, consequently, elevated resting FFA flux, exercise will increase the FFA flux further [99]. This, combined with the high glucagon concentrations commonly present in these situations, will result in high rates of ketone body production.

FFA concentrations commonly are increased in the postabsorptive and postprandial state in people with T2DM [78, 100]. The ability of insulin to suppress lipolysis is impaired, likely because of decreased sensitivity of hormone-sensitive lipase to insulin [101]. Insulin also promotes FFA disposal, however, by stimulating re-esterification in adipocytes to form triglyceride. This process is dependent on the provision of glycerol-3-phosphate derived from glucose uptake (also insulin driven) and intra-adipocyte glycolysis. It is unknown, however, whether defects in adipose FFA esterification contribute to the FFA elevation observed in diabetes [87].

Circulating plasma triglycerides are dependent on the activity of lipoprotein lipase (LPL) to deliver FFAs to the adipocyte. Insulin and glucose preferentially stimulate adipose LPL and inhibit muscle LPL, thereby partitioning triglyceride and lipoprotein-derived fatty acids away from muscle and into adipose tissue [102]. By contrast, in T2DM, insulin-induced activation of adipose LPL is delayed while skeletal muscle LPL is activated [103]. Given that elevated FFA concentrations decrease muscle glucose uptake, this is especially of consequence in individuals with already diminished insulin action. FFAs decrease muscle glucose uptake by inhibiting glucose transport, glucose phosphorylation, and muscle glycogen synthase [104].

Although elevated FFA concentrations have been reported to decrease hepatic insulin metabolism in animals, direct measurement of splanchnic insulin clearance suggests that this may not be the case in humans [105]. Elevated FFA concentrations stimulate both hepatic gluconeogenesis and triglyceride synthesis. Acute increases in FFA concentration stimulate insulin secretion whereas chronic elevations inhibit insulin secretion [106]. Thus, elevated FFA concentrations have been implicated in many, but not all, of the metabolic abnormalities associated with T2DM.

Protein metabolism in type 1 and type 2 diabetes

Substrate availability and the hormonal milieu regulate protein synthesis and breakdown at any given time. Insulin is an important hormone in this regard and profound changes in body composition occur after the initiation of therapy in people with T1DM, especially if insulin deficiency has been severe and prolonged [107]. Urinary nitrogen excretion, a marker of protein catabolism, increases during insulin deprivation. If this is sufficiently prolonged, cachexia and a loss of muscle mass occur [108, 109]. Insulin deprivation increases the concentration of circulating amino acids because of the net increase in protein breakdown with an accompanying decline in amino acid disposal (utilization in protein synthesis or amino acid oxidation) [110, 111]. Of note, insulin-resistant states are characterized by an increase in circulating branched-chain amino acids (BCAAs). Indeed, plasma concentrations of BCAAs and their metabolites can predict the development of type 2 diabetes [112].

Glucagon secretion is enhanced by ingestion of protein and facilitates the disposal of glucogenic amino acids such as alanine or glutamine. The elevated glucagon concentrations present in poorly controlled T1DM stimulate alanine and glutamine uptake, resulting in normal or low concentrations despite increased appearance from protein breakdown from insulin deprivation [113]. Concentrations of BCAAs are elevated in these situations but are rapidly lowered to non-diabetic levels by treatment with insulin [110, 114].

In contrast, the effect of T2DM on protein metabolism is less clear cut, with some studies showing no evidence of increased catabolism [115, 116]; indeed, withdrawal of insulin for 10 days in people with type 2 diabetes does not change amino acid concentrations or protein metabolism [115]. On the other hand, others have reported increased protein turnover and/or amino acid catabolism [117–119]. In the presence of hyperinsulinemia and hyperaminoacidemia, people with T2DM exhibit impaired protein synthesis [120]. This observation might explain in part the reduced mitochondrial protein synthesis and ATP production observed in T2DM [121]. Insulin's stimulatory effects (and glucagon's opposite effects) on protein synthesis are mediated through mammalian target of rapamycin (mTOR) signaling and therefore defective insulin action would be expected to impair protein synthesis to some extent [122]. This may also have relevance to impaired synthesis of cardioregulatory molecules such as nitric oxide in the diabetic state [123].

The difference in protein metabolism between T1DM and T2DM likely occurs because people with T2DM have sufficient residual insulin secretion to limit protein catabolism and preserve lean body mass. Nevertheless, whole-body nitrogen flux and protein synthesis and breakdown are increased in people with poorly controlled diabetes. These defects are restored to normal when glycemic control is improved by treatment with either oral agents or insulin [117, 118].

Relatively few studies have examined regional protein dynamics in T2DM. Increased 3-methylhistidine excretion, an index of myofibrillar protein breakdown, has been demonstrated in people with poorly controlled T2DM when compared with healthy and obese individuals without diabetes [117]. Improved glycemic control reduced 3-methylhistidine excretion. People with T2DM and/or insulin resistance have been noted to have elevated circulating concentrations of certain clotting factors such as tissue plasminogen activator and plasminogen activator inhibitor 1 (PAI-1). This would imply that the synthesis of certain proteins by the liver and endothelium is clearly abnormal [124]. Preliminary evidence suggests that agents that improve the ability of insulin to regulate muscle and hepatic glucose metabolism (e.g. thiazolidinediones) will also restore concentrations, and possibly the activity, of these proteins to normal [125, 126].

Counter-regulatory hormones

In humans without diabetes, insulin and glucagon exhibit coordinated and reciprocal changes in concentration in response to glucose ingestion [22]. In people with T1DM, however, carbohydrate ingestion fails to suppress glucagon [127, 128], whereas protein ingestion commonly results in an excessive rise in glucagon concentrations [129]. The cause of these abnormalities in glucagon secretion is thought to be intra-islet insulin deficiency as insulin infusion inhibits glucagon secretion [130] and neutralization of intra-islet insulin with anti-insulin antibodies stimulates glucagon secretion [131]. Treatment with exogenous insulin rapidly lowers glucagon concentrations in people with T1DM but does not restore hypoglycemia-induced glucagon secretion [132].

Glucagon excess exacerbates hyperglycemia by increasing hepatic glucose release and decreasing hepatic glucose uptake [133, 134]. In humans without diabetes, any increase in glucose concentration is promptly accompanied by an increase in insulin secretion, which antagonizes the effects of glucagon on the liver. In contrast, in people with diabetes who cannot increase insulin secretion (and consequently glucose disposal) to compensate for the increase in glucagon concentrations, increased hepatic glucose release is accompanied by further increases in glucose concentration [133].

Fasting epinephrine and norepinephrine concentrations may be elevated in individuals with poorly controlled diabetes [135, 136] and may cause further deterioration in glycemic control by impairing insulin action at the hepatic and extrahepatic tissues [137]. Epinephrine also stimulates glucagon secretion, leading to further increases in endogenous glucose production [138]. In the absence of circulating insulin, catecholamines will enhance lipolysis, thereby increasing FFA concentrations and production of ketone bodies [139].

In the presence of severe defects in endogenous insulin secretion, as usually encountered in people with T1DM, the normal diurnal variation in plasma cortisol concentrations can adversely

affect glycemic control [140]. Cortisol increases endogenous glucose production while decreasing tissue glucose uptake. The nocturnal rise in cortisol also increases ketone body concentrations, gluconeogenesis, and lipolysis [140,1415].

Growth hormone release increases in both amplitude and frequency in people with poorly controlled diabetes [142, 143]. Growth hormone stimulates gluconeogenesis, proteolysis, and lipolysis while impairing insulin-induced suppression of endogenous glucose production and stimulation of glucose uptake [144]. This is likely to occur in situations where insulin secretion cannot rise to match the increased insulin requirements because of excessive growth hormone secretion.

Diabetic ketoacidosis

Insulin deficiency to a degree sufficient to allow unrestrained lipolysis and hepatic ketogenesis is a necessary condition for the development of diabetic ketoacidosis [145]. Because of this, ketoacidosis is more commonly encountered in people with T1DM than in those with T2DM because the latter generally have some degree of residual insulin secretion. Although insulin deficiency is a necessary condition for the development of ketoacidosis, the condition is often triggered by physical stress such as infection or surgery.

Glucagon concentrations rise in the presence of insulin deficiency and during physical stress. A decrease in effective circulating volume may also increase glucagon concentrations because glucagon is cleared by the kidneys. The concentrations of other counter-regulatory hormones also rise, which in turn further increases lipolysis [146].

Ketone bodies and glucose produce an osmotic diuresis that exacerbates the hypovolemia and electrolyte disturbances caused by metabolic acidosis. Furthermore, ketone bodies can induce vomiting, causing electrolyte and fluid losses. These losses also can directly contribute to metabolic acidosis. Cardiovascular collapse can occur if acidosis is sufficiently severe. Intracellular metabolic acidosis interferes with the activity of several enzymatic processes, which exacerbates the consequences of circulatory failure. Death is often caused by underlying comorbidities, the physical illness that precipitated ketoacidosis—myocardial infarction, pneumonia—or as a direct consequence of severe metabolic acidosis [147].

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16 Obesity and Diabetes

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Key points

- Obesity is characterized by an excess of body fat mass and is defined by a body mass index equal to or greater than 30 kg/m^2. Its prevalence has increased considerably over the past decades in all parts of the world and currently affects 15–30% of the adult population in Western countries.
- Overweight and/or obesity represents by far the most important modifiable risk factor for type 2 diabetes mellitus (T2DM). An abdominal type of body fat distribution is also closely associated with T2DM, particularly in the lower body mass index categories.
- Both obesity and T2DM have a strong genetic background. The known susceptibility genes for obesity mainly affect central pathways of food intake, whereas most risk genes for T2DM compromise β-cell function.
- Important environmental factors contributing to the development of obesity include energy-dense diets including large portion sizes and permanent availability of foods, lack of physical activity, and low socioeconomic status.
- An expanded adipose tissue impairs insulin action and causes insulin resistance in muscle, adipose tissue, liver, and possibly other organs.
- Obesity is also characterized by subacute chronic inflammation in adipose tissue because of an impaired paracrine–endocrine function of adipose tissue, but also by mitochondrial dysfunction, local hypoxia, and other still poorly understood disturbances at the cellular level.
- Weight loss in obese individuals is followed by rapid amelioration of all metabolic disturbances including chronic inflammation and insulin resistance. These improvements are brought about by caloric restriction rather than the macronutrient composition of the dietary intervention.
- Bariatric surgery is the most powerful approach to treat morbid obesity and may lead to a marked improvement of the metabolic disturbances if not the resolution of T2DM.

Introduction

Obesity is defined as a common chronic disorder of excessive body fat and has become a global epidemic which is present not only in the industrialized world but also in many developing and even in underdeveloped countries. At present, the prevalence of obesity (defined as body mass index (BMI) ≥30 kg/m^2) is in the range 15% to 35% in the adult populations in Europe, North America, and in many Arabic countries, with an unequivocal trend for further increases [1]. This condition increases the risk of developing a variety of adverse consequences to human health ranging from metabolic disturbances including type 2 diabetes mellitus (T2DM) and cardiovascular complications to disorders of the locomotor system and many types of cancer [2]. In addition, obesity impairs the subjective quality of life in affected people and can reduce life expectancy [3]. Although there is a very specific close relationship between excessive body weight and the risk of diabetes, the presence of obesity may induce many other disturbances that may aggravate the diabetic state.

Definition of obesity and the body fat distribution pattern

The diagnosis and classification of obesity is usually based on the BMI. This simple anthropometric index can be calculated from body weight and height, is independent of body height and correlates reasonably well with body fat mass ($r = 0.4$–0.7). The current classification of body weight according to the World Health Organization (WHO) is presented in Table 16.1. A BMI greater than 30 kg/m^2 is considered to be the central formal criterion for the definition of obesity which is further subdivided into three classes depending on the severity of excessive body fat. The BMI range of 25–29.9 kg/m^2 represents the category of overweight or preobesity which requires additional criteria to assess the concomitant health risks. In Western countries, 30–50% of the population fall into the category of overweight [1].

Not only the extent of excessive body fat mass, but also the anatomic location of the body fat mass determines the risk for metabolic and cardiovascular complications. This is particularly

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Table 16.1 Classification of human obesity based on body mass index (BMI) (kg/m^2).

Classification	kg/m^2
Underweight	<18.5
Normal weight	18.5–24.9
Overweight	≥25.0
Obesity	
grade I	30–34.9
grade II	35–39.9
grade III	≥40

Source: Data from World Health Organization [1].

important for the category of overweight and even in the upper normal range of BMI. At a defined BMI, the pattern of fat distribution can vary substantially. This has been most impressively shown using computed tomography (CT) or magnetic resonance imaging (MRI) scans which are the only imaging techniques to provide a direct assessment of the size of the intra-abdominal visceral adipose tissue. For practical means, waist circumference measured mid-way between the lower rib margin and the upper iliac crest is used as a simple anthropometric measure to assess the fat distribution pattern. This variable has been used in many cross-sectional and longitudinal studies; therefore, the threshold levels demonstrated in Table 16.2 are now well based on human data sets concerning associated health risks. The waist circumference is closely correlated with BMI but cannot discriminate between subcutaneous and intra-abdominal fat depots. Due to this limitation, there is growing clinical interest for more precise imaging methods to obtain a better insight into intra-abdominal and ectopic fat deposition (visceral fat, hepatic fat) in order to improve individual risk assessment.

Obesity is the most potent risk factor for type 2 diabetes

A large body of clinical data consistently demonstrates a close relationship between body fat mass and the risk of diabetes. It is noteworthy that in contrast to other obesity-associated metabolic disturbances, the diabetes risk is already increased in the upper normal range of BMI. This has been shown for both men and women. In the prospective Nurses' Health Study, women in the upper normal range with a BMI of 23.0–24.9 kg/m^2 had a four- to fivefold increased risk of developing diabetes over a 14-year observation period compared with women with a BMI of <22 kg/m^2. In women with a BMI of 29.0–30.9 kg/m^2 the risk of diabetes was 27.6-fold higher than in the lean reference group. Almost two-thirds of women with newly diagnosed T2DM were obese at the time of diagnosis [4]. Similar observations were made for men in the Health Professionals' Study [5]. Moreover, changes in body weight also predicted the risk of diabetes. Weight gain in women after the age of 18 years of 11.0–19.9 kg, which is the average range of weight change between adolescence and menopause in industrialized countries, was found to be associated with a 5.5-fold higher risk of diabetes compared with weight-stable women, whereas weight reduction of the same extent reduced the risk of diabetes by about 80% [4]. Very similar data were reported for men [5]. A recent analysis of the EPIC Potsdam cohort revealed that a weight gain of 1 BMI unit between the age of 25 and 40 years increased the relative risk of T2DM by 25% and had a greater effect than the same weight gain between 40 and 55 years of age [6]. It is also important to note that the duration of obesity has a strong impact on the risk of developing T2DM.

In a recent analysis of the relative contributions of different levels of overweight and obesity to the prevalence of diabetes between 1976–1980 and 2000–2004 in the USA it was found that the increase in total diabetes prevalence from 5.08% to 8.83% was largely caused by the increase in obesity. Of the increased number, 81% was attributed to the different classes of obesity (Figure 16.1). The authors concluded that the increase in diabetes prevalence over recent decades has disproportionately included persons with extreme levels of obesity [7]. Thus, obesity appears to be the main environmental driving force for the manifestation of T2DM.

In addition to the level and the duration of obesity, the risk of developing diabetes is also potently influenced by the fat distribution pattern. In an early study in humans, an abdominal pattern of fat distribution was found to be an independent risk factor for T2DM [8]. Subsequent studies confirmed this observation in many age groups and ethnic populations. Particularly at low degrees of overweight, and even in the upper normal range, the fat distribution pattern strongly predicts the risk for diabetes and the metabolic syndrome. Therefore, waist circumference should be routinely assessed when estimating the risk of diabetes even in normal-weight individuals. In the clinical setting, it is striking to observe that the majority of people with diabetes, particularly those of middle age, show a visible preferential truncal accumulation of excess body fat. It is also interesting to note that similar observations were made for the association between BMI and cardiovascular disease. Among overweight and obese individuals, only those with an abdominal type of fat distribution are at increased risk of coronary heart disease as documented in the INTERHEART study [9].

Table 16.2 Classification of fat distribution pattern, threshold values for the moderately and markedly elevated risk for metabolic and cardiovascular diseases.

	Waist circumference (cm) Elevated metabolic and cardiovascular risk	
	Moderately	Markedly
Men	>94	>102
Women	>80	>88

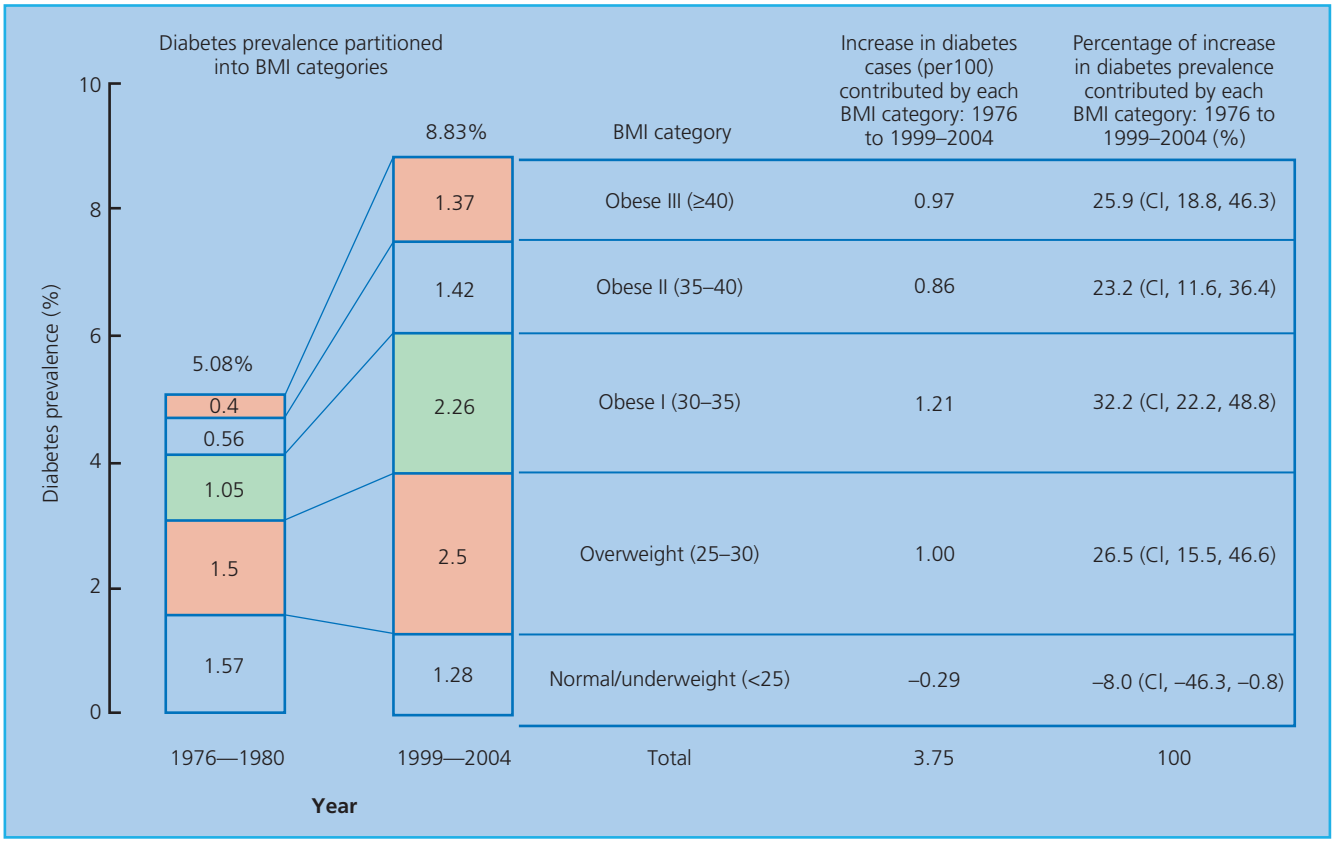

Figure 16.1 Contribution of five body mass index (BMI) categories to the overall prevalence of diabetes. National Health and Nutrition Examination Survey (NHANES) samples of 1976–1980 and 1999–2004 were compared. Source: Gregg et al. 2007 [7]. Copyright 2007 Elsevier.

Genetic predisposition for obesity and type 2 diabetes

It is well known from family, adoption, and twin studies that obesity, like T2DM, has a strong genetic basis. In the classic adoption study by Stunkard et al. [10] there was no resemblance between the adult BMI of adopted Danish children and the BMI of the adopting parents, but a significant correlation to the BMI of the biologic parents, especially to the BMI class of the biologic mother. In a twin study of obesity, concordance rates for different degrees of overweight were twice as high for monozygotic twins as for dizygotic twins. This high heritability for BMI was seen at the age of 20 years and to a similar extent at a 25-year follow-up, suggesting that body fatness is under substantial genetic control [11]. There is also a very close correlation in monozygotic twins who were reared apart, also indicating a high heritability of the BMI trait. In a recent study of 5092 twins living in the London area, the authors estimated the heritability of BMI and waist circumference as 0.77, further supporting the strong effect of the genetic components irrespective of the force of the obesogenic environment [12].

During the last decade, a number of monogenic disorders that result in human obesity have been uncovered. These genetic disorders were only found in rare cases, however, usually children and adolescents with early onset of obesity. At present, a variety of homozygous and compound heterozygous mutations have been described in the leptin–melanocortin signaling pathway, some of them with functional consequences resulting in human obesity. Functional mutations in the melanocortin-4-receptor gene are considered to be the most frequent cause of monogenic obesity in children with a frequency of 2–4% of all obese cases. It is striking that these defects affect mainly genes that are involved in the central control of food intake.

Genome-wide association (GWA) studies in large cohorts with BMI as phenotype reported common genetic variants on various chromosomes. In a recent GWA study, the analysis identified 97 BMI-associated loci. Subsequent pathway analyses provided evidence for a role of the central nervous system, but also pathways related to insulin secretion/action, energy metabolism, lipid biology and adipogenesis [13]. A genome-wide association meta-analysis of traits related to waist and hip circumference reported 49 loci associated with waist/hip ratio adjusted for BMI and an additional 19 loci associated with related waist and hip measures. The identified loci were enriched for genes expressed in adipose tissue. Pathway analyses implicated adipogenesis, angiogenesis, transcriptional regulation, and insulin resistance as processes

affecting fat distribution [14]. Among the gene variants found in GWA studies so far, variants near to the *FTO* and the *MC4R* gene appear to have the strongest effect size on body weight, whereas the effect size of most of the novel "obesity genes" is rather modest. Individuals who are homozygous for the high-risk allele of the *FTO* gene weigh on average 3 kg more than individuals with two low-risk alleles [15]. A recent study elucidated the mechanistic basis of this association and identified a single-nucleotide variant (rs1421085 T-to-C) that shifts the developmental program from energy-dissipating beige adipocytes to energy-storing white adipocytes, thereby reducing mitochondrial thermogenesis in white adipose tissue [16]. Thus, it is apparent from recent work that obesity represents a rather heterogeneous disorder in terms of genetic background and susceptibility to etiologic environmental factors. In addition, the risk for developing comorbidities including T2DM may strongly depend on the individual genetic predisposition towards such diseases. In the case of T2DM, the lifetime risk of developing this disease is about 30–35% in the white North American population and similar in other ethnic groups [17]. It is currently assumed that only those obese individuals who exhibit a genetic failure of the pancreas to compensate for insulin resistance, which is a characteristic consequence of obesity, will develop T2DM [18]; even among the most severely obese (BMI $\geq$40 kg/m^2) only 30–40% will develop diabetes throughout life. Thus, the development of T2DM requires the presence of "diabetes genes" which affect susceptibility via two main mechanisms: (1) through insulin resistance and/or (2) through β-cell dysfunction [19].

Developmental programming of obesity and diabetes

A new component that may have a major role in the development of obesity and T2DM is the modification of gene expression by epigenetic mechanisms during fetal life. Although this is still a poorly defined phenomenon and it is rather unclear which mechanisms may underlie this association, there is some clue that epigenetics may also operate in this context. Observational studies suggest that infants of mothers with gestational diabetes are at increased risk of developing childhood obesity [20]. In another study, siblings born after the mother had developed gestational diabetes (i.e. exposed to diabetes *in utero*) have a much greater risk of T2DM in young adulthood than siblings not exposed to diabetes *in utero* (odds ratio 3.7; $p = 0.02$) [21].

Another interesting clinical observation is that excessive weight gain during pregnancy, independent of initial BMI, may also increase the risk of gestational diabetes in pregnant women [22] as well as early development of obesity in the offspring [23]. It is speculated that both chronic overnutrition and hyperglycemia during pregnancy may cause fetal hyperinsulinemia, hypercortisolemia, and hyperleptinemia. These hormonal changes may result in a persisting malprogramming of hypothalamic centers controlling energy homeostasis and metabolism, thereby increasing the lifetime risk for obesity and T2DM and possibly the risk for other adverse long-term health consequences [24]. The mechanisms mediating these effects are largely elusive, but it is speculated that epigenetic processes such as DNA methylation, histone modification, and changes of the microRNA pattern are involved. Animal experiments suggest that this imprinting process may mainly affect central neuroendocrine pathways which may finally modify appetite regulation [24].

Pathophysiology of obesity

Irrespective of the strong genetic influence on body weight, there is also no doubt that the evolving worldwide epidemic of obesity is primarily a consequence of substantial changes in the environment and lifestyle (see Chapter 9). It is rather new to mankind that food is abundant in many countries and that physical activity is no longer a prerequisite for survival. These dramatic changes in environment and the subsequent changes in lifestyle have occurred within a few decades, a period probably too short to result in adaptations of the genetic background and biologic systems to optimize survival. To date, the relative contributions of the various environmental factors to the epidemic of obesity are hard to quantify in detail and there exist considerable differences between populations.

Humans, like other mammals, are characterized by a tight control of energy homeostasis allowing a stable body weight to be maintained. This setpoint of body weight can vary substantially among individuals and may also vary across lifetime. A complex regulatory system controls energy homeostasis which involves central pathways and peripheral components such as the size of adipose tissue which is sensed to the brain via the secretion of leptin. In addition, gut hormones, signals from the gastrointestinal nervous system and nutrients signal to the brain and induce a complex central integration according to the dietary intake and nutrient requirements of the organism. Central pathways are the anorexigenic leptin–melanocortin link and the orexigenic NPY–AgRP pathway. Many other factors such as insulin modify these signaling processes and thereby influence energy balance [25]. This complex and potent homeostatic system also serves to defend body weight against a critical energy deficiency but also against chronic overnutrition. Several adaptive systems are known to restore the initial body weight under such fluctuations of energy intake and expenditure. This may explain why obese humans exhibit a strong tendency to regain weight after intentional dietary weight reduction. The same tendency to return to initial body weight is observed after experimental overfeeding.

The role of energy homeostasis in the development of obesity has been elaborated by previous studies using indirect calorimetry to investigate the contribution of the resting metabolic rate (RMR) to the risk of obesity. In a study of Pima Indians, RMR was found to be a familial trait and to vary considerably across families [26]. In

prospective studies in Native Americans a reduced rate of energy expenditure assessed in a respiratory chamber turned out to predict body weight gain over a 2-year follow-up period. This finding was confirmed in another group over a 4-year-follow-up period, indicating that a low rate of energy expenditure may contribute to the aggregation of obesity in families [27]. At present, the genetic components for these differences in energy metabolism are still unknown.

Environmental factors promoting obesity and type 2 diabetes

It is now established that a complex gene–environment interaction determines the individual risk to develop obesity (Table 16.3). Even in societies with an abundance of affordable, highly palatable food there is a high variation in body weight across the populations ranging from lean individuals to extremely obese persons. Many other factors such as physical activity, education, and socioeconomic status may also act as strong modifiers of body weight. After two to three decades of modern lifestyle the trend towards obesity appears to reach a plateau, as suggested by recent data from the USA and other Western countries.

Despite the genetic predisposition it is widely accepted that the current worldwide epidemic of obesity is largely a consequence of dramatic changes in lifestyle and environment which emerged over the past 30–50 years. A dramatic change in eating habits and food selection took place, whereas physical activity decreased remarkably because of technologic development concerning transportation and workplaces. Although dietary abundance and sedentary lifestyles have multiple origins, both may equally contribute to a chronic positive energy balance which may result in excess energy storage in adipose tissue.

A rather novel phenomenon is the expansion of the fast-food culture characterized by high-fat, low-starch foods together with a high sugar intake including sugar-sweetened beverages. In addition to having a high energy density, fast-food menus have large portion sizes. This combination has led to the assumption that frequent fast-food consumption is linked to body weight gain and maintenance of overweight and obesity in the population. A recent systematic review of six cross-sectional and seven prospective cohort studies concluded that sufficient evidence exists for this link, at least for the adult population [28]. According to a recent survey, people from the USA obtain one-third of their daily caloric intake from restaurant meals, and one-third of customers of chain restaurants in New York purchased meals containing more than 1000 calories [29]. Thus, there is a growing need to develop new public health policies to limit fast-food consumption and to facilitate a healthier food selection.

Table 16.3 Environmental factors promoting the development of obesity.

Ready availability of food
High palatability of food
High energy density
Relatively low cost of foods
High consumption of sugar-sweetened beverages
Aggressive commercial food promotion
Low physical activity

In addition, a high intake of added sugar in solid foods and sugar-sweetened beverages is another part of the global fast-food culture. A systematic review clearly concluded that among free living people intake of free sugars or sugar-sweetened beverages is a determinant of body weight [30]. In addition, a recent meta-analysis revealed that habitual consumption of sugar-sweetened beverages is associated with a greater incidence of T2DM, even independently of obesity, with an estimated population attributable fraction of 8.7% [31].

Another aspect in the context of high fast-food consumption which may further explain the elevated risk of obesity is the energy density of modern foods. There is convincing evidence that energy density of foods is a key determinant of caloric intake. From an evolutionary point of view, the human regulatory system for energy intake is adapted to starchy foods with low caloric content which require large volumes to obtain sufficient energy. Today, most fast-foods have a high energy density which may favor a passive overconsumption of calories. A recent study showed that the average energy density of fast-food menus is approximately 1100 kJ/100 g, which is 65% higher than the average British diet (approximately 670 kJ/100 g) and more than twice the energy density of recommended healthy diets (approximately 525 kJ/100 g). It is 145% higher than in traditional African diets (approximately 450 kJ/100 g) which represent the levels against which human weight regulatory mechanisms have evolved. The authors concluded that the high energy density of many fast foods challenges human appetite control systems with conditions for which they were never developed [32].

A large cohort study in the USA reported an increase of total daily energy intake by 570 kcal per day between 1977–1978 and 2003–2006, with the largest increase in the last decade. Over this 30-year period, the three components under investigation, that is, energy density, portion size, and eating occasions, contributed to a greater or lesser extent to changes in energy intake, with changes in eating occasions being the largest contributor [33]. Finally, socioeconomic status is a strong determinant of obesity and of T2DM. In most countries there is a gradient between education and household income and the prevalence of obesity. A low socioeconomic status is associated with an unfavorable lifestyle including poor nutrition, low leisure-time physical activity, and low health consciousness. This gradient is usually greater in females than males. Thus, the association between low household income and obesity may be mediated by the low costs of energy-dense foods, whereas prudent healthy diets based on lean meats, fish, vegetables, and fruit may be less affordable for those of lower socioeconomic status [34].

Pathophysiologic links between obesity and type 2 diabetes

T2DM is characterized by an impaired insulin action or a defective secretion of insulin or both. Both defects are thought to be required for the manifestation of the disease and both are present many years before the clinical onset of the disease [35]. To date, the mechanisms by which obesity increases the risk of developing T2DM are only partly understood and the evolving picture is becoming more and more complex. The main adverse effect of obesity is on the action of insulin, particularly in liver, muscle and adipose tissue, but obesity also affects insulin secretion. Substantial advances have been made over recent years in our understanding of how an excessive fat mass, but also chronic overnutrition, may cause metabolic disturbances resulting in overt T2DM in those with a genetic predisposition for the disease.

Lipids and insulin resistance

The earliest hypothesis to explain the relationship between obesity and T2DM is the "glucose–fatty acid cycle" which is based on the observation of a competition between glucose and fatty acid oxidation in the heart muscle and was introduced by Randle et al. [36]. The increased supply of non-esterified fatty acids from expanded adipose tissue depots competes with glucose utilization, particularly in muscle, which represents the organ that oxidizes the largest proportion of glucose. The proposed mechanism is an inhibition of the glycolytic enzymes pyruvate dehydrogenase, phosphofructokinase, and hexokinase. As a consequence, the rate of glucose oxidation is reduced and glucose concentrations rise. The concomitant increased fatty acid turnover is accompanied by an increased release of glycerol from adipose tissue which is reutilized for hepatic glucose production, further augmenting the imbalance of glucose metabolism. Increased hepatic glucose output is another early disturbance contributing to glucose intolerance [37].

In addition, it was reported that elevated free fatty acids can directly impair insulin action. Recent studies suggested that obese individuals and those with T2DM have a high intramyocellular lipid accumulation which is an important feature of the insulin-resistant state. Exposure of skeletal muscle to an excessive lipid supply may lead to intramuscular accumulation, not only of neutral fatty acids, but also of lipid-derived metabolites such as ceramide, diacylglycerol, and fatty acyl coenzyme A (CoA). This lipid accumulation is associated with coincident disturbances in insulin action mediated by an activation of a serine–threonine kinase cascade leading to serine–threonine phosphorylation of insulin receptor substrate 1 (IRS-1) and IRS-2 which may cause an impairment of insulin signaling including an impaired activation of phosphoinositol-3 (PI_3) kinase and other downstream elements [37]. This condition is also caused and exacerbated by chronic overnutrition with a high dietary fat intake. Thus, the increased availability of fatty acids may be the single most critical factor in disturbing insulin action in obesity.

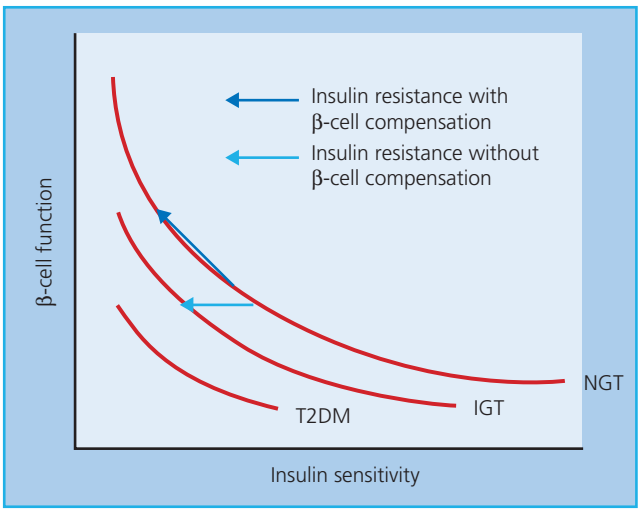

Figure 16.2 Hyperbolic relation between β-cell function and insulin sensitivity. IGT, impaired glucose tolerance; NGT, normal glucose tolerance; T2DM, type 2 diabetes mellitus. Source: Stumvoll M, et al. Type 2 diabetes: Principles of pathogenesis and therapy. *Lancet* 2005; **365**:1333–1346. Copyright 2005 Elsevier.

Lipids and β-cell function

Obesity is characterized by an elevated insulin secretion and a decreased hepatic insulin clearance. Human studies suggested that the β-cell volume is increased by about 50% in healthy obese people, probably because of hypertrophy of existing β cells. Insulin release and insulin sensitivity are closely reciprocally related in a non-linear manner (Figure 16.2). Failure of this feedback system is known to result in a progressive decline in β-cell function and to underlie the development of T2DM. In addition to glucose, long-chain fatty acids may also exert a stimulatory effect on insulin secretion from the pancreatic β cells via generation of fatty acyl CoA and activation of protein kinase C [37]. Another effect of fatty acids on insulin secretion is via binding to the G-protein-coupled receptor GPR 40 on the β-cell membrane which may result in a subsequent increase in intracellular calcium and secretory granule exocytosis [38]. Although fatty acids are critical for normal insulin secretion, a chronic exposure of β cells to excessive fatty acids is associated with marked impairment of glucose-stimulated insulin secretion and decrease in insulin biosynthesis [39]. Another mechanism by which elevated fatty acids may impair insulin secretion in response to glucose is via an increased expression of uncoupling protein 2 (UCP-2) in β cells. UCP-2 was found to be upregulated under glucolipotoxic conditions and mitochondrial superoxide has been identified as a post-translational negative regulator of UCP-2 activity in islets [40].

Glucose sensing of the pancreatic β cells requires an intact oxidative mitochondrial metabolism to generate ATP. The resulting high ATP : ADP ratio is a prerequisite for normal insulin secretion. Studies in humans suggest that insulin resistance may also

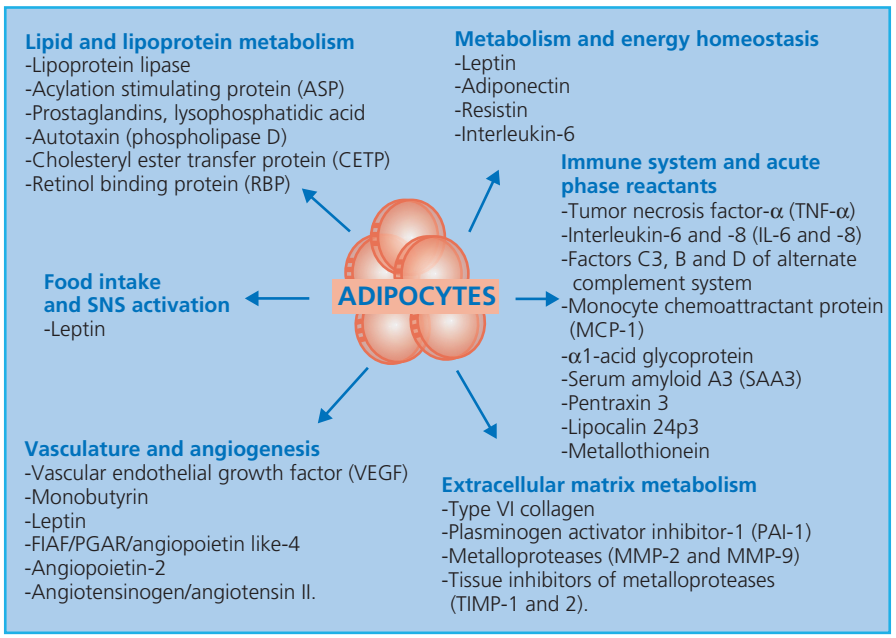

Figure 16.3 Secretory products from adipose tissue and functional relationship. SNS: sympathetic nervous system. Source: Lafontan M. Fat cells: Afferent and efferent messages define new approaches to treat obesity. *Annu Rev Pharmacol Toxicol* 2005; **45**:119–146. Reproduced with permission from Annual Reviews.

arise from defects in mitochondrial fatty acid oxidation which may lead to increased intracellular fatty acid metabolites (fatty acid CoA, diacylglycerol). It was recently shown that young insulin-resistant offspring of parents with T2DM have features of impaired mitochondrial function [41]. Furthermore, it was reported that obese individuals have smaller mitochondria with reduced bioenergetic capacity than lean people [42, 43]. Although studies on this topic are still limited, there is growing evidence that a defective mitochondrial function could be a prominent feature of disturbances in both insulin secretion and action [44].

Adipose tissue as a secretory organ

Another hypothesis that may explain the association between obesity and T2DM is the observation that adipose tissue is a secretory organ that produces and releases a variety of factors that may contribute to the development of insulin resistance and other health risks (Figure 16.3; Table 16.4). Among these factors most data have been collected for a mediator role of tumor necrosis factor α (TNF-α). TNF-α is a multifunctional cytokine which was the first found to be expressed in adipose tissue [45]. It was subsequently shown that TNF-α exerts a variety of catabolic effects in adipose tissue. In addition to TNF-α, it was reported that its two receptor subtypes are overexpressed in adipose tissue from obese individuals [46–48]. The upregulated TNF-α system induces multiple adverse effects at the local organ level such as inhibition of glucose uptake because of an impairment of insulin signaling and suppression of GLUT-4 expression, a reduction of lipoprotein lipase expression and activity, and an increase in lipolysis [49]. Moreover, TNF-α activates the NF-κB pathway in adipose tissue which leads to an increased expression of many proinflammatory proteins such as interleukin 6 (IL-6), IL-8, and monocyte chemotactic protein 1 (MCP-1) among others. Finally, TNF-α was demonstrated to reduce the expression of adiponectin, a protein that is abundantly expressed in fat cells and exerts direct antidiabetic and anti-atherosclerotic actions. A key mechanism by which TNF-α causes insulin resistance may be that this cytokine stimulates the phosphorylation of IRS-1 at the serine residue 307 which inhibits the transduction of the insulin signal to downstream elements [50].

Using an *in vitro* co-culture model of human adipocytes and muscle cells it was recently demonstrated that other fat cell secretory products, in addition to TNF-α, are also involved in the development of muscle insulin resistance [51]. Thus,

Table 16.4 Secretory function of adipose tissue in obesity and potential clinical consequences.

Product	Secretion	Consequence
Free fatty acids	↑	Dyslipidemia (TG ↑), insulin resistance
TNF-α, IL-6, MCP-1 and other cytokines/chemokines	↑	Insulin resistance, type 2 diabetes
Angiotensinogen, angiotensin II and other vasoactive factors	↑	Hypertension
PAI-1	↑	Thromboembolic complications
CETP	↑	Low HDL cholesterol
Adiponectin	↓	Insulin resistance, atherosclerosis
Estrogens	↑	Endometrial and breast cancer

CETP, cholesterol ester transfer protein; HDL, high density lipoprotein; IL, interleukin; MCP, monocyte chemotactic protein; PAI, plasminogen activator inhibitor; TG, triglycerides; TNF, tumor necrosis factor.

it is likely that the negative effect on muscle insulin action is brought about by a combination of adipokines. Although we have currently little information on the nature and the complex interplay of such proinflammatory and anti-inflammatory factors, a few relevant players have been identified. One such element may be MCP-1 [52]. Other potential candidates with a prodiabetes action may include plasminogen activator inhibitor 1 (PAI-1), but also lipid metabolites such as diacylglycerols and ceramides. Retinol-binding protein 4 (RBP-4) was also shown to contribute to insulin resistance via reduced PI_3 kinase signaling and enhanced hepatic expression of the gluconeogenic enzyme phosphoenolpyruvate carboxykinase. An interesting observation in this context is that adiponectin may be able to antagonize the insulin resistance-promoting activity of proinflammatory cytokines released from adipose tissue in an autocrine fashion.

Adipocytes are also able to release products with anti-inflammatory properties including factors such as adiponectin, IL-1 receptor antagonist, and IL-10. By far the most interesting component is adiponectin, which is the most abundantly expressed protein in adipose tissue. It was shown in a number of clinical studies that circulating adiponectin levels are inversely associated with BMI and that low concentrations predict the development of T2DM [53]. Adiponectin is now known to exert a variety of antidiabetic and anti-atherosclerotic effects (e.g. adiponectin stimulates fatty acid oxidation in an AMP-activated protein kinase-dependent manner) [54].

Signaling pathways of inflammation in adipose tissue

Current research has shown that the inflammatory response in human obesity is mediated via activation of the c-Jun N-terminal kinase (JNK) and IKKβ–NF-κB pathways. Both pathways are simultaneously stimulated by cytokines such as TNF-α and IL-6, but also by lipids. It has been convincingly demonstrated in experimental studies that genetic or chemical inhibition of these pathways can reduce inflammation and improve insulin resistance (for review see [55]) (Figure 16.4). In obesity, JNK activity is elevated not only in adipose tissue, but also in liver and muscle. Loss of JNK1 prevents the development of insulin resistance and diabetes in both genetic and dietary mouse models of obesity [56]. IKKβ can act on insulin signaling through at least two pathways. First, it can directly phosphorylate IRS-1 on serine residues and, second, it can phosphorylate the inhibitor of NF-κB (IκB) thus activating NK-κB, a transcription factor that stimulates the production of many proinflammatory mediators including TNF-α and IL-6 [57]. Mice heterozygous for IKKβ are partially protected against insulin resistance caused by lipid infusion, high-fat diet or genetic obesity [58]. Both the JNK and the IKKβ–NF-κB pathways are activated via pattern recognition receptors that function as membrane receptors for a variety of external signals. It is interesting to note that endogenous lipids and lipid conjugates were found to activate toll-like receptors (TLRs) in obesity. It was recently reported that saturated fatty acids bind and activate TLR-4 on adipocytes, thereby suggesting a direct link between exogenous nutrients that are redundant in the obese state and inflammation [59]. Mice with

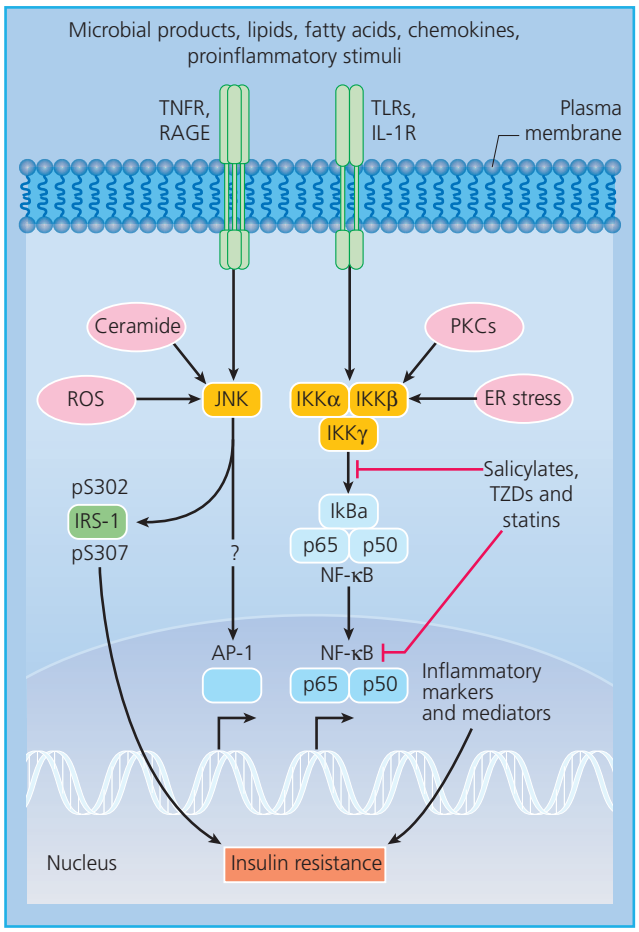

Figure 16.4 Potential cellular mechanisms for inflammation and development of insulin resistance. AP-1, activator protein 1; ER, endoplasmic reticulum; IKK, Iκ kinase; IL, interleukin; IRS, insulin receptor substrate; JNK, c-Jun N-terminal kinase; NF-κB, nuclear transcription factor κB; PKC, protein kinase C; ROS, reactive oxygen species; TLR, toll-like receptor; TNFR, tumor necrosis factor receptor; TZD, thiazolidinedione. Source: Shoelson and Lee 2006 [55]. Reproduced with permission from the American Society for Clinical Investigation.

a loss-of-function mutation of TLR-4 were found to be protected from diet-induced obesity and insulin resistance. These mice also showed a reduced NF-κB and JNK activity under a high-fat diet compared to wild-type control mice [60].

It is noteworthy that most proteins released from adipose tissue are not produced by fat cells but rather by pre-adipocytes and invading immune cells such as activated macrophages. While leptin and adiponectin are true adipokines, which are almost exclusively produced by adipocytes, TNF-α, IL-6, IL-8, MCP-1, visfatin, PAI-1 and others are mainly expressed by pre-adipocytes, macrophages resident in adipose tissue and possibly other cells. The relative contributions of the various cellular components in adipose tissue to the secretion of these products remains unknown and may vary substantially according to depot and model. Nevertheless, all these locally secreted factors appear to participate in the induction and maintenance of the subacute

inflammatory state associated with obesity. It is also important to mention that the invading macrophages release factors that substantially augment adipocyte inflammation and insulin resistance [61]. Another interesting observation in this context is that preadipocytes and macrophages share many common features [57].

The regulation and biologic functions of the secretory products are diverse and only poorly understood. In addition to the direct effects of fatty acids and their intracellular products, other factors may also contribute to the chronic inflammatory state in adipose tissue. It was recently shown that fat cell size may be a critical determinant of the production of pro-inflammatory and anti-inflammatory factors. Enlarged hypertrophic fat cells are characterized by a shift towards a pro-inflammatory state [62], thereby promoting insulin resistance. This is in agreement with clinical data showing that fat cell hypertrophy is associated with an increased risk of developing T2DM [63].

Obesity and endoplasmic reticulum stress

A recent observation suggests that obesity and chronic overnutrition overload the functional capacity of the endoplasmic reticulum (ER) and that the resulting ER stress contributes to the activation of the inflammatory signaling pathways including the JNK pathway. In both high-fat diet induced and genetic obesity models, obesity was shown to cause ER stress with inositol-requiring kinase-1α (IRE-1α) having a crucial role in insulin receptor signaling as a mediator of JNK activation [64]. Subsequent studies further supported the role of ER stress in the pathogenesis of obesity and T2DM. Such studies showed that ES stress is operating in various tissues such as hypothalamus, liver, muscle, and adipose tissue and may induce inflammation, insulin resistance and impaired insulin secretion in a tissue-specific manner [65]. In a mouse model of T2DM, systemic overexpression of 150-kDa oxygen-regulated protein (ORP150), a molecular chaperone located in the ER, improved insulin intolerance and enhanced glucose uptake indicating that this chaperone has an important role in insulin sensitivity and is a potential target for the treatment of T2DM [66].

Obesity and oxidative stress

Increased fat accumulation was reported to be associated with systemic oxidative stress in humans and mice [67]. There was a selective production of reactive oxygen species (ROS) in adipose tissue of obese mice, accompanied by an increased expression of NADPH oxidase and a decreased expression of antioxidative enzymes. The authors also showed that fatty acids increased oxidative stress in cultured adipocytes via NADPH oxidase activation which was followed by dysregulated production of adipokines such as adiponectin, PAI-1, IL-6, and MCP-1. In addition, treatment with an NADPH oxidase inhibitor reduced ROS production, restored the dysregulation of adipokines in adipose tissue and improved diabetes, dyslipidemia, and hepatic steatosis, indicating that the redox status in adipose tissue is a critical factor in the development of the metabolic syndrome [67].

Adipose tissue hypoxia

An expansion of the adipose tissue mass leads to fat cell hypertrophy and subsequent hypoxia of the tissue. A number of mainly animal studies convincingly support the concept that hypoxia has an important if not central role in the development of chronic inflammation, macrophage infiltration, impaired adipokine secretion, ER stress, and mitochondrial dysfunction in white adipose tissue in obesity [68, 69]. These consequences are also accompanied by an inhibition of adipogenesis and triglyceride synthesis and elevated circulating free fatty acid concentrations. Measurement of the interstitial partial oxygen pressure (PO_2) in adipose tissue showed a reduction of up to 70% leading to oxygen levels of about 2% in obese animals compared to lean controls [69]. This observation was further substantiated by the determination of hypoxia response genes such as hypoxia-inducible factor 1α (HIF-1α), vascular endothelial growth factor (VEGF), heme oxygenase 1 (HO-1), and others. The low oxygen pressure may also contribute to a reduced mitochondrial respiration with a consequent increase in lactate production. In humans, HIF-1α was also shown to be increased in white adipose tissue of obese people and its expression was reduced after surgery-induced weight loss [70].

The physiologic basis of adipose tissue hypoxia may be related to a reduction in adipose tissue blood flow and capillary density which has been reported in both obese humans and animals. Although the hypoxic state leads to an increased production and release of pro-angiogenic factors from adipose tissue such as VEGF and others, this compensatory mechanism may not be sufficient to keep the PO_2 at a normal level as the free diffusion of oxygen in the adipose tissue may be limited [69]. Although hypoxia may drive adipose dysfunction in obesity, the functional consequences of altered PO_2 in human adipose tissue are still poorly characterized and await further elucidation [71].

Accumulation of immune cells

Leptin, TNF-α, MCP-1 and other chemokines have an essential role in the recruitment of macrophages to adipose tissue. The secretory profile of both pre-adipocytes and adipocytes includes a variety of chemo-attractants for immune cells. It was recently reported that the attraction of T-lymphocytes possibly caused by stromal cell-derived factor 1 (SDF-1) represents the initial step that subsequently leads to the invasion and activation of circulating monocytes–macrophages resembling the scheme originally described for atherosclerosis [72]. Such accumulation of immune cells and inflammation of adipose tissue has been shown in obese humans [73] and appears to be related to CCR expression of circulating monocytes. As a consequence, a higher migration activity into adipose tissue of obese women was observed which was associated with markers of insulin resistance [74].

Role of body fat distribution pattern

Another important issue in this context is the distribution of body fat. It has long been known from early clinical studies that people with a more abdominal type of body fat distribution are at

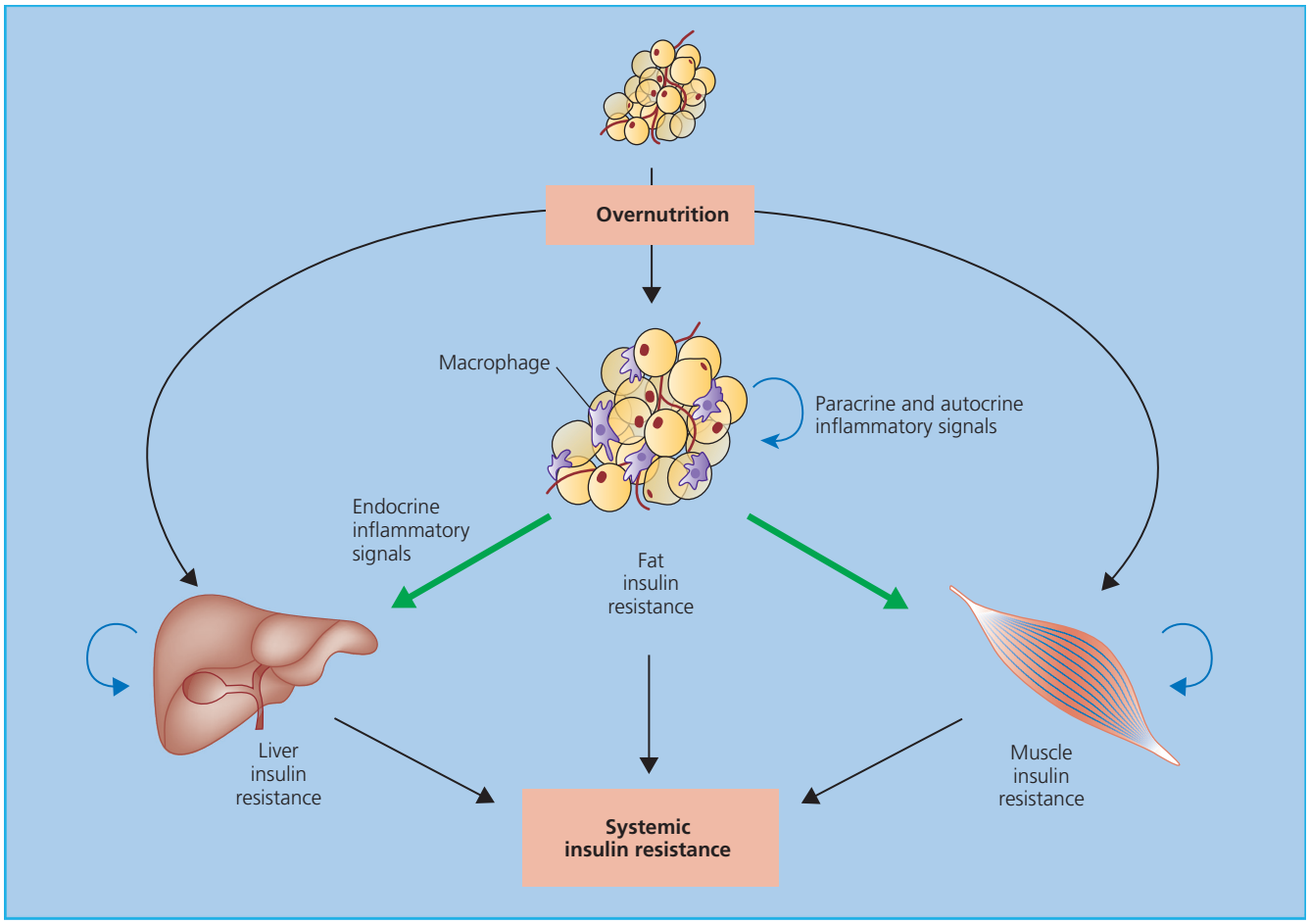

Figure 16.5 Nutrition and obesity-induced inflammation and development of systemic insulin resistance. Source: De Luca C, Olefsky JM. Stressed out about obesity and insulin resistance. *Nat Med* 2006; **12**:41–42. Reproduced with permission from Nature Publishing Group.

increased risk of developing T2DM and other metabolic and cardiovascular complications [75–77]; however, the underlying cause has only recently become evident. Intra-abdominal fat cells exhibit a differing expression profile and are lipolytically more active than subcutaneous adipocytes. Moreover, they show a greater accumulation of lymphocytes and macrophages, indicating greater proinflammatory activity. Visceral adipose tissue also has a much higher blood vessel and nerve density leading to a much greater metabolic activity. Visceral adipose tissue drains into the portal vein and thus the liver is directly exposed to fatty acids and proteins released from this active fat depot promoting insulin resistance in the liver. Thus, the inflammatory process is detected, not only at the level of adipose tissue, but may also affect the liver and possibly other organs. As enlarged visceral fat depots are frequently associated with fat accumulation in the liver, it was also hypothesized that secretory products from the visceral adipose tissue may directly cause hepatic insulin resistance.

In summary, a variety of data suggests that chronic overnutrition with a high-fat, high-sugar diet and as a consequence an accumulation of body fat, particularly in the visceral depots and ectopically in liver, muscle, and other organs, is the primary cause of chronic inflammation in obesity and may promote the development of systemic insulin resistance which affects many tissue including liver, muscle, and the brain (Figure 16.5). It should not be neglected that apart from an unhealthy diet, other lifestyle factors such as lack of physical activity may substantially contribute to these pathologic processes.

Treatment of obesity in the context of the metabolic syndrome and type 2 diabetes

The fact that obesity is the most powerful driving force for the development of T2DM provides the rationale to consider weight management as the most important initial treatment step. Numerous studies have consistently shown that weight loss is not only an effective means to prevent the development of T2DM in those at increased risk, but may also improve the metabolic disturbances and associated risk factors in those with overt T2DM. In addition, weight reduction facilitates reaching the primary treatment goal of a metabolic control close to normal. Interestingly, almost all disturbances mentioned earlier are potentially reversible by weight

loss. This was particularly demonstrated for elevated circulating adipokines. A modest to moderate weight reduction was found to reduce significantly the concentrations of circulating factors such as leptin, C-reactive protein, PAI-1, IL-6, IL-8, MCP-1, and others by 10–50%. By contrast, adiponectin levels are known to rise in relation to weight reduction. In a recent study in surgically treated morbidly obese individuals a significant reduction in macrophage infiltration was documented in adipose tissue samples after a mean weight loss of 22 kg within 3 months [70].

Management of obesity in people with type 2 diabetes

For the reasons outlined, management of obesity should represent a central component in the treatment strategy for T2DM. Although currently available weight reduction programs for people with diabetes have only limited success rates, particularly in the long run, in contrast to common beliefs, recent studies show that obese people with T2DM can achieve clinically significant weight loss. Despite this positive development, treatment of obese individuals with T2DM is usually considered to be more difficult than treating obese people without diabetes for several reasons. People with T2DM are usually older than those without diabetes, which may mean a smaller weight loss as energy expenditure decreases with age. Another reason is that individuals with diabetes focus more on blood glucose control which could result in neglecting other health problems. Finally, the effect of various antidiabetes agents to increase weight or prevent weight loss has to be considered [78]. In the prospective LookAHEAD study, the average weight loss in overweight and obese participants with T2DM in the intensive lifestyle intervention group after 1 year of treatment was 8.6% of the initial body weight and was accompanied by substantial improvements of all weight-associated risk factors despite reductions in the dosage of glucose-lowering agents [79]. However, these effects were not maintained in the following years and were only moderately distinguishable from the control group. After a median follow-up of 9.6 years, the rates of the primary outcome, a composite of death from cardiovascular events, non-fatal myocardial infarction, non-fatal stroke, or hospitalization for angina, did not differ between both groups. Thus, the intensive lifestyle intervention did not reduce the risk of cardiovascular disease in overweight/obese adults with T2DM [80].

Dietary approaches

The cornerstones of a weight reduction program for obese people with diabetes include a moderately hypocaloric diet, an increase in physical activity, and behavior modification, very similar to the recommendations for obese people without diabetes. Numerous studies have applied and examined such concepts and have been critically evaluated in reviews and guidelines [81, 82].

The gold standard in the dietary treatment of obese individuals patients with T2DM is a balanced moderately energy-restricted diet with an energy deficit of at least 500 kcal/day (see Chapter 25). The most important single measure is the reduction in fat intake, particularly in saturated fatty acids. A low-fat, high-carbohydrate diet is generally recommended, but other concepts are equally acceptable. A diet rich in fiber and complex carbohydrates has some beneficial effects on measures of glucose and lipid metabolism but these effects may be small and possibly of limited clinical importance [83]. The concept of a high-carbohydrate, low-fat diet was challenged by clinical studies showing that replacement of saturated fat by monounsaturated fat compared to high-carbohydrate intake is equally favorable or even has advantages with regard to glycemic response and lipids [84]. More importantly, recent studies using a low-carbohydrate, high-protein diet were at least equally effective. In a recent meta-analysis of such studies, HbA_{1c}, fasting glucose and some lipid fractions improved with lower carbohydrate content diets [85]. In a study from Israel, a Mediterranean type of weight loss diet showed small advantages in comparison to the classic low-fat, high-carbohydrate diet in a subgroup of overweight participants with diabetes [86]. Concerning weight loss, a landmark study clearly established that the macronutrient composition of the diet is secondary for weight reduction [87]. A recent systematic review and meta-analysis showed that low-carbohydrate, low glycemic index (GI), Mediterranean, and high-protein diets are effective in improving glycemic control and cardiovascular risk factors in people with T2DM. In comparison to the conventional low-fat diet, these diets produced a slightly greater improvement in glycated hemoglobin and, therefore, should be considered in the overall strategy of diabetes management [88]. From a practical point of view it is extremely important to assess the habitual diet of people with T2DM and to focus counseling on timely changes of their eating habits in order to approach current dietary recommendations [89]. It should be stressed that all efforts for dietary changes should be made as simple as possible as people with diabetes may also be burdened by many requirements to manage their diabetes. For obese individuals with T2DM the frequent recommendation to distribute their allowed calories over 5–6 meals is difficult to meet and may even hinder weight loss without being of any advantage for metabolic control [90]. Therefore, in people without insulin, three meals a day may be more appropriate and advantageous to reach the individual dietary and weight goals.

Another dietary approach is the use of a very-low-calorie diet (VLCD) for initial weight loss. This option may be particularly valuable for those with poor metabolic control or failure of conventional dietary treatments. This mode of dietary restriction is known to be associated with a rapid improvement of insulin resistance and glycemic control after even short periods. To date, the potential benefits and risks of VLCD or (intermittent) fasting concepts in the dietary treatment of obese individuals with T2DM are still poorly studied.

However, there is strong evidence that in addition to the improvement in cardiovascular risk factors the pattern of adipokines and macrophage-associated gene expression changes dramatically under such conditions [91]. Very-low-calorie diets, however, can only be applied for a limited period of time and require intensive medical surveillance. The long-term results of VLCD are moderately better than those of conventional diets, although there is usually considerable weight regain [92, 93].

Therefore, there is need for new sophisticated solutions such as intermittent VLCD in combination with conventional hypocaloric diets to obtain better long-term results. Another possibility is to change the pattern of nutrient intake to modify adipose tissue inflammation. To date, there is little practical information available to indicate whether specific effects of single components in the diet can ameliorate adipose tissue inflammation independent of calorie restriction. In a recent review of dietary components and nutritional strategies for the prevention and treatment of T2DM, the central message was that the quality of dietary carbohydrates and fats consumed is more crucial than the quantity of these macronutrients. The dietary patterns described above were considered to be equivalent and can be tailored to the personal and cultural food preferences including adequate caloric intake for weight management [94].

Antidiabetes drugs and body weight

It has long been recognized that antidiabetes drugs can promote weight gain in people with T2DM (see Chapters 29 and 31). The strongest weight-promoting effect is exerted by insulin. In the Diabetes Control and Complications Trial (DCCT), intensified insulin treatment was associated with substantial weight gain that resulted in unfavorable changes of lipid levels and blood pressure similar to those seen in the insulin resistance syndrome [95]. In the UK Prospective Diabetes Study (UKPDS), insulin treatment caused a mean weight gain of approximately 7 kg over 12 years of treatment in people with newly diagnosed T2DM [96]. In addition, sulfonylureas are known to promote weight gain because of their action to promote insulin secretion. In the UKPDS, the average weight gain under glibenclamide treatment amounted to about 5 kg [96].

Administration of glitazones, PPAR-γ agonists with insulin sensitizing activity, leads to substantial weight gain of 4–5 kg on average. There is growing evidence, however, that weight gain under glitazone treatment occurs mainly in subcutaneous fat, not in the visceral depot, which should have less deleterious metabolic consequences. In contrast, metformin and α-glucosidase inhibitors have a modest weight-lowering potential. The class of DPP-4 inhibitors is rather weight neutral, whereas the administration of GLP-1 receptor agonists, such as exenatide or liraglutide, results in a substantial weight loss [97]. The recently introduced class of SGLT2 inhibitors was found to produce a moderate weight loss of 2–3 kg, due to the urinary loss of glucose [98].

Weight-lowering drugs

Another component in the treatment of obesity is the adjunct administration of weight-lowering drugs. As the efficacy of currently approved drugs is limited, drug treatment is only recommended if the non-pharmacologic treatment program is not sufficiently successful and if the benefit : risk ratio justifies drug administration. At present, only a few compounds are available that have demonstrated efficacy and safety in obese individuals with and without T2DM [99] (Table 16.5). A recently released Clinical Practice Guideline provides information and recommendations for the use of weight-lowering agents, and also on their adverse effects and contraindications [99].

Table 16.5 Weight-lowering drugs approved in the USA and Europe(*)

- Phentermine
- Orlistat(*)
- Lorcaserin
- Phentermine/topiramate
- Naltrexone/bupropion(*)
- Liraglutide(*)

Bariatric surgery

Bariatric surgery is now an established method to reduce body weight in people with extreme obesity (≥40 kg/m^2), but there is growing consensus that this method can also be applied in individuals with T2DM at a BMI ≥ 35 kg/m^2. In this group of people surgery is by far the most effective treatment mode with excellent long-term results compared to all other methods [82]. In the Swedish Obese Subjects study, a large prospective trial comparing bariatric surgery with conventional dietary treatment, sustained weight loss ≥20 kg was achieved in the surgically treated participants with practically no significant weight change in the control group. The surgical intervention not only reduced the incidence of T2DM, but also significantly reduced total mortality [100]. A recent meta-analysis of studies on the effect of bariatric surgery in obese people with T2DM demonstrated that between 70% and 90% had a complete remission of diabetes within the first years after surgery. Weight loss and diabetes resolution was greatest in those undergoing combined restrictive and malabsorptive surgical methods [101]. The majority of insulin-treated patients can stop insulin treatment within a few weeks after surgery and frequently other medications for diabetes and, in addition, for other cardiovascular risk factors can be considerably reduced or discontinued. There are also many studies indicating how rapidly most circulating adipokines are normalized in relation to the degree of weight loss in these individuals.

Conclusions

There is now growing information on how obesity is increasing the risk of developing T2DM. It is apparent that an excess of body fat as well as an unfavorable fat distribution including ectopic fat deposition promotes insulin resistance and impairs insulin secretion. As most people with T2DM are overweight or obese, weight management must be a central component of any treatment strategy, as weight loss has been convincingly shown to provide a marked improvement in metabolic control. In parallel, most if not all underlying disturbances benefit from weight loss or dietary interventions. Conventional concepts combining an energy-reduced diet and an increase in physical activity frequently

have poor long-term results, therefore more effective weight loss strategies should be developed and evaluated.

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17 The Microbiome and Diabetes

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Key points

- The intestinal microbiome is a diverse collection of over 1000 bacterial species that are increasingly recognized as playing critical roles in host functioning and subsequently health and disease.
- Diet has been shown to influence the composition of the intestinal microbiome and associations between the microbial composition and both body mass and type 2 diabetes have been reported.
- The intestinal microbiome can influence intestinal permeability and thereby play a regulatory role in the development of what is referred to as "metabolic endotoxemia."
- Metabolic endotoxemia has the potential to activate innate immune pathways that interface with insulin signaling pathways and can affect glycemic control.
- Microbial metabolites can act locally at the intestinal mucosal to regulate enteroendocrine cell function, incretin signaling and subsequently glycemic control.
- The intestinal microbiome can modulate the composition of the bile acid pool and downstream intracellular signaling pathways, including FXR and TGR5, to influence glycemic control.
- The intestinal microbiota may also contribute to risk for type 1 diabetes; inappropriate immune education by the microbiota may potentiate autoimmune destruction of pancreatic β cells in genetically susceptible individuals.

The microbiome

The human body is inhabited by a diverse and populous array of microorganisms, termed the microbiome, including bacteria, viruses, fungi, and archaea. The genetic material from this collection of microbes, termed the metagenome, is now estimated to be 150 times larger than that of the human genome [1]. The gastrointestinal tract contains the majority of commensal microbes; however, the urogenital tract, skin, and oral cavity provide niche environments for additional species [2]. Microbes colonize the sterile gastrointestinal tract during birth and from this point are implicated in early life programming of the immune and metabolic systems, protection from infection, and the synthesis of vitamins, minerals, and fatty acids, which continue throughout the lifespan of an individual [3]. Given its size and diversity of function, the microbiome has been considered as an organ in its own right.

Bacterial microbes have received the greatest focus within the intestinal microbiome. Over 1000 bacterial species, numbering as high as 10^{14} in the colon and with a total cell count now estimated at 10 times those of human origin, have been reported [4]. Given the dominance of anaerobic species, early attempts to characterize the diversity of the intestinal microbiome were limited by available sample collection methods and culture techniques [5]. More recently, advances in molecular biology techniques, including use of deep- and next-generation sequencing, have facilitated a number of large-scale projects, including the European MetaHIT Project [6] and the National Institutes of Health Human Microbiome Project [7], which have provided additional insights into the diversity of the commensal species. Initially, these projects classified 90% of gut bacteria as belonging to either one of two phyla, namely Bacteroides or Firmicutes. Within these two divisions, three enterotypes were defined based on variation in either *Bacteroidetes* (enterotype 1), *Prevotella* (enterotype 2), or *Ruminococcus* (enterotype 3) that appeared stable across continents [8, 9]. Classification of stable enterotypes is now considered oversimplified, with the abundance of resident species along the gastrointestinal tract alone displaying up to 90% diversity between individuals in similar geographical locations and thought to be shaped by age, hygiene, medication use, and diet [10].

The microbial species resident in the gastrointestinal tract are increasingly recognized as playing critical roles in host functioning and subsequently health and disease [11–13]. The

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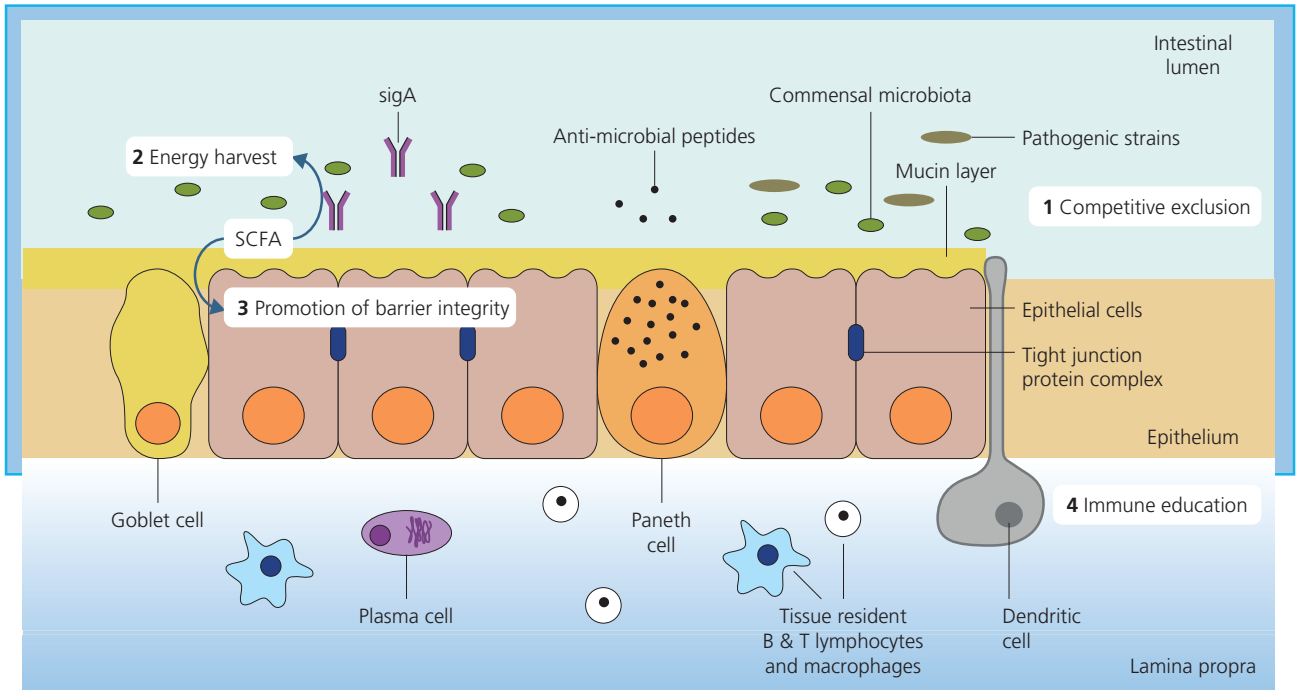

Figure 17.1 A synergistic relationship between the intestinal microbiome and host provides a number of benefits, including (1) competitive exclusion of pathogenic strains, (2) energy harvest, (3) promotion of barrier integrity, and (4) immune education. Source: Modified from Cox et al. 2014 [11]. Copyright 2014 Elsevier.

synergistic relationship between the intestinal microbiota and host provides a number of benefits to host function, including (i) resistance to infection by pathogenic microorganisms through direct competition for nutrients and attachment sites and production of antimicrobial substances; (ii) promotion of epithelial cell proliferation and differentiation to maintain an intact mucosal surface; (iii) promotion of the development of the gut-associated lymphoid tissue via initiation of dendritic cell maturation and B- and T-lymphocyte differentiation; and (iv) energy harvest from non-digestible dietary starches [13–17] (Figure 17.1).

Bacterial fermentation of non-digestible dietary starch occurs predominantly in the colon [18] and produces short-chain fatty acids (SCFAs) (primarily acetate, propionate and butyrate), which have received particular attention as mediating the beneficial effects provided by the intestinal microbiome. Butyrate in particular is recognized as the main energy source for colonic epithelial cells, and is thought to stimulate blood flow and the secretion of gut hormones, enhance fluid and electrolyte uptake, and increase mucin release, all of which contribute to a local tropic effect, epithelial cell proliferation and differentiation, and maintained integrity of the intestinal mucosa [18–20]. The application of -omics technologies has further broadened the knowledge of the roles of the commensal microbial species in health [21], with bacterial communities identified with specific functions in regulating biochemical and metabolic pathways [22, 23].

Greater understanding of the role of the microbiota in metabolic function and immune homeostasis has also led to a growing focus on the role of microbes as a contributing factor for diabetes. The composition of the microbiota is altered in obesity to promote the extraction of energy from food, alter intestinal permeability, and upregulate inflammatory processes in the body. Links between the microbiota and the biochemical processes underpinning the onset and progression of diabetes offer promise that microbial manipulation may be a strategy to reduce the growing burden of associated disease. This chapter explores the way in which the intestinal microbiota contributes to diabetes by promoting the accumulation of adipose tissue and altering metabolic and immune homeostasis.

The intestinal microbiome is associated with body mass

Given the documented relationship between excess body mass and risk for type 2 diabetes mellitus (T2DM), data linking the intestinal microbiome with excess body mass are of interest when considering the role of the microbiome in diabetes pathogenesis. In animal models, lower body mass/body fat in germ-free mice compared with wild-type counterparts [24], even following exposure to a high-fat and sugar-rich Western-style diet [25], suggests that the absence of microbial colonization in the gastrointestinal tract impairs energy harvest. Studies involving transplantation of the intestinal microbiota further implicate the microbiome as a contributor to excess body mass; transplantation of wild-type microbiota to germ-free mice normalizes body weight between groups [24] whereas transplantation of microbiota from obese mice results in an increase in fat mass in germ-free animals [26]. Data such as these suggest a unique microbial composition among

obese animals that favors accumulation of excess body weight, itself a risk factor for T2DM.

In humans, direct comparison of the composition of the intestinal microbiota between overweight and lean individuals has produced mixed findings, likely the result of the small sample sizes examined (groups ranging from two to 70 individuals). A significant decrease in the relative abundance of Bacteroidetes, but an increase in Firmicutes, in obese individuals has been reported [27]. Similarly, reductions in overall bacterial diversity [28, 29] and reductions in the relative abundance of Bacteroidetes, increased relative abundance of Actinobacteria but no significant change in Firmicutes between obese and lean individuals have also been observed [29]. However, others have reported no difference in the dominant phyla [30, 31] and an increased relative abundance of Bacteroidetes in obese compared with lean individuals [32]. Regardless of the discrepant findings, these data suggest that the intestinal microbiota is not static and that the composition of the microbiome can vary within and between populations.

Dietary intervention studies further support the dynamic nature of the intestinal microbiome. Increased caloric content (2400 or 3400 kcal/day at similar macronutrient profiles; 24% protein, 16% fat, and 60% carbohydrates) in otherwise healthy humans for as little as 3 days has been reported to increase the abundance of Firmicutes and decrease the abundance of Bacteroidetes [30]. Even more acute changes have been suggested, with a subsequent study in otherwise healthy adults noting changes in the composition of the intestinal microbiota within 24 h of initiation of a high-fat diet [33]. Changes in the intestinal microbiota in response to weight-reducing diets have also been reported, including reductions in the abundance of some specific Firmicutes species following a 4-week low-carbohydrate weight-reducing diet in obese men [31] and a decreased relative abundance of Bacteroidetes in obese men following a 4-week high-protein, low-carbohydrate diet [34]. It remains to be determined if alterations in the intestinal microbiota that promote energy harvest are a cause or a consequence of Western diets and excess body mass. However, given the functions of the intestinal microbiota beyond energy harvest, additional mechanisms may also contribute to risk for obesity and associated disease.

Composition of the intestinal microbiome is altered in T2DM

To date, few studies have directly compared the intestinal microbial composition between individuals with and without T2DM. However, increased utilization of molecular biology techniques has facilitated this type of analysis. Fecal microbial profiling using 16s RNA characterization has produced conflicting outcomes in terms of overall microbial diversity; some groups reported no difference in overall microbial diversity between people with and without T2DM [35, 36] whereas others suggested a decrease in microbial diversity in those with T2DM [37]. Despite the discrepancies relating to microbial diversity, the majority of studies have reported differences in the relative abundance of specific microbial species between people with and without T2DM [35, 38], including decreased relative abundance of specific Bacteroidetes species, including Bifidobacteria [36] and Bacteroides [37]. An additional study involving microbial characterization of the cecal contents of obese insulin-resistant compared with obese insulin-sensitive individuals reported differing molecular signatures between the groups [39], further supporting a potential relationship between the intestinal microbiota and risk for T2DM.

These early studies were limited by the small sample sizes (groups from eight to 64 individuals) and the degree of species identification possible using pyrosequencing and gel electrophoresis methods. Recently, more extensive metagenome shotgun sequencing has been performed in an ethnic Chinese T2DM case–control cohort ($n = 345$) in a two-stage design [40] and in a cohort of almost 3000 European women classified into T2DM-affected, impaired glucose tolerance, or control groups [41]. Both studies reported differences in the microbial composition between groups, including a decrease in butyrate-producing bacteria in individuals affected with T2DM [40], and support the utility of metagenomic markers to predict disease status. Lastly, a large ($n = 3280$) prospective study quantified the total 16s rDNA concentration present in the circulation at baseline and after 9 years of follow-up and assessed association with T2DM development [42]. Higher baseline concentrations were predictive of T2DM development over follow-up and, although causality was not established, these data suggest that translocation of the intestinal microbiota into the circulation may be an important biological event underpinning the risk for T2DM development.

The intestinal microbiome can influence intestinal permeability

A permeable intestinal mucosa is necessary to facilitate critical absorptive functions, but maintenance of barrier exclusion is essential in isolating the intestinal microbiota within the intestinal lumen. The interaction between various integral membrane proteins and cytoskeletal components provides a structural framework to maintain the integrity of the intestinal mucosa via intercellular tight junctions; however, the intestinal microbiota has been suggested to contribute to the ongoing remodeling of the mucosal surface [13]. *In vitro* experiments demonstrate that exposure of cultured intestinal epithelial cells to both commensal and probiotic microbial species results in upregulation and increased phosphorylation of key tight junction proteins [43, 44]. Likewise, colonization of germ-free mice has been shown to result in the upregulation of key tight junction proteins [45] and normalization of intestinal barrier function in animal models of disease [43, 45]. Further, human clinical studies involving manipulation of the intestinal microbiota via probiotic supplementation reported outcomes that include increased tight junction protein expression in collected duodenal biopsy samples [46], decreased fecal

excretion of the key tight junction protein zonulin [47], and a reduction in intestinal permeability assessed using a dual-sugar absorption test [48], all suggesting preserved integrity of the intestinal mucosa mediated by the intestinal microbiota. Conceivably, altered composition of the intestinal microbiota reported in obesity could impact adversely on intestinal permeability and contribute to translocation of the intestinal microbiota to the circulation and subsequent systemic responses that may contribute to risk for T2DM.

Metabolic endotoxemia

Regardless of the initiating sequence of events, alterations in intestinal permeability have the potential to trigger metabolic endotoxemia (ME). Metabolic endotoxemia is a relatively new concept, coined to describe modest concentrations of circulating bacterial lipopolysaccharide (LPS) in response to non-infectious stimuli [49]. LPS is a cell-wall component of Gram-negative bacterial species and the intestinal microbiota represents a significant reservoir for LPS entry into the circulation. The appearance of LPS in the circulation has been proposed to result from passive diffusion across an intestinal mucosa where tight junction integrity has been compromised and intestinal permeability increased [50], and more recently active transport pathways have also been implicated in metabolic endotoxemia. LPS has been found to be incorporated in chylomicron fractions [51, 52], suggesting that active absorption across the intestinal mucosa as part of normal digestion and absorption may also account for the appearance of LPS in the circulation.

Indeed, diet has been one factor shown to influence LPS translocation across the intestinal mucosa. A dose-dependent relationship between dietary fat content (40–70% total caloric content over 4 weeks) and plasma endotoxin levels has been reported in several murine feeding studies [49, 53]. The same murine model has also shown that antibiotic treatment, resulting in a decreased intestinal microbial load, attenuates the increase in plasma LPS concentrations following the 4-week high-fat feeding [54] and provides further confirmation that the intestinal microbiota is a critical component of metabolic endotoxemia. Likewise, attenuation of the increase in plasma LPS concentrations following a 14-week high-fat (70%) diet has also been reported in a mouse model where the diet was supplemented with a fermentable dietary fiber [55], thought to preserve the integrity of the intestinal mucosa, further implicating intestinal permeability as a determinant of metabolic endotoxemia.

An association between dietary composition and metabolic endotoxemia has also been reported in human studies. Acute increases in plasma LPS have been reported within 1 h [51, 56] to 3 h [57] following consumption of a high-fat meal by otherwise healthy volunteers, with elevations persisting for up to 5 h postprandially [58]. Further, dietary fat content was significantly correlated with plasma LPS concentrations in an epidemiological study of 201 healthy middle-aged men [53], and a small feeding study demonstrated that, even among healthy volunteers ($n = 8$), a month-long Western-style (40% fat) diet was associated with significant (~70%) increases in plasma LPS [59]. These data support the potential for dietary habits associated with risk for obesity and obesity-associated disease to trigger translocation of the intestinal microbial contents to the circulation as well.

Metabolic endotoxemia in T2DM

Whereas the relationships between obesity, diet, and metabolic endotoxemia have received particular attention, few studies have assessed these relationships in individuals with overt T2DM. That said, epidemiological data do implicate circulating endotoxin in the risk for T2DM. Higher plasma LPS concentrations have been reported in a sample of middle-aged individuals affected with T2DM ($n = 25$) compared with a matched control group [60] and in a cohort of treated individuals with T2DM ($n = 346$) [61]. More recently, a larger analysis involving the FINRISK97 cohort ($n \approx 6600$ Finnish adults) found that circulating endotoxin concentrations at baseline were significantly higher in the individuals with T2DM and were predictive of those who developed overt T2DM over the 10-year follow-up period [62]. Given these relationships, understanding the physiological responses to circulating endotoxin may provide further insight into the pathogenesis of T2DM.

Although the impact of sepsis on glucose control and metabolism has been established [63, 64], ethical and logistic challenges mean that few studies have directly manipulated plasma LPS and/or the intestinal microbiota as a way to establish causality for T2DM. However, LPS infusion in a mouse model has been shown to induce changes in insulin sensitivity and glucose control, supporting a causal role for metabolic endotoxemia in T2DM development [49]. Chronic low-dose subcutaneous LPS infusion (300 mg/kg/day) over 4 weeks was shown to elicit increases in fasting glucose and insulin, impaired glucose clearance in response to an oral glucose load, and increased hepatic gluconeogenesis, all suggesting the loss of glycemic control [49]. In healthy humans, the acute effects of intravenous LPS infusion (20 U/kg, ~2 ng/kg total dose) have been assessed during a 10-h euglycemic hyperinsulinemic clamp protocol and significant reductions in glucose utilization were noted [65]. In a subsequent human study, low-dose LPS infusion (3 ng/kg total dose) over a 60-h endotoxemia protocol also resulted in decreased insulin sensitivity (measured as insulin sensitivity index, S_i) and increased insulin resistance (measured as HOMA-IR) at 24 h following LPS infusion [66], further implicating LPS as a causal factor in the development of insulin resistance.

Modulation of the intestinal microbiome is associated with improvements in insulin sensitivity

Beyond these seminal studies implicating bacterial LPS as an initiating factor in impaired glucose control, direct modulation of

the intestinal microbiota has also been show to affect indices of glucose homeostasis. Use of a broad-spectrum antibiotic treatment over 4 weeks in high-fat fed and genetically modified phenotypically obese mice (*ob*/*ob*) has been shown to modulate the intestinal microbial contents, reduce the level of endotoxemia, and elicit reductions in both glucose-induced insulin secretion and insulin resistance index [54]. Subsequent animal models also reported modulation of the intestinal microbial content, reduced endotoxemia, reduced fasting glucose and insulin, and improvements in glucose and insulin tolerance in high-fat fed animals receiving antibiotics [67]. Further, probiotic supplements have also been shown to affect both the intestinal microbial content and indices of glucose control. Single-strain probiotic supplements administered over 14 weeks of high-fructose feeding and over 8 weeks in a diabetic rat model were associated with lower fasting glucose and insulin and improved glucose clearance following a glucose tolerance test [68] and lower fasting insulin and HOMA-IR [69], respectively. Similarly, in high-fat fed mice, improved glucose clearance following glucose tolerance tests was noted following single-strain probiotic supplementation over 5 [70] and 10 weeks [71]. Collectively, these data support the potential for modulation of the intestinal microbiota to mediate improvements in insulin sensitivity.

Although findings from antibiotic studies have yet to be widely replicated in humans in the context of glycemic control, the effects of probiotic supplementation and intestinal microbial transplant have been assessed. Two trials from the same laboratory reported reductions in fasting glucose, fasting insulin, and HOMA-IR in a cohort of overweight adults [72] and reductions in fasting insulin and HOMA-IR in otherwise healthy young adults [73] following 6 weeks of probiotic supplementation. Similarly, 4 weeks of probiotic supplementation was associated with improved insulin sensitivity, assessed via a hyperinsulinemic–euglycemic clamp, in a cohort of overweight adults ($n = 45$) with ranging glucose tolerance [74]. However, not all probiotic trials have been able to demonstrate definitive benefits on glycemic control [75, 76]. Further, in the lone fecal transplant study, men with metabolic syndrome received either an autologous gut microbiota duodenal infusion ($n = 9$) or an allogenic gut microbiota duodenal infusion from healthy lean donors ($n = 9$) with a hyperinsulinemic–euglycemic clamp performed before and 6 weeks following infusion [77]. Gut microbial diversity was significantly increased and improvements in peripheral insulin sensitivity and a trend towards reduced endogenous glucose production were noted 6 weeks following the allogenic infusion only. Although these data further implicate the intestinal microbiota in mediating insulin resistance, they fail to provide insights into the signaling pathways mediating these effects.

The microbiome contributes to T2DM risk via innate immune pathways

As a key component of Gram-negative pathogenic strains, LPS is recognized by pattern recognition receptors that play a critical role in the activation of immune and inflammatory pathways. Immune responses to circulating LPS are well characterized in models of infection and sepsis, but activation of similar signaling pathways would also be anticipated in metabolic endotoxemia and understanding these pathways provides insights into how the intestinal microbiota contribute to risk for T2DM. Regardless of the trigger for LPS translocation, once in the circulation LPS binds to LPS-binding protein (LBP), a constitutively expressed plasma protein, which facilitates the interaction between LPS and various receptors and binding sites. Among these receptors are the toll-like receptor 4 (TLR4) cell surface molecule and its associated co-receptor, cluster of differentiation 14 (CD14). TLR4 activation initiates an extensive intracellular signaling cascade that initially involves recruitment of the MyD88 adaptor protein and activation of IL-1R1-associated protein kinases (IRAKs) [78], which can trigger (i) subsequent phosphorylation of IkB kinase (IKK-B), the degradation of IkB and NF-kB translocation to the nucleus to facilitate transcriptional regulation of inflammatory mediators, including interleukin (IL)-1, tumor necrosis factor (TNF)-α, and IL-6 [79], and (ii) c-Jun N-terminal kinase (JNK) activation [80]. Interestingly, saturated fatty acids also act as ligands for TLR4 [78] and provide an additional stimulus for initiating these same signaling pathways in obesity.

The cross-talk between TLR4 and insulin signaling pathways provide a mechanism linking the intestinal microbiota to insulin resistance (Figure 17.2). Classic insulin signaling pathways involve a complex series of phosphorylation events initiated by the interaction between insulin and its cell surface receptor. Receptor–ligand binding triggers the autophosphorylation of the intracellular domain of the insulin receptor and subsequent phosphorylation (predominately at tyrosine residues) of the intracellular insulin receptor substrate (IRS) family members with additional kinase activity, including Akt involvement, culminating in the exocytosis of glucose transporters to the cell surface to facilitate glucose uptake [81]. Insulin signaling can be regulated by a negative feedback loop where phosphorylation of IRS members (predominately at serine/threonine residues) inhibits further signal transduction, essentially impeding further cellular glucose uptake [82, 83]. Insulin signaling pathways also contribute to the regulation of glycogen synthesis (via glycogen synthase activation [81]) and regulation of metabolic pathways (via transcription factor regulation [82]) and in this way contribute to glycemic control more globally beyond cellular glucose uptake.

Signaling cascades initiated by LPS–TLR4 binding have the potential to regulate the insulin signaling pathways at multiple points. Notably, JNK activation downstream of TLR4 activation can trigger phosphorylation of IRS members at serine/threonine residues, inhibiting further insulin signaling [84, 85]. Additional triggers have been identified for JNK activation and subsequent disruption of insulin signaling, notably ER stress [86, 87]; although these pathways are also relevant in understanding the pathogenesis of T2DM, particularly in the context of obesity and nutrient excess, there is little evidence suggesting direct modulation by the intestinal microbiota. However, inflammatory

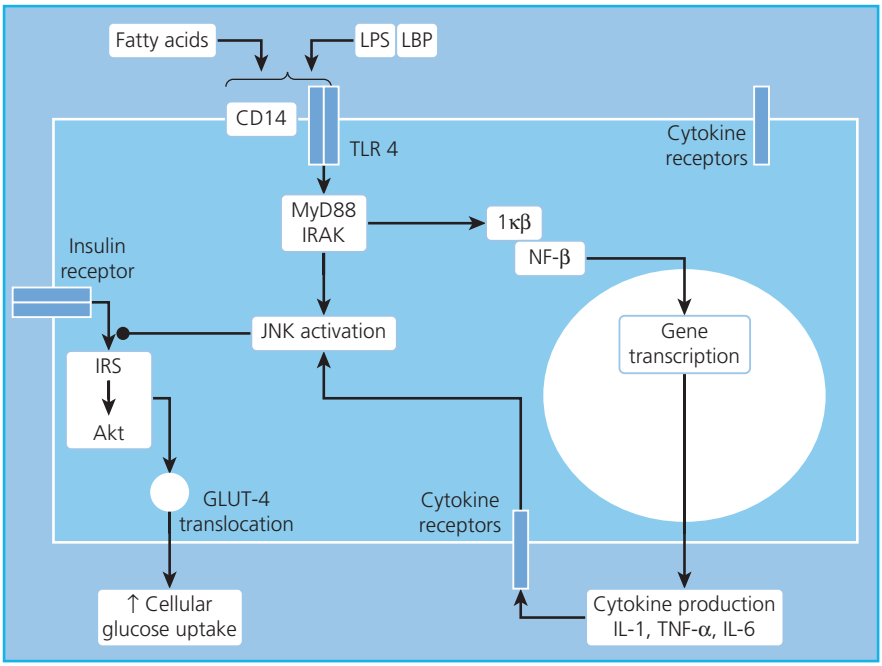

Figure 17.2 Components of the intestinal microbiota (namely lipopolysaccharide, LPS) have the potential to activate innate immune pathways. Cross-talk between TLR4 and insulin signaling pathways provide a mechanism linking the intestinal microbiota to insulin resistance.

cytokines secreted in response to TLR4 signaling and as part of the unfolded protein response can signal back to cells in an autocrine or paracrine fashion and, via their own cell surface receptors, trigger further activation of the JNK pathway, contributing to a cycle of persistent amelioration of insulin signaling [88, 89].

Indeed, studies involving animal knockout models, loss of function mutations, and receptor antagonists provide support for the involvement of the TLR4 and JNK pathways in linking the microbiome and insulin resistance. Animal models involving TLR4 mutants or knockouts [90, 91] and a human clinical trial involving infusion of an anti-CD14 antibody [92, 93] all demonstrate attenuated inflammatory responses to LPS exposure, confirming the role of TLR4/CD14 signaling in mediating the inflammatory response to LPS exposure. Similarly, the murine model mentioned earlier whereby LPS infusion was sufficient to trigger changes in insulin sensitivity and glucose control also demonstrated that this series of responses was attenuated in CD14-deficient mice [49]. These findings are consistent with those from a murine model with a TLR4 loss of function mutation and utilizing a high-fat feeding protocol; the downregulated TLR4/CD14 signaling pathway was protective for metabolic dysregulation and was associated with attenuated IKKB and JNK signaling [94]. Similarly, JNK knockout mice have been shown to be protected from insulin resistance triggered by high-fat feeding [95] and, in an obese diabetic mouse model administered a JNK inhibitory peptide, lower fasting glucose and insulin concentrations and improved glucose control and insulin sensitivity in response to glucose and insulin tolerance tests have been reported [96]. Although these findings are from animal studies only, collectively these data highlight key signaling pathways that link the intestinal microbiome and risk for T2DM.

The microbiome contributes to T2DM risk via modulation of enteroendocrine cell function

Beyond the purported roles of bacterial fermentation products in promoting colonocyte health [20], identification of the signaling pathways via which SCFAs may contribute to metabolic regulation further implicate the intestinal microbiome in the pathogenesis of T2DM. SCFAs have been identified as ligands for a series of G protein-coupled receptors (GPRs) expressed on the intestinal epithelium and also by adipose tissue and immune cells [97]. SCFAs differentially activate various GPRs; propionate shows the highest affinity for GPR41 (also known as free fatty acid receptor 3) and GPR43 (also known as free fatty acid receptor 2), acetate for GPR43, and butyrate for GPR41 and GPR109A [98]. Activated downstream signaling pathways include those implicated in enteroendocrine cell function [99, 100], as discussed below (Figure 17.3), and also the regulation of immunity and inflammation [101], which has the potential to influence insulin signaling pathways.

Potential regulation of enteroendocrine function, particularly glucagon-like peptide (GLP) and polypeptide YY (PYY) secretion, may be especially relevant when considering the role of the intestinal microbiome in T2DM pathogenesis. GLP-1 and PYY are co-secreted from enteroendocrine cells resident in the colonic mucosa in response to nutrient sensing [102, 103]. Some effects of GLP-1 and PYY are similar, including attenuation of gastrointestinal motility and gastric acid secretion [103–105] and induction of satiety, likely via centrally mediated mechanisms [102, 106]. However, GLP-1 and PYY have opposing effects on insulin secretion. GLP-1 acts to increase glucose-stimulated insulin secretion

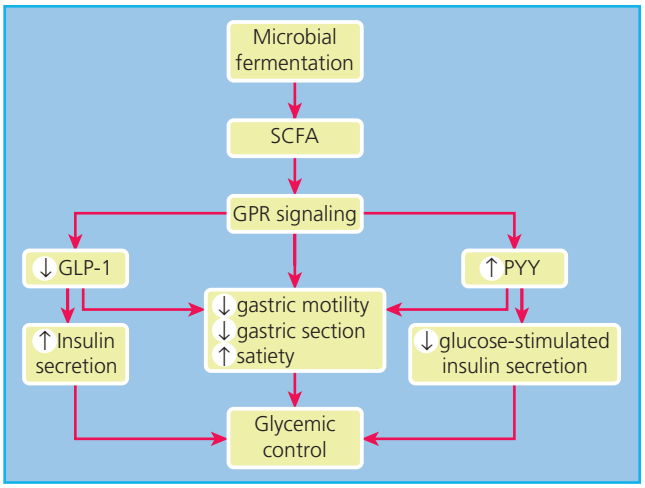

Figure 17.3 Short-chain fatty acids (SCFAs) are produced during microbial fermentation of non-digestible dietary starches. SCFA signaling via G protein-coupled receptors (GPRs) can regulate incretin signaling, namely glucagon-like peptide 1 (GLP-1) and polypeptide YY (PYY), with downstream effects on glycemic control.

by binding to GLP receptors on pancreatic β cells and triggering an intracellular signaling cascade that results in the exocytosis of insulin-containing granules [104, 106]. In contrast, PYY has been shown to inhibit glucose-stimulated insulin release from the pancreas, although the signaling mechanisms underpinning this effect are less well defined [107, 108]. Both GLP-1 and PPY undergo enzymatic cleavage by dipeptidyl peptidase (DPP)-4; for GLP-1 this plays a role in clearance of the active form [109], but for PYY it generates the biologically active form [108]. Given the documented effects of GLP-1 and PPY in the context of glucose control, it is not surprising that both GLP agonists and DPP-4 inhibitors have been developed as T2DM treatments [110].

The potential for the intestinal microbiome, via SCFAs, to modulate GLP-1 and PYY secretion [111] represents a further pathway via which the intestinal microbiome may contribute to insulin resistance and T2DM risk. *In vitro* and animal models and human supplementation studies support this possibility. In primary colonic cultures from wild-type mice, treatment with SCFAs induced GLP-1 secretion, an effect that was attenuated in tissue from GPR41 and GPR43 knock-out mice [100]. Similarly, more pronounced impairments in plasma GLP-1 in response to oral glucose load were noted in the knockout animals [100], further supporting SCFA-induced signaling via GPR41/43 as a key trigger for incretin secretion. A similar study in a rodent model assessing both GLP-1 and PYY responses to SCFAs reported similar outcomes for both primary colonic cultures and systemic responses [112]. Several small-scale human intervention trials in otherwise healthy adults have demonstrated that supplementation with a fermentable prebiotic fiber for 2–12 weeks can result in higher breath-hydrogen excretion (as a surrogate for colonic fermentation) [113] and higher glucose-induced plasma concentrations of PYY [114] and GLP-1 [113, 115]. In a subsequent trial involving hyperinsulinemic adults ($n = 40$), 12 months' supplementation with dietary high-fiber cereal (a form of non-digestible starch and a substrate for the intestinal microbiota) resulted in significant increases in plasma acetate, propionate, and butyrate concentrations, and increases in both basal and postprandial GLP-1 concentrations [116], further supporting an association between SCFAs and GLP-1 and PYY, and highlighting the potential for modulation of the intestinal microbiota to mitigate disrupted incretin signaling in metabolic disease.

The microbiome contributes to T2DM risk via modulation of bile acids

The role of bile acids in lipid digestion and absorption is well established, with bile acid turnover providing a pathway for cholesterol excretion [117]. Beyond these actions, regulatory roles of bile acids in glucose metabolism have also been acknowledged. Bile acid composition has been associated with features of insulin resistance in European adults [118] and altered bile acid composition has also been noted in adults with diabetes [119, 120]. Further, over recent years, clinical trials have demonstrated the effects of bile acid sequestrants on glycemic control. Among these observations are significant reductions in fasting blood glucose in a group of middle-aged men with metabolic syndrome ($n = 20$) after 8 weeks in a placebo-controlled crossover trial [121]; significant reductions in fasting blood glucose and postprandial blood glucose in middle-aged individuals affected with T2DM ($n = 38$) after 12 weeks in a placebo-controlled trial [122]; and significant reductions in glycated hemoglobin, glycated albumin, and postprandial blood glucose in middle-aged individuals affected with T2DM ($n = 59$) after 12 weeks in a placebo-controlled trial [123]. Collectively, these findings all support an association between regulation of the bile acid pool and glucose control.

Although the exact mechanisms linking the bile acid pool and glucose control are yet to be fully defined, two pathways have received particular attention (Figure 17.4). Bile acids are known ligands for the nuclear receptor farnesoid X receptor (FXR), which activates the transcription factor short heterodimer protein (SHP) [124] and regulates the expression of a number of genes involved in bile acid synthesis and metabolism, thereby establishing a feedback loop facilitating bile acid self-regulation [117, 125, 126]. Feedback inhibition of bile acid synthesis has also been reported to involve FXR-independent activation of the JNK signaling pathways [127–129], which, as mentioned above, can inhibit insulin signaling. Beyond this, FXR-mediated signaling has been associated with glucose homeostasis [117]. FXR receptor knockout mice have been shown to have impaired plasma glucose clearance in response to both glucose and insulin tolerance tests [130, 131]. Conversely, administration of FXR agonists in a diabetic mouse model was shown to decrease fasting glucose and insulin [132], suggesting preserved insulin sensitivity. In both settings, intracellular signaling pathways were also examined and either decreased (in the FXR knockouts) or increased (in response to FXR agonist)

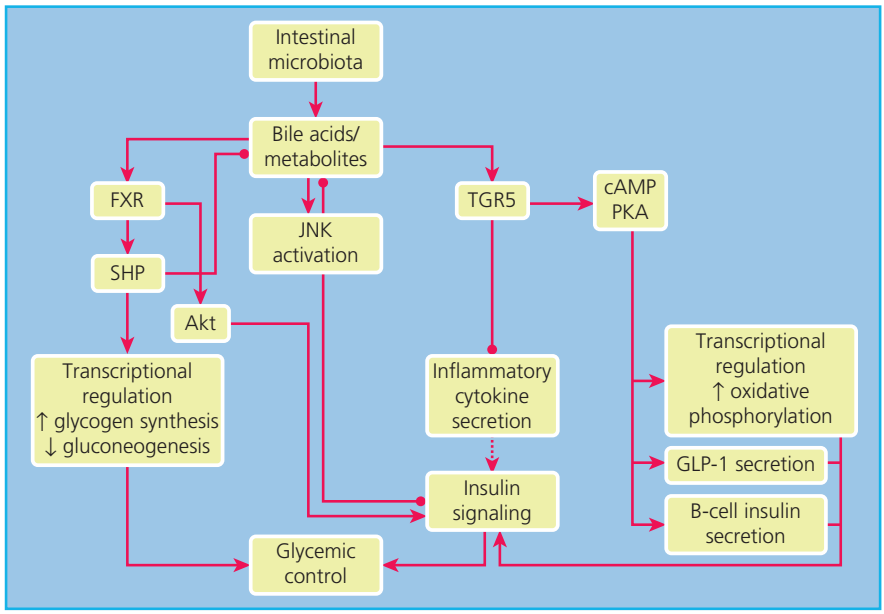

Figure 17.4 The intestinal microbiome influences the composition of the bile acid pool and metabolites. Bile acid signaling through the farnesoid X receptor (FXR) and the G protein-coupled receptor TRG5 pathways can effect transcriptional regulation of various metabolic pathways. Regulation of other signaling pathways can also contribute to alterations in glycemic control.

Akt phosphorylation was reported [130, 132], suggesting that FXR signaling may contribute directly to regulation of insulin signaling pathways. Other studies have implicated FXR in the downregulation of genes involved in hepatic gluconeogenesis [131, 133], and also in glucose-induced insulin secretion from pancreatic β cells [134, 135], providing further mechanisms via which bile acids may contribute to insulin resistance.

In addition to signaling via FXR, bile acids have also been identified as a ligand for the G protein-coupled receptor TGR5 [136, 137]. Activated intracellular signaling pathways are thought to involve protein kinase A and the cyclic AMP response element binding protein, which can regulate gene expression and allows for a range of downstream effects [125]. In the context of insulin resistance, i*n vitro* models have shown that bile acid signaling is able to induce GLP-1 secretion from enteroendocrine and primary intestinal cell cultures, with small interfering RNAs and TGR5 agonists confirming that these responses are mediated via TGR5 [138, 139] activation. Animal models also support a role for TGR5 signaling in mediating glucose homeostasis [140]. Use of selective TGR5 agonists in high-fat fed mice have been shown to decrease plasma glucose and insulin and improve glucose clearance rates in glucose tolerance tests [141, 142]. Further, TGR5 overexpression in a transgenic mouse model resulted in improved glucose clearance rates in a glucose tolerance test and augmented postprandial GLP-1 and insulin secretion, whereas glucose tolerance and GLP-1 secretion were impaired in TGR5 knockout animals [142]. In some human clinical studies involving bile acid sequestrants, GLP-1 responses have been shown to parallel changes in insulin sensitivity [143], further supporting GLP-1 as a link between bile acid signaling and risk for diabetes. Finally, evidence suggesting that TGR5 activation by bile acids may have inhibitory effects on inflammatory cytokine production [137, 144] provides a further mechanism via which bile acid signaling may indirectly contribute to the regulation of insulin signaling pathways.

Given the potential for bile acids to contribute to the regulation of glucose control, modulation of the bile acid pool by the intestinal microbiota provides another interface between the microbiota and risk for diabetes. Although enterohepatic circulation recovers a large proportion of secreted bile acids from the distal ileum, a proportion reach the large bowel where the microbiota catalyze a series of reactions, including deconjugation, dehydrogenation, and dehydroxylation reactions, resulting in the formation of secondary bile acids [145, 146]. Secondary bile acids may themselves contribute to the feedback inhibition of bile acid synthesis and secretion, and other downstream effects via the FXR and TGR5 signaling pathways [147, 148]. Animal models support the involvement of the intestinal microbiota in modulation of the bile acid pool. The composition of the bile acid pool has been shown to differ between germ-free and conventional animals in both rodent [149] and murine models [150]. Further, in several murine experiments, antibiotic treatment has been shown to modulate the composition of the bile acid pool in favor of primary bile acids and upregulation of FXR signaling pathways [151–153], whereas probiotic supplementation appears to favor the production of secondary bile acids and attenuation of FXR signaling [154]. Modulation of the intestinal microbiota in humans has also been show to influence the composition of the bile acid pool. In a study trialing fecal transplantation for recurrent *Clostridium difficile* infection, the composition of the fecal bile acid pool was significantly different following transplantation and tended to favor secondary bile acids [155]. Also of particular interest is a 7-day antibiotic intervention in obese men ($n = 20$) where a reduction in fecal secondary bile acids was noted and alterations in bile

acid composition were correlated with alterations in peripheral insulin sensitivity pre- to post-intervention [156]. Although the bile acid signaling pathways are complex and involve multiple intracellular pathways, effects on glycemic control are plausible and, given the established roles of the intestinal microbiota in regulating the composition of the bile acid pool, further implicate the intestinal microbiota in risk for T2DM.

Type 1 diabetes

It would be remiss to ignore a potential role of the intestinal microbiota in the pathogenesis of type 1 diabetes mellitus (T1DM). Although the precise mechanisms and molecular signaling pathways remain under investigation, support for the interplay between the intestinal microbiota, intestinal permeability, and immune aberrations in initiating the autoimmune destruction of pancreatic β cells continues to grow [157]. Although epidemiological studies are of limited value given the low prevalence of T1DM, reports confirm differences in the composition of the intestinal microbiota between individuals with and without T1DM [158, 159], including decreases in butyrate-producing strains [160, 161], suggesting, at the minimum, an association between the intestinal microbiota and T1DM risk. Studies involving germ-free animal models that report increased T1DM incidence [162] support the importance of a robust intestinal microbiome in mitigating T1DM risk. Similarly, animal models demonstrating that modulation of the intestinal microbiota, using either antibiotics [163] or probiotic supplementation [164], results in delayed onset and reduced incidence of diabetes provide further evidence in support of a potential link between gut microbiome and T1DM risk. Alterations in intestinal permeability have also been noted in both animal models of T1DM [165, 166] and human clinical studies [167–169] and provide insight into the mechanisms that may link the intestinal microbiome and T1DM risk. Given the identified roles of butyrate-producing bacterial strains in promoting the integrity of the intestinal mucosa [43, 45], alterations in the microbial composition may underpin diminished mucosal integrity in T1DM. Increased intestinal permeability and associated translocation of LPS and other antigens across the mucosal surface may trigger aberrations in immune regulation and the development of autoimmune responses in genetically susceptible individuals. Indeed, a role for the activation of innate immune mechanisms in T1DM has been demonstrated in a murine model whereby knockout of the MyD88 intracellular signaling intermediary, activated downstream of TLR receptor–ligand binding, conferred protection against development of T1DM [162].

The role of the microbiota in shaping host immune development also cannot be overlooked in the context of T1DM risk. The increased prevalence of T1DM in developed nations has been interpreted by some to support the hygiene hypothesis, whereby inappropriate immune development in response to limited microbial exposure is considered a risk factor for the development of autoimmunity [170–172]. Immunological aberrations reported previously in T1DM include reduction in FoxP3$^+$ regulatory T cells (Tregs) in the intestinal mucosa of individuals with T1DM [173], reduction in peripheral Tregs [174] and Nk T cells [174, 175], and dysregulated cytokine signaling, suggestive of impaired T-cell function [176, 177]. More recently, Th17 responses have received particular attention for their roles in inflammatory control and autoimmune disease [178–180], and an upregulation of peripheral Th17 cells has been reported in individuals with T1DM [181]. Of further interest are the growing number of reports suggesting a critical role for the intestinal microbiota in regulating Th17 and Treg phenotypes [182–185]; although the precise mechanisms underpinning these effects are yet to be elucidated, these associations do further implicate the intestinal microbiome, via modulation of the immune system, in the risk for T1DM.

Conclusions and perspectives

Given the considerable size of the metagenome and associated metabolic machinery, it is not surprising that the interface between intestinal microbiome and human host has the potential to affect health, including risk for disease. In the context of T1DM, inappropriate immune education by the microbiome may potentiate autoimmune destruction of pancreatic β cells in otherwise susceptible individuals. The potential for cross-talk between the microbiome and immunological and metabolic pathways is also relevant in T2DM; activation of innate immune pathways, modulation of enteroendocrine cell function, and regulation of metabolic signaling pathways by the microbiome all have the potential to disrupt insulin signaling pathways and contribute to loss of glycemic control. Given the increasing prevalence of both T1DM and T2DM, particularly in the developed world, understanding the molecular mechanisms by which the microbiome contributes to risk for diabetes may prove beneficial in the development of additional risk stratification tools. Further, the potential to manipulate the composition of microbiome may enhance existing treatment and management strategies.

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4 Other Types of Diabetes

18 Monogenic Causes of Diabetes

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Key points

- Monogenic diabetes should be suspected where:
  - presentation is atypical for type 1 or 2 diabetes;
  - there is an autosomal dominant (or maternally inherited in mitochondrial disorders) family history;
  - there are characteristic associated features such as deafness in mitochondrial diabetes or fat loss in lipodystrophy or;
  - diabetes has been diagnosed within the first 6 months of life.
- Mutations in the glucokinase gene, which is important in "sensing" blood glucose levels in the pancreas, result in resetting of fasting glucose to a higher level (5.5–8.0 mmol/L). People with glucokinase mutations have dominantly inherited mild fasting hyperglycemia with only modest changes in glycated hemoglobin. Complications are rare and no treatment is needed.
- Mutations in the transcription factor genes *HNF1A* and *HNF4A* result in dominantly inherited progressive hyperglycemia with symptomatic diabetes in adolescence or young adulthood. People with *HNF1A* or *HNF4A* diabetes are very sensitive to sulfonylurea treatment and may not require insulin until middle or old age.
- Mitochondrial mutations can result in maternally inherited diabetes often with sensorineural hearing loss and a range of other disorders.
- Diabetes diagnosed before 6 months is unlikely to be type 1 diabetes and a genetic cause should be sought even where the patient is now an adult. High-dose sulfonylurea treatment is often more effective than insulin where mutations affecting Kir6.2 and SUR1 subunits of the β-cell potassium channel are identified.
- Acanthosis nigricans is the key feature of insulin resistance and a genetic cause should be considered where there is no concomitant obesity. Partial lipodystrophy results in thin muscular limbs with hypertriglyceridemia and insulin resistance and suggests a mutation in *LMNA* or *PPARG*. In the absence of lipodystrophy an insulin receptor mutation is the commonest cause.

Introduction

Monogenic diabetes results from inheritance of one or more mutations in a single gene and accounts for 1–3% of diabetes cases diagnosed under the age of 30 years. Mutations may be inherited in a dominant or recessive fashion. The majority (90%) of monogenic diabetes cases are initially misdiagnosed as type 1 (T1DM) or type 2 diabetes (T2DM).

Correct genetic diagnosis is important to predict clinical course, explain other associated clinical features, enable genetic counseling, diagnose family members, and most importantly guide appropriate treatment.

Monogenic diabetes where the primary disorder affects the β cell has four main clinical presentations: (1) familial mild fasting hyperglycemia (glucokinase maturity-onset diabetes of the young [MODY]), (2) familial young-onset diabetes (transcription factor MODY), (3) neonatal diabetes, and (4) diabetes with extrapancreatic features. Clinical and biochemical features that help differentiate the common forms of monogenic diabetes that result in β-cell dysfunction from T1DM and T2DM are summarized in Table 18.1. Classification and key features of monogenic diabetes are further summarized in Figure 18.1 and their role in β-cell physiology is depicted in Figure 18.2. Single-gene mutations may also cause diabetes through insulin resistance as occurs in the inherited lipodystrophies and insulin receptor mutations. A number of monogenic multisystem diseases (e.g. hemochromatosis and cystic fibrosis) may cause diabetes; these are beyond the scope of this chapter and are discussed elsewhere (see Chapter 21).

Maturity-onset diabetes of the young

Maturity-onset diabetes of the young (MODY) is autosomal dominantly inherited diabetes that, despite a young age of onset, is not insulin-dependent [1, 2]. It results from β-cell dysfunction rather than insulin resistance [1]. The underlying genetic etiology has now been defined allowing MODY to be subclassified according to the gene involved [3, 4]. Mutations in at least nine genes

Textbook of Diabetes, Fifth Edition. Edited by R. Holt, C. Cockram, A. Flyvbjerg and B. Goldstein.

Table 18.1 Differentiating β-cell monogenic diabetes from type 1 and 2 diabetes. DM, diabetes; GCK, glucokinase; *HNF1A*, hepatocyte nuclear factor 1A (*HNF4A* is similar); MIDD, maternally inherited diabetes and deafness; PNDM, permanent neonatal diabetes; Pop freq, population frequency (frequency of obesity seen in the general population).

Features	Type 1 diabetes	Young type 2	*GCK* MODY	*HNF1A* MODY	MIDD	K_{ATP} PNDM
Insulin dependent	Yes	No	No	No	+/–	Yes
Parent affected	2–4%	Usually	Yes	Yes	Mother	15%
Typical age of onset	6 months – young adult	Adolescent and young adult	Birth (may be diagnosed at any age)	Teens – young adult	Young adult	Under 6 months
Obesity	Pop freq	Yes	Pop freq	Pop freq	Rare	Pop freq
Acanthosis nigricans	No	Yes	No	No	No	No
Glycemia	High	Variable	Mild	High	Variable	High
β-cell autoantibodies	Usually	No	No	No	No	No

have been linked to MODY [5, 6]. These include mutations in the gene encoding the glucose-sensing enzyme glucokinase (*GCK*) and mutations in several transcription factors that affect β-cell development and function, the frequencies of which are summarized in Figure 18.3. Clinical presentation varies greatly depending on the underlying genetic mutation. Table 18.2 summarizes the clinical features of glucokinase and transcription factor diabetes. The strikingly different subtypes of MODY mean it is important to define the underlying genetic etiology. We recommend the use of clinical categories based on underlying genetic cause, e.g. familial mild fasting hyperglycemia resulting from glucokinase gene mutations (*GCK* MODY), familial young-onset progressive diabetes resulting from *HNF1A* and *HNF4A* mutations (transcription factor MODY), and renal cysts and diabetes syndrome (RCAD) resulting from *HNF1B* mutations.

Mutations in the genes associated with MODY should be considered in people with diabetes diagnosed under 25 years of age, who do not fully fit the phenotypes of T1DM or T2DM and who have a strong family history of diabetes (Table 18.1). Differentiating from apparent T1DM is particularly important as these individuals can often be most effectively treated without the use of injected insulin. The differentiation of MODY from other types of diabetes is challenging and attention has turned to strategies that will enable better stratification of those requiring genetic testing,

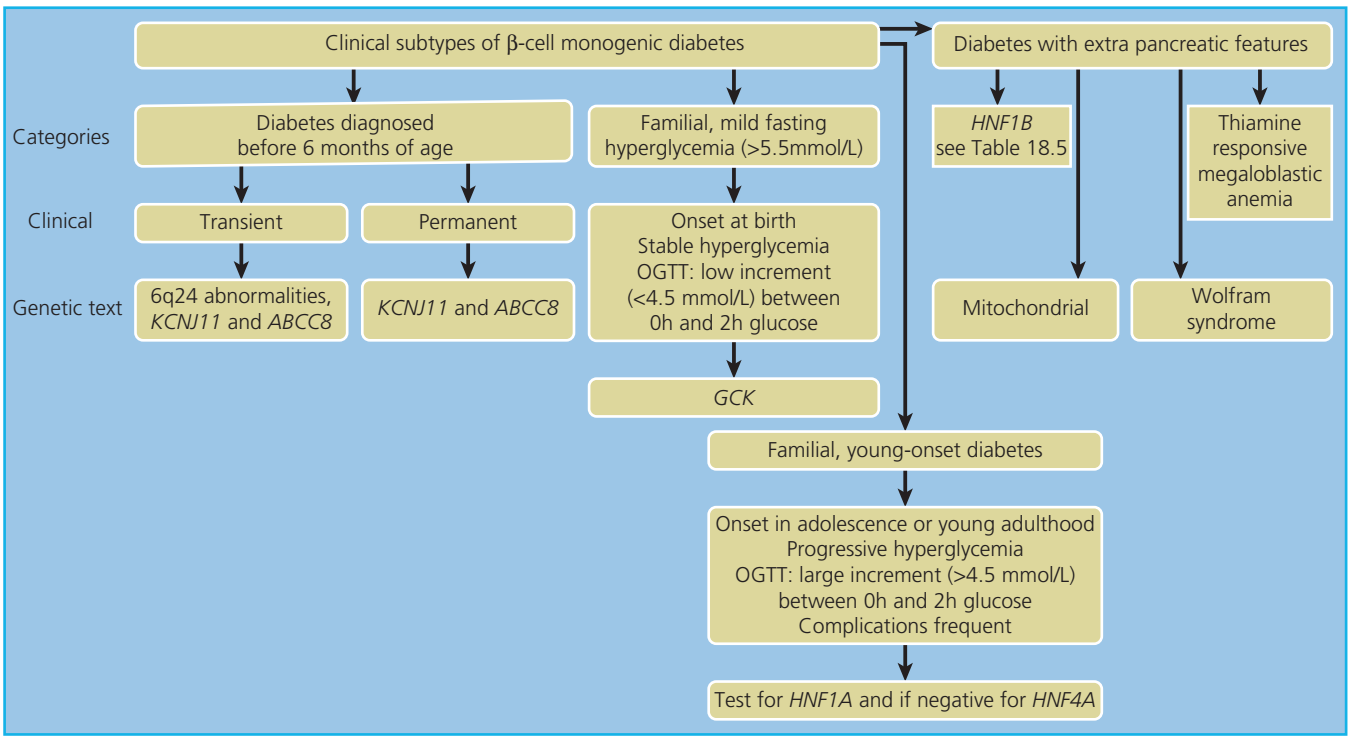

Figure 18.1 Clinical subtypes of monogenic β-cell diabetes. To convert plasma glucose measurements to mg/dL multiply by 18. ABCC8, ATP binding cassette subfamily C; *GCK*, glucokinase gene; HNF, hepatocyte nuclear factor; *KCNJ11*, potassium inwardly rectifying channel, subfamily J, member 11 gene; OGTT, oral glucose tolerance test.

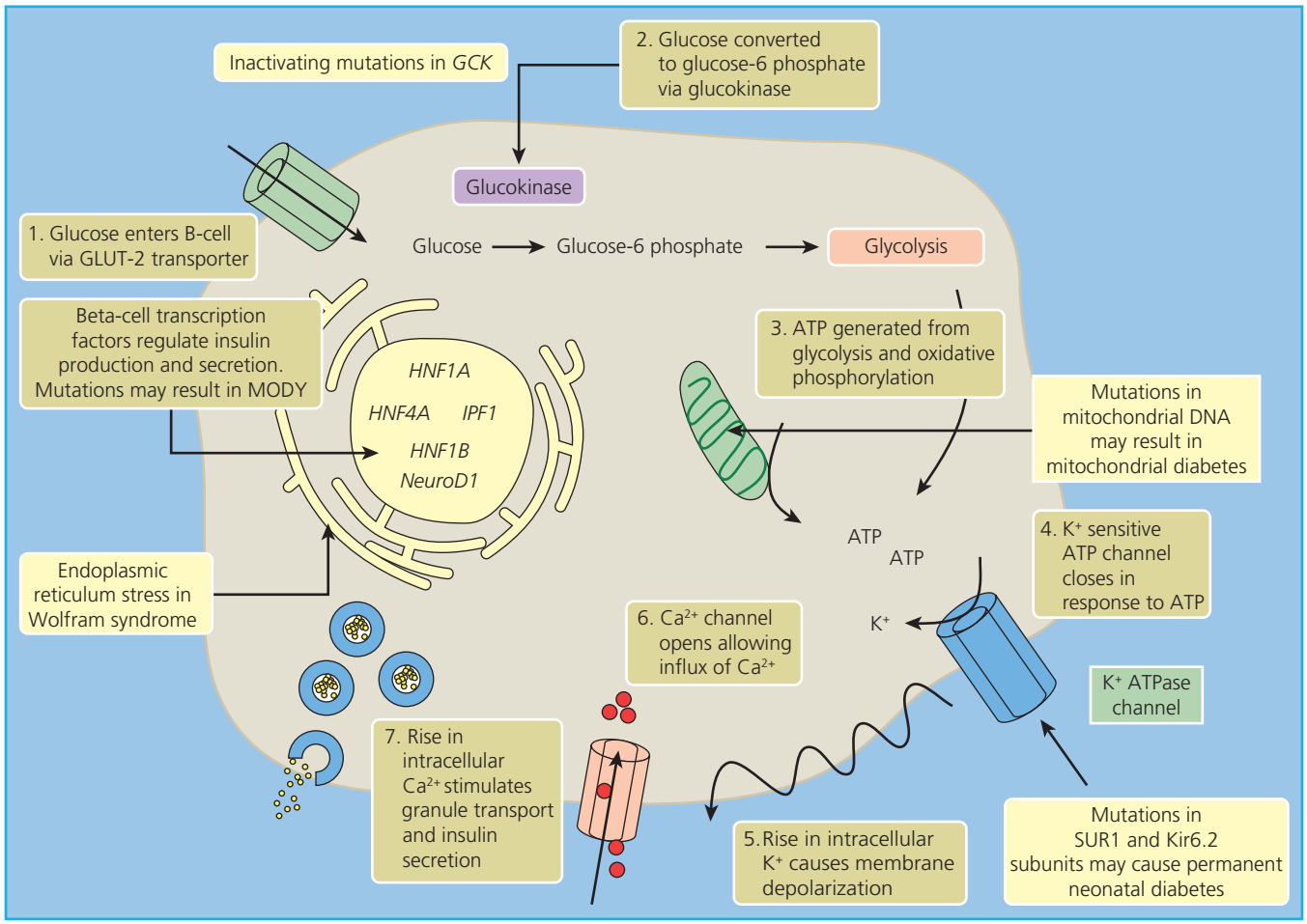

Figure 18.2 Schematic of β cell depicting key steps in glucose sensing and insulin secretion (brown boxes) and transcription factors, enzymes, organelles, and protein channels that may, if mutated, be a cause of monogenic diabetes (pale yellow boxes). Source: Adapted from Fajans et al. [5].

which include the use of a probability calculator, measurement of C-peptide and autoantibodies as well as advances in genetic testing that allow panels of genes to be tested simultaneously.

Prevalence of MODY mutations

MODY has a minimum estimated population prevalence of 108 cases per million, but this is likely to be an underestimate [7]. Prevalence estimates from large systematic surveys are between 1–3% of young-onset diabetes; in the UK UNITED study, 3% of all diabetes diagnosed <30 years of age had MODY (unpublished) while the SEARCH study undertaken in the USA found that 1.2% of all cases diagnosed under 20 years of age had MODY [8]. A population study based on screening pregnant women estimated the glucokinase prevalence to be 1.1 in 1000 population prevalence (or 1100 cases/million population) [9] suggesting most people with glucokinase mutations are not coming to medical attention or are not being diagnosed. Based on current estimates of MODY prevalence, 80–90% of cases are likely to be

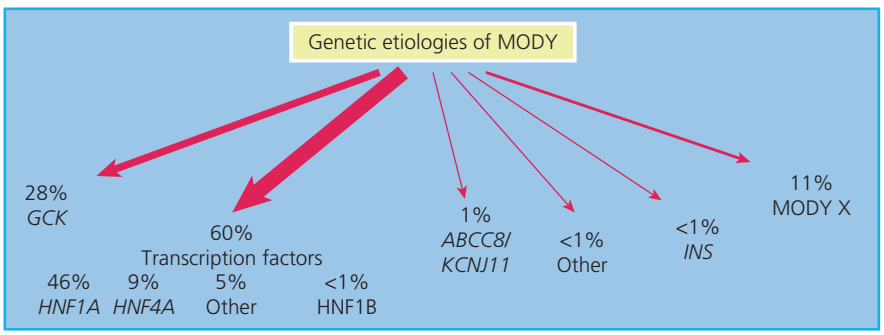

Figure 18.3 The different genetic etiologies in a UK maturity-onset diabetes of the young (MODY) series. MODY X denotes dominantly inherited young-onset non-insulin-dependent diabetes fitting clinical criteria for maturity-onset diabetes of the young where mutations in known MODY genes have not been identified. Source: Adapted from McCarthy and Hattersley [6] and Shields et al. [7].

Table 18.2 Comparison of the clinical characteristics of glucokinase and transcription factor maturity-onset diabetes of the young (MODY). FPG, fasting plasma glucose.

	Glucokinase MODY	Transcription factor MODY
Onset of hyperglycemia	Birth	Adolescence/early adulthood
Presentation	Usually asymptomatic, detected by screening or on routine testing	Usually symptomatic
Nature of hyperglycemia	Minimal increase in glycemia with age Mild (FPG usually 5.4–8.3 mmol/L) HbA_{1c} 40–60 mmol/mol	Progressive deterioration of glycemia with age May be severe (FPG frequently >14 mmol/L off treatment) HbA_{1c} variable depending on age and treatment, may be high
Pattern in an oral glucose tolerance test	FPG >5.5 mmol/L (2 hour – FPG) usually <3.5 mmol/L	FPG often <5.5 mmol/L (2 hour – FPG) usually >3.5 mmol/L
Microvascular complications	Rare	Frequent
Pathophysiology	β-cell defect (glucose sensing defect)	β-cell defect (initially insulin secretion maintained at normal glucose values but not increased in hyperglycemia)
Extrapancreatic manifestations	Altered birth weight	See Table 18.3
Treatment	Pharmacologic treatment rarely needed	Sensitive to sulfonylurea treatment May progress to require insulin

misdiagnosed or unrecognized, highlighting the need for improved case-finding.

Strategies to improve case-finding

The key approach to diagnosing MODY is to consider whether there are clinical features that are unusual for T1DM and T2DM and to undertake genetic testing in these individuals to confirm mutations (Figure 18.4). Though the cost of molecular testing continues to fall, it is still relatively expensive and it is therefore recommended that testing is restricted to those individuals with a moderate to high possibility of a positive result. Traditional clinical features, such as age at onset, a parental history of diabetes, and non-insulin treatment, overlap considerably between MODY and other types of diabetes [7] and therefore independently have poor discriminatory value.

A MODY probability calculator (available at diabetesgenes.org) offers an excellent way to establish if a diagnosis of MODY is likely: it combines clinical information to predict the probability of

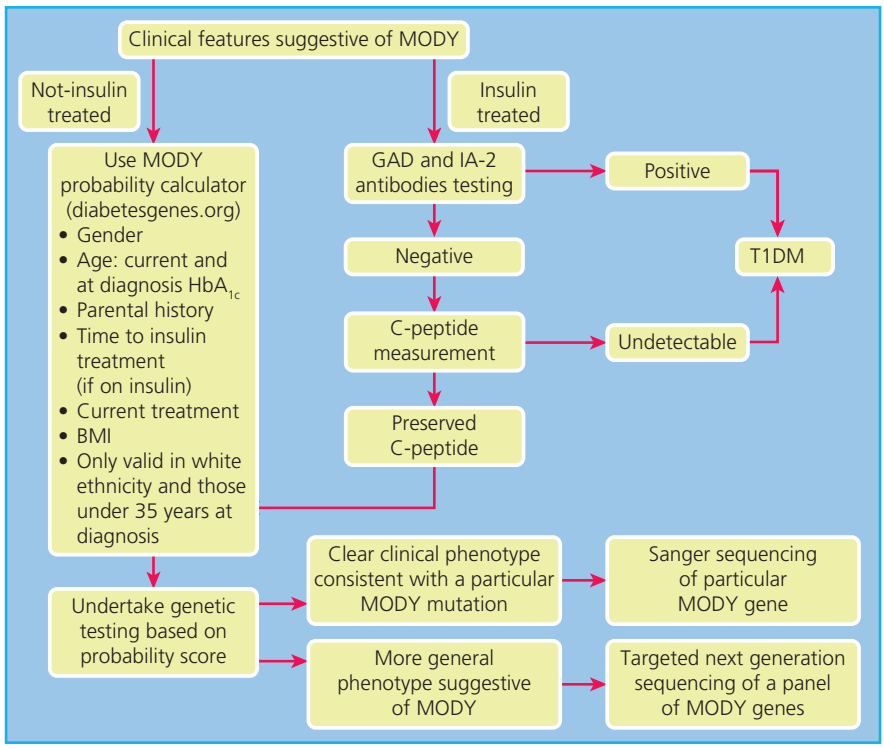

Figure 18.4 An approach to genetic testing in people with suspected MODY mutations. BMI: body mass index. Source: Shields et al. [10] and de Franco et al. [19].

testing positive for MODY [10]. The calculator markedly improved the sensitivity and specificity for identifying MODY compared with standard criteria of diagnosis, age <25 years with an affected parent.

Biomarkers such as C-peptide measurement, pancreatic autoantibodies, lipid profiles, and high-sensitive C-reactive protein (CRP) have all been shown to have some discriminatory value in differentiating cases of MODY from other subtypes; however, they are not without limitation [11–16]. Pancreatic autoantibodies are positive close to diagnosis in 80% of people with T1DM if glutamine acid decarboxylase (GAD) and islet antigen 2 (IA2) antibodies are measured [13]; however, positivity may decrease with duration of diabetes, therefore a negative test does not exclude T1DM. Testing pancreatic autoantibodies in people treated with insulin is therefore of value, if positive, in excluding MODY. The presence of preserved C-peptide secretion in a person with T1DM of long duration may also help stratify those in whom MODY testing should be considered; however, 8% of people with long-term T1DM have stimulated C-peptide levels of >200 pmol/L [17].

Use of diagnostic and predictive molecular testing in monogenic diabetes

Diagnostic testing for the major causes of monogenic diabetes is now widely available. Molecular genetic testing is traditionally guided by the clinical phenotype and also the relative prevalence of mutations within that population. A good example of this approach is in people with a very specific clinical phenotype, where Sanger sequencing of the selected gene alone may be pragmatic, for example, GCK testing in someone with fasting hyperglycemia or *HNF1B* testing in a person with renal cysts and diabetes. However, for other types of monogenic diabetes, for example, transcription factor MODY or neonatal diabetes, it may be difficult to predict the affected gene using clinical features alone. In the past this would result in sequential testing of multiple genes with associated delays in obtaining a diagnosis. However, advances in DNA sequencing technologies now mean panels of genes can be tested simultaneously using next generation sequencing platforms without the considerable costs and time associated with earlier sequencing approaches [18, 19].

Some caution is needed, however, as monogenic diabetes can occur in families that also have T1DM or T2DM. For similar reasons the results of molecular testing should be interpreted in the context of the clinical findings. For example, a person with glucokinase diabetes could also develop T1DM or T2DM.

Where a family member has a confirmed genetic diagnosis, phenotypically unaffected relatives should be tested to assess whether they will be at risk of developing diabetes in the future. Where the main mutation phenotype is diabetes, regular urine or blood testing may be preferable as there is little clear extra benefit from prospective testing. Where families request predictive testing, they should receive full counseling on the potential benefits and disadvantages and be allowed to make their own decisions on this.

Glucokinase MODY

Glucokinase catalyzes the phosphorylation of glucose to glucose-6-phosphate, the first and rate-limiting step in intracellular glucose metabolism in both β cells and hepatocytes (Figure 18.2). Owing to the unique catalytic properties of the enzyme, the rate of glucose phosphorylation is proportional to the glucose concentration, thus allowing β cells and hepatocytes to respond to changes in glycemia. In the β cell, glucokinase acts as a glucose sensor ensuring insulin release is appropriate to the glucose concentration [20]. Heterozygous loss-of-function mutations in *GCK* result in a shift of the dose–response curve to the right [21]. Glycemia is therefore regulated at a higher set point but remains tightly controlled. People with glucokinase mutations are still able to stimulate their β cells maximally [21]. Glucokinase is also present in the liver and as a result these individuals have reduced hepatic glycogen synthesis [22].

Over 200 loss-of-function mutations in *GCK* have been identified, all causing a similar clinical picture. Homozygous loss-of-function glucokinase mutations are a rare cause of insulin-requiring diabetes presenting in the neonatal period [23]. Gain-of-function mutations cause congenital hyperinsulinism [24].

Clinical features

People with *GCK* MODY have mild fasting hyperglycemia from birth, usually 5.4–8.3 mmol/L and HbA_{1c} results range between 40–60 mmol/moL (5.8–7.6%) [25, 26]. There is only a minor increase in HbA_{1c} with age, but this is also seen in older healthy people (Figure 18.5) [25, 27]. People with *GCK* MODY do not have symptoms of hyperglycemia. Post meal glucose values are only mildly raised and there is frequently only a small increase

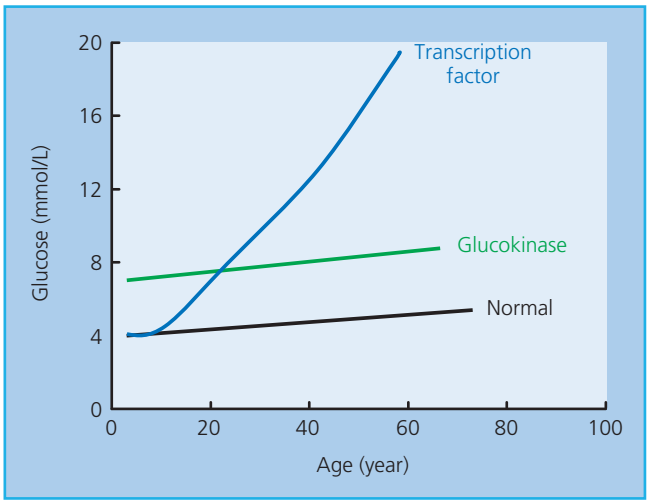

Figure 18.5 Variation of blood glucose concentration with age in people with glucokinase and transcription factor MODY.

(<3 mmol/L in 70% of those with *GCK* MODY) seen at 2 hours on an oral glucose tolerance test [28] which may explain the near normal HbA_{1c} and rarity of complications [29]. Glycated hemoglobin values above 60 mmol/mol (7.6%) would be suggestive of an alternative diagnosis and marked worsening of the glycemia suggests the development of T1DM or T2DM in addition to *GCK* MODY. Microvascular and macrovascular complications are rare even when no treatment is given [30]. As glucokinase MODY is asymptomatic there may be no known family history of diabetes, despite its autosomal dominant inheritance. Testing of apparently unaffected parents can reveal that one parent has mildly raised fasting plasma glucose.

Differentiating from type 1 and 2 diabetes

Diagnosis of glucokinase MODY is most important in young individuals who may otherwise be thought to have T1DM and treated with insulin [31]. Unlike T1DM, hyperglycemia remains mild and β-cell antibodies are usually negative. Fasting C-peptide will remain detectable and the post meal rise in glucose concentration will be far less than in T1DM. Differentiating glucokinase MODY from T2DM can be challenging as both conditions can cause mild hyperglycemia with a strong family history. Lack of obesity and features of insulin resistance, a small increment on oral glucose tolerance testing and non-progression all suggest glucokinase MODY.

Management

Outside of pregnancy, hypoglycemic medication is not recommended as hyperglycemia is mild, complications are rare and medication appears to have minimal effect in lowering glucose because the homeostatic regulation of glycemia is preserved [32, 33]. Once diagnosis is confirmed, treatment can usually be discontinued; however, this should be done with caution as it is possible for T1DM or T2DM to coexist with a *GCK* mutation.

Glucokinase MODY and pregnancy

Clinical features

Women with *GCK* mutations are frequently found to have hyperglycemia during screening in pregnancy and represent 2% of white European women with gestational diabetes [9, 26, 34]. Their identification is important because they have a different clinical course than others with gestational diabetes. The birth weight of the newborn infant will depend on the mutation status of both the mother and the fetus (Figure 18.6). Where only the mother carries the mutation, maternal hyperglycemia may result in increased fetal insulin secretion and growth causing the fetus to be large for gestational age [35]. If the fetus inherits the mutation from the father, however, birth weight is reduced by approximately 500 g as a result of reduced fetal insulin secretion and insulin-mediated fetal growth [35]. If both mother and fetus have the *GCK* mutation the two opposing effects are cancelled out and the newborn infant is of normal weight, providing maternal blood glucose has been left untreated.

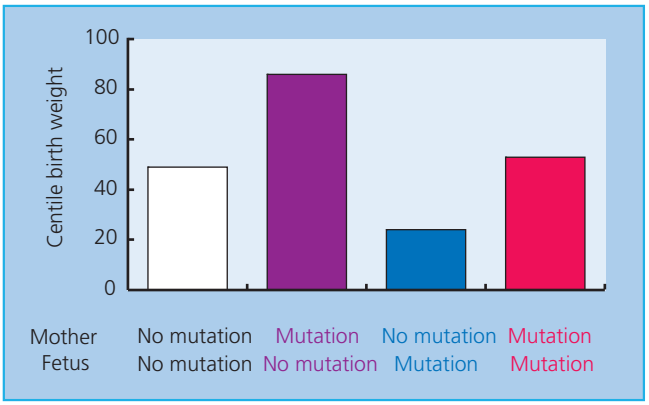

Figure 18.6 The centile birth weight of children in families with glucokinase mutations. The weight is increased by the presence of a maternal mutation and decreased by the presence of a fetal mutation. Source: Data from Hattersley et al. [35].

Genetic testing for *GCK* mutations in pregnancy

We recommend testing for *GCK* mutations when a pregnant woman is found to have persistently raised fasting plasma glucose 5.4–8.3 mmol/L and an increment of <4.6 mmol/L on at least one oral glucose tolerance test (either during or outside pregnancy). An absence of family history should not exclude the diagnosis as asymptomatic hyperglycemia in a parent may not have been detected. Genetic testing of women with a body mass index (BMI) <25 kg/m^2 and a fasting blood glucose >5.5 mmol/L has a sensitivity of 68% and on average 2.7 women will need to be tested to identify one case of *GCK* MODY [9].

Management

Women with hyperglycemia resulting from glucokinase mutations are often treated with insulin during pregnancy in an attempt to correct the fasting hyperglycemia. Fetal genotype, however, is a far greater determinant of fetal birth weight than maternal treatment and insulin appears to have little effect on fetal growth [36]. This probably reflects the difficulty in lowering the blood glucose in women with *GCK* MODY because of increased counter-regulation [37]. Women stop producing their own insulin and produce counter-regulatory hormones if blood glucose is reduced to normal levels, making successful control of blood glucose with insulin difficult. This results in frequent hypoglycemic symptoms at non-hypoglycemic blood glucose concentration and means that large doses of insulin may be required to reduce fasting hyperglycemia to normal levels [37, 38]. In some cases where the fetus has inherited the mutation, intensive insulin treatment has resulted in a low birth weight child [38]. This is to be expected as a small baby is seen when the fetus inherits a mutation from the father and is born to a normoglycemic mother [35, 39]. Testing fetal genotype *in utero* is not without risk and is not recommended unless amniocentesis or chorionic villus sampling is being undertaken for an alternative reason [40]. Assays to detect cell-free fetal DNA in maternal serum are under development and will allow non-invasive fetal genotyping in the future. At present treatment

decisions in glucokinase gestational diabetes are related to fetal growth as shown by scans rather than being made solely on maternal glycemia [38]. If the abdominal circumference is greater than the 75th centile insulin may be used but early delivery is the most successful strategy [26].

HNF1A and *HNF4A* (transcription factor MODY)

Transcription factors are proteins that bind to DNA and form part of a complex regulatory network controlling gene expression. The majority of people with MODY have a heterozygous mutation in a transcription factor gene, by far the commonest being mutations in the hepatic nuclear factors 1A and 4A (*HNF1A* and *HNF4A*). Diabetes resulting from mutations in other transcription factor encoding genes including *HNF1B* and insulin promoter factor 1 (IPF-1) are discussed elsewhere in this chapter.

Transcription factor mutations alter insulin secretion in the mature β cell as well as altering β-cell development, proliferation, and cell death. Mutations in the hepatic nuclear factors appear to alter levels of proteins critical in metabolism including the GLUT-2 glucose transporter and key enzymes in the mitochondrial metabolism of glucose [41–43]. Reduced β-cell proliferation and preserved or increased apoptosis could explain the progressive deterioration in β-cell function seen in these individuals [43–46].

Mutations in *HNF1A* account for up to 70% of cases of MODY with nearly 200 different mutations reported. *HNF4A*, the next most common, accounts for approximately 3% of cases [47].

Clinical features

Heterozygous transcription factor mutations cause autosomal dominant diabetes presenting in adolescence or early adulthood resulting from progressive failure of insulin secretion. While diabetes is similar in *HNF1A* and *HNF4A* mutation carriers as a result of a common pattern of β-cell dysfunction, a number of differences in extrapancreatic features occur (Table 18.3).

Table 18.3 Extrapancreatic features assisting in the differential diagnosis of transcription factor maturity-onset diabetes of the young (MODY). HDL, high density lipoprotein cholesterol; LDL, low density lipoprotein cholesterol.

Transcription factor	Extrapancreatic clinical features
HNF1A	Low renal glucose threshold (glycosuria) Raised HDL Raised cardiovascular risk (in excess of type 2 diabetes)
HNF4A	Increased birth weight/macrosomia Neonatal hypoglycemia Low HDL, low lipoprotein A1 and A2, raised LDL
HNF1B	Renal cysts and renal development disorders and multiple others. See Table 18.5
NeuroD1	None described

Diabetes

People with transcription factor MODY are usually born with normal glucose tolerance and then show progressive β-cell dysfunction until they develop diabetes, usually aged 10–30 years (Figure 18.5). Sixty-three percent of *HNF1A* carriers are diagnosed with diabetes by the age of 25 years and 79% by the age of 35 years; the age of diagnosis is partly related to the location of the underlying mutation within the gene [48–50]. Those show deteriorating glycemia with age require pharmacologic treatment. In the oral glucose tolerance test, in contrast to people with glucokinase mutations, the fasting glucose is often normal initially but there is marked elevation of glycemia at 2 hours and consequently a large 2-hour increment (>5.0 mmol/L) [28]. This occurs because insulin secretion rates in early *HNF1A* MODY remain appropriate, with blood glucose values <8.0 mmol/L but are reduced significantly in comparison to non-diabetic non-mutation carriers above this level [51]. Microvascular complications are frequent particularly when hyperglycemia is inadequately treated [52]. People with transcription factor MODY tend to be lean and insulin-sensitive. Obesity occurs at similar levels to the normal population.

Extrapancreatic clinical features

These are summarized in Table 18.3 and discussed in more detail below.

HNF1A

People with *HNF1A* mutations have elevated levels of high density lipoprotein cholesterol (HDL) which contrasts with the reduced HDL levels seen in T2DM [53]. Despite this they appear to have a greater risk of coronary heart disease than people with T1DM. Frequency of microvascular complications is similar to that seen in T1DM and T2DM and relates to degree of glycemic control [52]. *HNF1A* mutations are associated with a reduced renal threshold for glucose. Mutation carriers without diabetes may develop glycosuria after a glucose challenge even if glycemia remains within normal limits[54].

HNF4A

HNF4A mutations are associated with an 800 g increase in birth weight compared with non-mutation carrying siblings [55]. This means the offspring of *HNF4A* mutation carrying fathers, as well as the offspring of *HNF4A* mothers, are at risk of macrosomia. There is also an increased risk of hypoglycemia in affected neonates. These features appear to relate to increased insulin secretion *in utero* and in early infancy which evolves into reduced insulin secretion and diabetes in later life [55]. *HNF4A* mutation carriers have reduced levels of HDL (and lipoprotein A1 and A2) and frequently have raised LDL, while triglyceride levels are similar to population norms [56].

Differentiating from type 1 diabetes

These individuals are usually diagnosed as having T1DM as they have symptomatic diabetes occurring in adolescence or young

adulthood. We recommend genetic testing for *HNF1A* mutations in any young adult with apparent T1DM, a parent with diabetes, and who is antibody-negative at diagnosis. Evidence of non-insulin dependence increases the likelihood of a positive result; this would include no ketosis in the absence of insulin treatment, good glycemic control on low doses of insulin, or detectable C-peptide with plasma glucose >8 mmol/L 3–5 years after diagnosis (outside the honeymoon period) [57]. While GAD antibodies are usually negative, positive GAD antibodies may be expected in up to 1–2% of people without diabetes, and therefore positive antibodies (particularly at low titer) may not exclude monogenic diabetes; testing should be considered where clinical suspicion is high [58, 59]. *HNF4A* testing should be performed in anyone with a high suspicion of having *HNF1A* who tests negative for *HNF1A* mutations, particularly where there is evidence of increased birth weight and/or neonatal hypoglycemia.

Differentiating from type 2 diabetes

HNF1A should be suspected and mutation screening performed in people otherwise suspected to have T2DM where the following features are present ([57] and www.diabetesgenes.org):

1 Young-onset diabetes: typically before 25 years old in at least one family member;

2 Family history of diabetes: at least two generations and ideally two individuals diagnosed in their twenties or thirties, particularly where affected individuals are non-obese;

3 Absence of obesity, acanthosis nigricans or other evidence of insulin resistance.

In addition, a large increment in the glucose tolerance test (>5 mmol/L), presence of glycosuria with blood glucose <10 mmol/L, marked sensitivity to sulfonylureas (hypoglycemia on low doses), and a lipid profile showing normal or raised HDL and normal or low triglycerides (atypical for T2DM) would all be supportive of a diagnosis of *HNF1A* instead of T2DM [53]. *HNF4A* should be suspected and tested in those who are suspected to have *HNF1A* mutations but test negative on *HNF1A* screening. These individuals have a normal renal glucose threshold and frequently have a personal and/or family history of high birth weights and/or neonatal hypoglycemia.

Management

People with both *HNF1A* and *HNF4A* mutations are sensitive to sulfonylurea therapy which we recommend as first-line treatment [56, 60]. Glycemic control with sulfonylureas is often better than with insulin and the fasting glucose lowering effect is four times greater than that seen in T2DM [60, 61]. Transfer to sulfonylurea treatment is successful in the majority of people although insulin therapy may be required as diabetes progresses [62]. Even very low sulfonylurea doses may cause hypoglycemia. The starting dose should therefore be low; we use a starting dose of 40 mg/day gliclazide or 2.5 mg/day glibenclamide in adults. If there is hypoglycemia with low doses of standard agents, a short-acting agent such as nateglinide may be appropriate [63]. GLP-1 receptor agonists have also been shown to be effective at reducing glycemia [64]. Because of the apparent increased risk of cardiovascular disease in *HNF1A*, statin therapy should be considered for those aged over 40 years.

Management in pregnancy

Evidence to support management strategies for *HNF1A* and *HNF4A* in pregnancy is very limited. Our current practice is to continue sulfonylureas if glycemic control is good before pregnancy on this treatment but otherwise institute treatment with insulin. Consideration should be given to switching other sulfonylureas to glibenclamide in the pre-conception period as this sulfonylurea has the most evidence for safety in pregnancy [65, 66]. However, sulfonylureas have been shown to cross the placenta and increase fetal birth weight independent of maternal glycemia [67]. The risks of placental transfer of sulfonylureas therefore needs to be balanced against a potentially improved control with sulfonylurea use in early pregnancy.

If a fetus carries *HNF4A*, the risk of macrosomia and neonatal hypoglycemia is extremely high whether the mutation comes from the mother or father [55] as it will add >800 g to the birth weight, which may result in considerable obstetric complications.

In women with *HNF4A* there is an additional contribution to fetal birth weight from maternal glycemia and it is very important to avoid adding to this further by glibenclamide use. We therefore recommend switching to insulin towards the end of the second trimester. If either parent is known to carry a *HNF4A* mutation, we recommend:

1 Very tight maternal glucose control to attempt to minimize macrosomia;

2 Serial antenatal ultrasound scans to look for macrosomia with early delivery if this is marked; and

3 Early measurement of neonatal glucose and consideration of diazoxide treatment if hypoglycemia persists.

Other transcription factor MODY

Other transcription factor mutations causing autosomal dominant β-cell diabetes have been identified in the genes *IPF1* and *NEUROD1*, but are very rare; *KLF11* and *PAX4* have been proposed but this work has not been replicated [68–73].

Neonatal diabetes and diabetes diagnosed within 6 months of life

Children diagnosed with diabetes within the first 6 months of life (referred to as neonatal diabetes) are likely to have monogenic diabetes and not T1DM [74–77]. These children commonly present with ketoacidosis and absent C-peptide. Neonatal diabetes is rare, affecting 1 in 100,000–200,000 live births [78]. Approximately half of cases remit spontaneously and are therefore termed

Table 18.4 Causes of neonatal diabetes. Source: De Franco et al. [19].

Pancreatic pathophysiology	Protein, chromosome or gene affected	Prevalence	Inheritance	Features in addition to neonatal diabetes and low birth weight
Reduced β-cell function	K_{ATP} channel (*KCNJ11* and *ABCC8*)	43% of permanent neonatal diabetes, 25% of transient neonatal diabetes	85% spontaneous. Remainder autosomal dominant or recessive	Developmental delay and epilepsy. Sulfonylurea responsive
	Chromosome 6q24	12.8% (70% of transient neonatal diabetes)	Variable	Macroglossia and umbilical hernia
	Glucokinase (homozygous for mutation)	1% (9.6% in consanguineous unions)	Autosomal recessive	Both parents have heterozygous glucokinase associated hyperglycemia
	SLC2A2	<1%	Autosomal dominant	Hypergalactosemia, hepatic failure
	GLIS3	<1%	Autosomal recessive	Congenital hypothyroidism, glaucoma, liver fibrosis, and cystic kidney disease
Reduced pancreatic mass	*PTF1A*	<1% (8.3% in consanguineous unions)	Autosomal recessive	Pancreatic and cerebellar agenesis
	PDX1	<1%	Autosomal recessive	Pancreatic agenesis
	HNF1B	<1%	Autosomal dominant	Exocrine pancreas insufficiency and renal cysts
	GATA6	3.7%	Autosomal dominant	Pancreatic agenesis
Increased β-cell destruction	*EIF2AK3*	2.5% (24.3% in consanguineous unions)	Autosomal recessive	Spondyloepiphyseal dysplasia, renal failure, recurrent hepatitis, and mental retardation
	FOXP3	1.4%	X-linked	Immune dysregulation, intractable diarrhea, eczematous skin rash, and elevated IgE
	STAT3	<1%	Autosomal dominant	Short stature, autoimmune-driven thyroid disease, enteropathy, and eczema
	INS	11% of permanent neonatal diabetes	Autosomal dominant	None

transient neonatal diabetes mellitus (TNDM) as opposed to permanent neonatal diabetes mellitus (PNDM) where diabetes persists. TNDM often recurs in later life [79]. Neonatal diabetes results from mutations of key genes involved in β-cell development or function [19]. Table 18.4 summarizes the known genetic causes of neonatal diabetes.

Permanent neonatal diabetes

Approximately half of PNDM is caused by mutations in the genes *KCNJ11* and *ABCC8* which encode the Kir6.2 and SUR1 subunits, respectively, of the β-cell ATP-sensitive potassium channel (K_{ATP} channel) [80–83]. This channel is constitutively open and regulates insulin secretion by closing in response to the raised intracellular ATP levels that occur as a consequence of hyperglycemia. Channel closure triggers depolarization of the β-cell membrane which leads to insulin secretion. Activating mutations in *KCNJ11* and *ABCC8* prevent closure of the potassium channel in response to increased ATP so the β cell remains hyperpolarized and unable to secrete insulin [84]. Sulfonylureas close the β-cell K_{ATP} channel by an ATP independent route and they have been used successfully in the management of children with neonatal diabetes resulting from *KCNJ11* and *ABCC8* mutations [85]. The K_{ATP} channel is also present in the brain, nerves, and muscles. Reflecting this distribution of channels, 20% of children with *KCNJ11* mutations (and occasionally those with *ABCC8* mutations) have associated neurologic features [77, 80, 81, 84].

Heterozygous mutations in the insulin gene (*INS*) have been identified in 12% of cases of isolated PNDM and insulin treatment is required [86, 87]. A number of other genetic causes have been found which all appear to be relatively rare [78] as outlined in Table 18.4. Parental consanguinity is more likely to result in autosomal recessive inheritance. In children born to consanguineous parents, the commonest cause of PNDM is a homozygous mutation in *EIF2AK3* gene, causing Wolcott–Rallison syndrome [18]. In offspring of unrelated parents the majority (85%) of PNDM resulting from K_{ATP} channel mutations arise spontaneously from *de novo* heterozygous mutations, with the remainder being familial and inherited mainly in an autosomal dominant pattern. About 40% of neonatal diabetes resulting from *ABCC8* mutations, however, are inherited in an autosomal recessive fashion [83].

Clinical features

Diabetes caused by *KCNJ11* mutations typically presents in the first 26 weeks of life (median 4–6 weeks) with marked hyperglycemia often accompanied by ketosis. C-peptide is usually undetectable and pancreatic auto-antibodies negative [80]. As with all neonatal diabetes subtypes, infants are often small for gestational age as a result of reduced fetal insulin secretion with consequent decreased insulin-mediated growth. About 20% of children with PNDM and *KCNJ11* mutations have neurologic features, the commonest being developmental delay, sometimes with muscle weakness and/or epilepsy. The most severe form where neonatal diabetes is accompanied by developmental delay and epilepsy has been named developmental delay, epilepsy and neonatal diabetes (DEND). "Intermediate DEND" refers to neonatal diabetes with less severe developmental delay and no epilepsy. The severity of the clinical condition relates closely to the underlying mutation and its effect on K_{ATP} channel ATP sensitivity [84, 88]. Children without apparent neurological manifestation have been found to have developmental coordination disorders and attention deficits when subjected to in-depth neuropsychiatric testing [89].

Neonatal diabetes caused by *ABCC8* mutation has a similar phenotype but leads to transient neonatal diabetes more commonly than PNDM and rarely has associated neurologic features [81–83]. Children with neonatal diabetes and *INS* mutations present at a median age of 9 weeks and are also often small for gestational age but do not have extrapancreatic features [86].

Management

Although insulin therapy is commonly used in the initial period after diagnosis, the majority of those with *KCNJ11* and *ABCC8* mutations can successfully transfer from insulin to sulfonylurea therapy, usually with significant improvements in glycemic control [82, 85]. Ninety percent of those with *KCNJ11* mutations are able to discontinue insulin, while HbA_{1c} appears to improve in all with a mean drop from 65 to 46 mmol/mol (8.1 to 6.4%) after 12 weeks [85]. Glibenclamide was initially selected as it is nonselective and widely available; it has been used in the majority of cases and may be more effective than other sulfonylurea agents [90]. The doses needed are often higher than those needed for the treatment of T2DM: a median dose of 0.45 mg/kg/day is required with doses up to 1.5 mg/kg/day in some cases [85, 91]. Diarrhea is a possible side effect but this usually only lasts 1–3 days [92]. Sulfonylurea therapy may result in some improvement in neurologic features even where they are commenced in adulthood [90, 93, 94]. Further information on transferring patients from insulin to sulfonylureas can be found at www.diabetesgenes.org. Earlier age at initiation of sulfonylurea therapy appears to correlate with better dose response [95]. Furthermore initiation of sulfonylurea therapy in those with *KNCJ11* or *ABCC8* mutations appears to reverse neuropsychomotor impairments, particularly when started early [96].

Neonatal diabetes resulting from *INS* mutations requires insulin treatment [86]. Affected individuals with a heterozygous *KCNJ11* mutation contemplating parenthood should be counseled that they have a 50% chance of passing on the mutation to their offspring. Where unaffected parents whose child is affected by a heterozygous mutation are planning further pregnancies, the risk of further affected children is low because the possibility of a germline mutation is approximately 5–10% [97]. Where parents have a child with neonatal diabetes caused by a recessive *ABCC8* mutation, there is a 25% chance of each further offspring being affected but the risk is low for subsequent generations.

Transient neonatal diabetes

The genetic etiology of more than 90% of transient neonatal diabetes has been established. The majority (70%) of cases result from abnormalities in the q24 region of chromosome 6 (6q24) affecting imprinted genes [78, 98]. Genetic imprinting occurs when only the maternal or paternally inherited allele of a gene is expressed and this is usually controlled by methylation. In TNDM paternal uniparental disomy, paternal duplication of 6q24 or abnormal methylation of the maternal copy of the chromosome causes overexpression of the paternal copies of the genes *PLAGL1* (also known as *ZAC*) and *HYMAI* [98, 99]. Paternal duplication of 6q24 can be inherited, therefore this abnormality causes the majority of inherited TNDM cases. Uniparental disomy causes sporadic TNDM; cases resulting from abnormal methylation of the maternal copy of chromosome 6 may be sporadic or inherited [98, 99]. The majority (90%) of TNDM not associated with 6q24 abnormalities are caused by mutations in *KCNJ11* and *ABCC8* [77, 79, 82, 100–104].

Clinical features

6q24 diabetes usually presents in the first week of life often with severe hyperglycemia and dehydration but usually without ketosis [98]. Pancreatic auto-antibodies are usually negative and C-peptide is low or negligible. Low birth weight is common (mean birth weight 2.1 kg), and there may be associated macroglossia and/or umbilical hernia. Insulin treatment is required for a median of 12 weeks before the child goes into remission. Diabetes recurs later in life in 50–60% as a result of β-cell dysfunction. The average age of recurrence is 14 years. In some cases hyperglycemia may be intermittent and seen only at times of stress [98, 105]. Where TNDM is caused by *KCNJ11* and *ABCC8* mutations, diabetes tends to present later (median 4 weeks), takes longer to remit and is associated with less intrauterine growth restriction (median birth weight 2.6 kg) [79].

Management

Insulin is required in the neonatal period whereas treatment requirements following relapse vary from diet to oral antidiabetes agents or insulin [105]. In TNDM cases resulting from *KCNJ11* and *ABCC8* mutations, diabetes may be successfully managed with sulfonylureas [79, 82].

Genetic counselling depends on the underlying genetic etiology. Cases caused by uniparental disomy are sporadic and therefore have low risk of occurrence in either siblings or offspring of the affected child. Methylation defects often result from homozygous mutations in the transcription factor gene *ZFP57* and

therefore may be inherited in an autosomal recessive manner [99]. Offspring of men with 6q24 duplication have a 50% chance of developing TNDM whereas if the abnormality is inherited from the mother they will not be affected but the TNDM may occur in the following generation [105].

Genetic testing in neonatal diabetes

At the time of diagnosis of neonatal diabetes it is unknown whether the diabetes will be transient or permanent. We recommend testing for 6q24 abnormalities, *KCNJ11*, *ABCC8*, and *INS* mutations at diagnosis in all diabetes diagnosed before 6 months. Identifying mutations in these genes is important as it will influence treatment. An early diagnosis and very low birth weight make 6q24 most likely. A genetic cause (*KCNJ11* or *INS*) can be established in ~7% of diabetes diagnosed between 6 months and 1 year of age and so consideration should be given to testing this age group, especially where autoantibody tests are negative [76].

Diabetes with extrapancreatic features

A number of monogenic causes of diabetes are associated with distinct features occurring outside the pancreas. In many cases extrapancreatic disease may be the presenting feature, for example in cystic fibrosis and hemochromatosis (see Chapter 21). Clinical subtypes and management of monogenic β-cell diabetes that have extrapancreatic features are summarized in Figure 18.7.

Maternally inherited diabetes and deafness

Maternally inherited diabetes and deafness (MIDD) results from a mutation in mitochondrial DNA and causes maternally inherited diabetes with sensorineural deafness that may be accompanied by a wide range of other features. It affects up to 1% of those with diabetes but is frequently misdiagnosed [106].

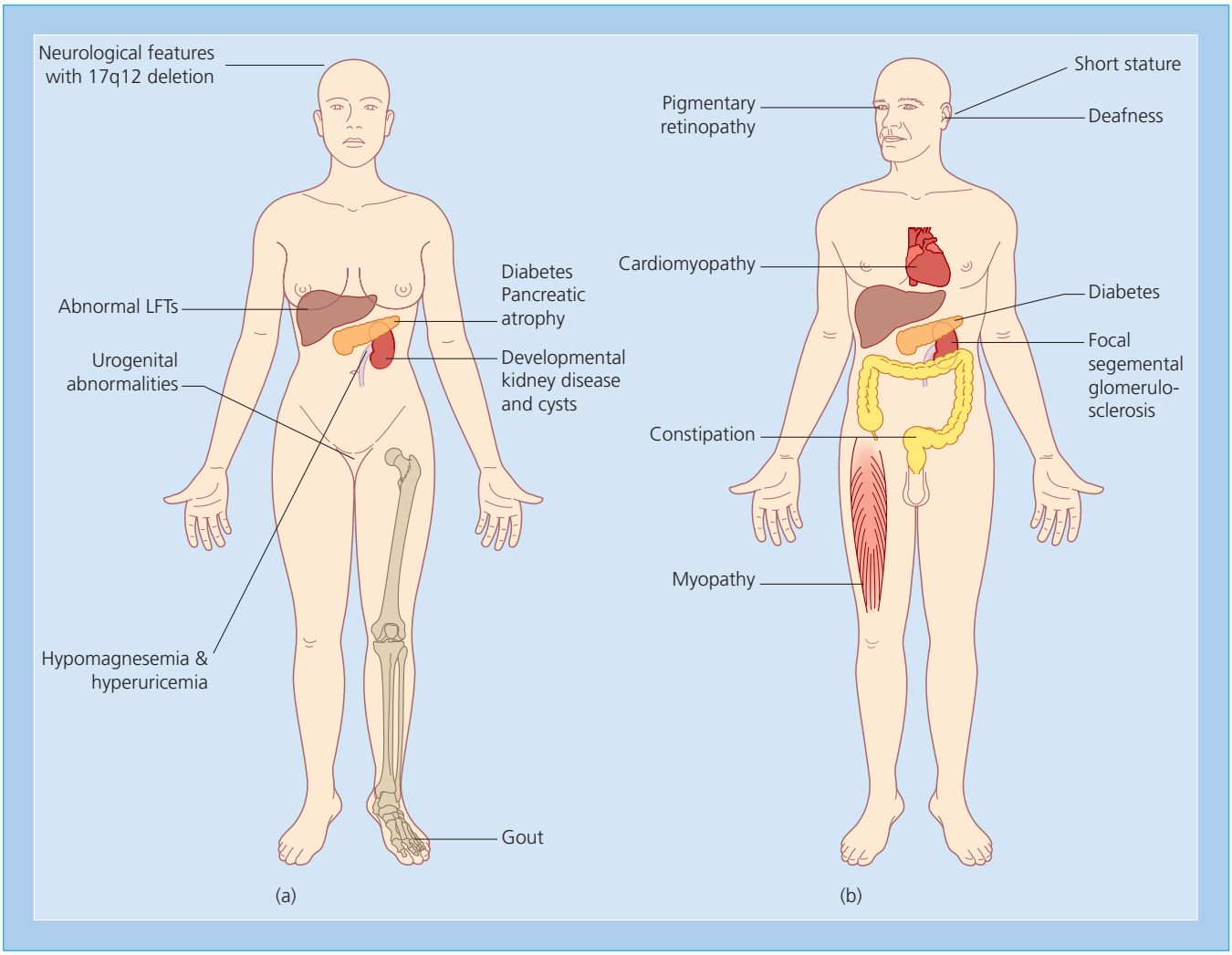

Figure 18.7 Phenotypes of: (a) renal cysts and diabetes syndrome due to *HNF1B* mutation or deletion; (b) maternally inherited diabetes and deafness caused by mitochondrial m.3243A>G mutation. LFTs: liver function tests. Source: Adapted from Murphy et al. [106] and Clissold et al. [129].

Pathogenesis and inheritance

The vast majority of mitochondrial diabetes results from the m.3243A>G point mutation in mitochondrial DNA and other mitochondrial DNA mutations are rare [107].

The m.3243A>G mutation affects the mitochondrial respiratory chain and therefore results in cellular energy deficiency. Organs with high metabolic activity including the endocrine pancreas and cochlea are most affected. Mitochondrial dysfunction in pancreatic islets results in abnormal β-cell function, loss of β-cell mass, and insulin deficiency [106]. As mitochondria are inherited from the mother, only the maternal line in a family is affected, and children of a male patient are not at risk. All children of an affected woman are likely to carry the mutation; however, phenotype varies widely within a family due to heteroplasmy. Offspring inherit a mix of mutant and wild-type mitochondrial DNA and the proportion of mitochondria carrying the mutation will vary as will segregation of mutant and wild-type mitochondria to different tissues [108].

Clinical features

The characteristic clinical features of MIDD are summarized in Figure 18.7. The majority of mutation carriers develop diabetes (over 85%) and sensorineural hearing loss (over 75%) [108–112]. Diabetes is progressive but may present acutely, with ketoacidosis occurring in ~8% of cases [108, 109, 113]. Mean age at diagnosis of diabetes is 37 years but age of diagnosis can range from early adolescence to old age [109, 113, 114].

Hearing loss typically develops in early adulthood [109, 111]. Those with the m.3243A>G mutation have a high prevalence of renal failure with focal segmental glomerular sclerosis found frequently on biopsy [109, 115]. Macular retinal dystrophy is a frequent finding but rarely causes visual symptoms [106, 109, 115]. Cardiac abnormalities include left ventricular hypertrophy, heart failure, and cardiac arrhythmias [116–120]. Other clinical manifestations of the m.3243A>G mutation include short stature, MELAS (mitochondrial encephalomyopathy, lactic acidosis, and stroke-like episodes), psychiatric disorders, proximal myopathy, and gastrointestinal symptoms [106].

Differentiating from type 1 and 2 diabetes

Diabetes caused by the m.3243A>G mutation is difficult to differentiate from T1DM or T2DM. GAD antibodies are usually but not always negative [121–123]. The presence of deafness in the patient or clustering of diabetes and/or deafness in maternal relatives should prompt investigation for the m.3243A>G mutation.

The diagnosis can be confirmed by testing for the m.3243A>G mutation in blood leukocytes or urine. In rare cases the result may be negative on blood-derived DNA because of heteroplasmy loads in leukocytes. Urine or mouthwash samples may therefore be preferable [106].

Management

Diabetes usually requires early insulin treatment [108, 109, 113, 123]. There is a theoretical basis for avoiding metformin in view of the risk of lactic acidosis [106, 108]. Whether there is benefit from use of co-enzyme Q10 supplementation is currently unclear [106, 124, 125]. Monitoring for cardiac manifestations should be considered from a young age. Aggressive blood pressure management and early angiotensin-converting enzyme (ACE) inhibitor treatment may be appropriate in view of the high risk of renal complications. Management of hearing loss involves avoidance of exacerbating factors, prompt treatment of ear infections, hearing aids if necessary, and consideration of cochlear implants where there is profound hearing loss [106, 126, 127].

Maternal relatives of affected individuals and children of female patients should be assumed to carry the m.3243A>G mutation. Therefore, periodic screening for the features and complications of MIDD may be advisable.

Renal cysts and diabetes (*HNF1B* MODY)

HNF1B is a transcription factor with a role in regulating gene expression in a number of tissues including the pancreas, kidneys, liver, genital tract, and gut [128]. Heterozygous deletions or mutations in *HNF1B* can cause developmental abnormalities in all these organs although the commonest phenotypes are renal abnormalities and diabetes. *HNF1B* abnormalities may show autosomal dominant inheritance, although up to 50% of cases arise spontaneously and there is a wide variation in phenotype even with identical mutations [129–134].

Clinical features

The clinical features are summarized in Table 18.5 and Figure 18.7. Developmental renal disease is the most consistent feature with renal cysts being the commonest manifestation [129]. Other possible renal abnormalities include glomerulocystic kidney disease, cystic renal dysplasia, and morphologic abnormalities such as horseshoe kidney. Renal function can range from normal to dialysis-dependent [135, 136]. Half of *HNF1B* mutations carriers have early-onset diabetes caused by both insulin deficiency as a result of reduced β-cell number and increased hepatic insulin resistance. The sensitivity to sulfonylureas found with *HNF1A* and *HNF4A* mutations is absent [137]. Diabetes is usually associated with pancreatic hypoplasia and may be associated with exocrine dysfunction although this is rarely symptomatic [138–140]. Low birth weight is common and transient neonatal diabetes may occur [139]. Other clinical manifestations include non-progressive abnormal liver function tests, genital tract malformations, hypomagnesemia, hyperuricemia, and familial hyperuricemic nephropathy [138, 141]. Learning difficulties and autism are common features particularly in those with a whole gene deletion (17q12). An association with chromophobe renal cell carcinoma has been reported reflecting a probable role for *HNF1B* as a tumor suppressor gene [142, 143].

Differentiating from type 1 and 2 diabetes

Approximately 50% of *HNF1B* mutations and deletions are spontaneous and so there may be no family history. Testing for *HNF1B* abnormalities should be considered where there is unexplained

Table 18.5 Features of people with *HNF1B* mutations causing RCAD (renal cysts and diabetes) in a UK cohort. Source: Adapted from Bingham and Hattersley [132] and Clissold et al. [129].

Clinical features		Details
Renal phenotype		
	Renal cysts	Common
	Renal impairment	Common (15% require dialysis/transplantation)
	Morphologic renal abnormalities	Horseshoe or single kidney
	Renal histology	Glomerulocystic kidney disease, cystic renal dysplasia, oligomeganephronia
	Hypomagnesemia	44%, proximal tubular defect
	Hyperuricemia and gout	20% (clinical gout)
Diabetes		58%. Mean age of diagnosis 26 years, range 10–61 years Insulin treatment common
Other features		
	Liver enzyme derangement	Mild, non-progressive
	Subclinical exocrine pancreatic failure	Reduced fecal elastase
	Genital tract malformations	17%
	Short stature	20% <2 SD below mean height
	Learning difficulties	Neuropsychiatric manifestations particularly associated with 17q12 chromosomal deletion (whole gene deletion)
Uncommon		Joint laxity, hearing loss, prognathism, pyloric stenosis, chromophobe renal cell carcinoma

cystic renal disease, glomerulocystic disease, or other renal developmental abnormalities with or without a past medical or family history of diabetes. It should also be considered in individuals with genital tract abnormalities associated with renal abnormalities. Both simple renal cysts and diabetes are common in the general population and should not lead to testing for *HNF1B* abnormalities. Testing for *HNF1B* should always include dosage analysis to detect gene deletions as these are common and will be missed if the laboratory performs sequencing only [144].

Management

Early insulin therapy is usually required for management of diabetes. The sulfonylurea sensitivity seen in other transcription factor diabetes is not seen in *HNF1B*. Renal management is similar to management of other chronic progressive renal diseases. Our recommendation is to repeat renal ultrasound imaging every 2 years in view of the possible increased risk of chromophobe renal carcinoma and to screen for diabetes yearly in mutation carriers without diabetes.

Other monogenic β-cell diabetes with extrapancreatic features

Wolfram syndrome

Wolfram syndrome (also known as DIDMOAD [diabetes insipidus, diabetes mellitus, optic atrophy, and deafness]) is a rare recessive neurodegenerative disorder characterized by diabetes insipidus, diabetes mellitus, optic atrophy deafness, and a variety of central nervous system abnormalities. Consideration should be given to this diagnosis where there is a combination of diabetes and optic atrophy [145, 146].

Thiamine responsive megaloblastic anemia

Thiamine responsive megaloblastic anemia is a rare autosomal recessive condition characterized by megaloblastic anemia (which may be mild), non-autoimmune diabetes mellitus and sensorineural hearing loss. Treatment with high-dose thiamine can improve some features including diabetes [147].

Wolcott–Rallison syndrome

Wolcott–Rallison syndrome is a rare autosomal recessive condition characterized by early-onset diabetes, spondyloepiphyseal dysplasia, acute hepatic failure, renal impairment, and developmental delay. Diabetes usually presents in infancy and requires insulin treatment [148].

Monogenic diabetes with pancreatic exocrine dysfunction

Mutations in the carboxyl ester lipase (*CEL*) gene have recently been identified as a rare cause of monogenic diabetes with pancreatic exocrine dysfunction [149].

Insulin resistance

Monogenic causes of diabetes resulting from insulin resistance include the inherited lipodystrophies, mutations affecting the insulin receptor or post-receptor signaling and other monogenic syndromes associated with insulin resistance where abnormalities

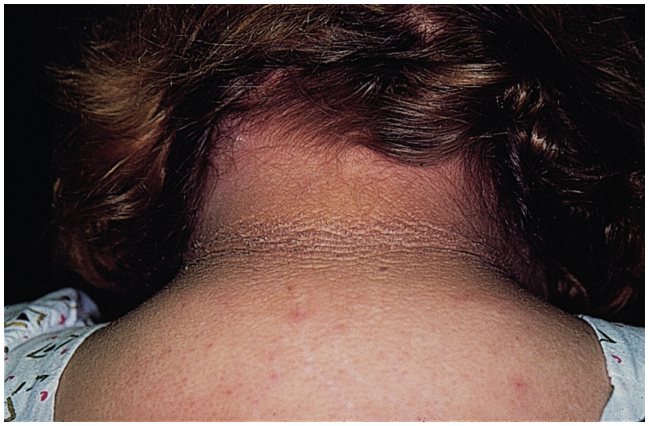

Figure 18.8 Acanthosis nigricans affecting the neck of a 26-year-old woman with severe insulin resistance. Source: Reproduced from Moller and O'Rahilly [207] with permission.

of insulin action are not the primary disorder. There can be considerable clinical overlap in clinical presentation between these conditions [150]. The key features of severe insulin resistance are:

- the presence of acanthosis nigricans (Figure 18.8) particularly in a lean individual;
- ovarian cysts, subfertility, and hyperandrogenism in women; and
- hyperinsulinemia as evidenced by raised endogenous insulin levels, or in those on insulin treatment, very high doses of exogenous insulin.

The presence of some or all of these features should prompt consideration of underlying monogenic causes of insulin resistance. The presence of other clinical features (see Figure 18.9) are related to the underlying cause. Monogenic forms of insulin resistance are comprehensively reviewed in [151, 152].

Insulin receptor gene mutations

Insulin exerts its effects through binding to a transmembrane receptor. Binding of insulin to the alfa subunit of the receptor activates beta subunit tyrosine kinase activity triggering protein activation cascades that lead to insulin's intracellular effects [153, 154]. Mutations in the insulin receptor gene lead to inherited insulin resistance syndromes. The severity of the resulting clinical phenotype depends on the extent of impairment of signal transduction resulting from the underlying mutation [155].

Clinical features

Individuals with severe insulin resistance resulting from insulin receptor mutations may have a number of common features including hyperinsulinemia, acanthosis nigricans, ovarian hyperandrogenism, and disturbances of glucose homeostasis which can include hypoglycemia (classically postprandial) as well as impaired glucose tolerance and diabetes [155]. Three main syndromes resulting from insulin receptor mutations leading to severe insulin resistance have been described: Type A insulin resistance syndrome, Rabson–Mendenhall syndrome, and Leprechaunism (Donohue syndrome). There may be considerable clinical overlap and these syndromes may simply represent varying clinical features from a continuum of severity of receptor dysfunction rather than completely distinct syndromes [155]. Many individuals with insulin receptor defects and severe insulin resistance (men in particular) may not fit into the syndromic descriptions.

Features of the Type A insulin resistance syndrome include severe insulin resistance, acanthosis nigricans, polycystic ovarian disease, hirsutism, and signs of virilization occurring in young females (often termed HAIR-AN syndrome). Those with an underlying insulin receptor mutation are usually slim [156, 157]. The most severe syndrome seen with insulin receptor mutations is

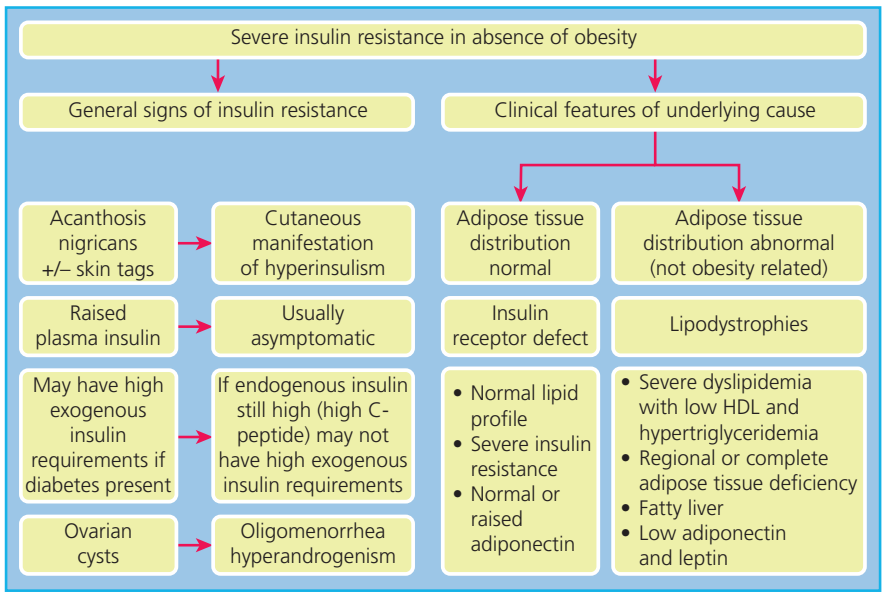

Figure 18.9 Features of monogenic severe insulin resistance.

Leprechaunism (Donohue syndrome), a rare autosomal recessive disorder characterized by low birth weight, growth restriction, disordered glucose homeostasis, characteristic dysmorphic features, and individuals usually do not survive infancy [157, 158].

Rabson–Mendenhall syndrome is an autosomal recessive disorder that is between Leprechaunism and Type A insulin resistance in terms of the severity of insulin resistance. Presentation occurs in childhood with acanthosis nigricans, extreme growth retardation, dysplastic dentition, coarse facial features, lack of subcutaneous fat, and pineal hyperplasia [157, 159, 160]. Reported renal abnormalities include medullary sponge kidney and nephrocalcinosis [159, 160]. There may be paradoxical fasting hypoglycemia at diagnosis but frank diabetes (occasionally with ketoacidosis) develops in later years [161]. Life expectancy is markedly reduced, early death often occurring from complications of diabetes or intractable ketoacidosis.

Differentiating from type 1 and 2 diabetes

The presence of features of insulin resistance in a thin but not an obese individual is suggestive of an underlying insulin receptor gene mutation. Serum adiponectin levels are typically high with insulin receptor mutations whereas they are low in other forms of insulin resistance. It has been suggested that adiponectin levels could be used as a screening test with sequencing of the insulin receptor gene reserved for those cases where adiponectin levels are raised [150, 162, 163].

Unlike T2DM and the lipodystrophies, triglyceride levels with insulin receptor mutations are typically normal [157].

Management

While insulin sensitizers such as metformin and the thiazolidinediones may have a role in management their effect is often limited and insulin therapy is required as β-cell function declines [157]. Glycemic control is often poor despite very high doses of insulin (doses in excess of 500 units/kg/day have been reported). U500 insulin has a role in reducing the insulin volumes required [157, 164]. Insulin-like growth factor I (IGF-I) is capable of stimulating glucose uptake and glycogen storage *in vivo* and has therefore been used in treatment of diabetes caused by insulin receptor mutations. Side effects were frequent in early studies but tolerability may be increased by combining IGF-I with its principal binding protein IGFBP-3 [165].

Inherited lipodystrophies

Lipodystrophies are rare clinically heterogeneous disorders that are characterized by the selective loss of adipose tissue. They are associated with insulin resistance and other features such as diabetes mellitus, acanthosis, dyslipidemia, hepatic steatosis, and (in women) hyperandrogenism, oligomenorrhea, and polycystic ovaries [166]. Lipodystrophies may be inherited or acquired.

Familial partial lipodystrophy

Familial partial lipodystrophies are autosomal dominant disorders associated with the loss of peripheral subcutaneous fat. The two main subtypes result from mutations in *LMNA* and *PPARG*.

Familial partial lipodystrophy associated with *LMNA* mutations (also known as Dunnigan lipodystrophy) results in gradual peripheral subcutaneous fat loss from puberty. This, and the associated muscle hypertrophy, gives a muscular appearance of the arms and legs (Figure 18.10). There may be fat loss from the anterior abdomen and chest and excess fat deposition in the face, neck, and intra-abdominally [167, 168]. Diabetes is common,

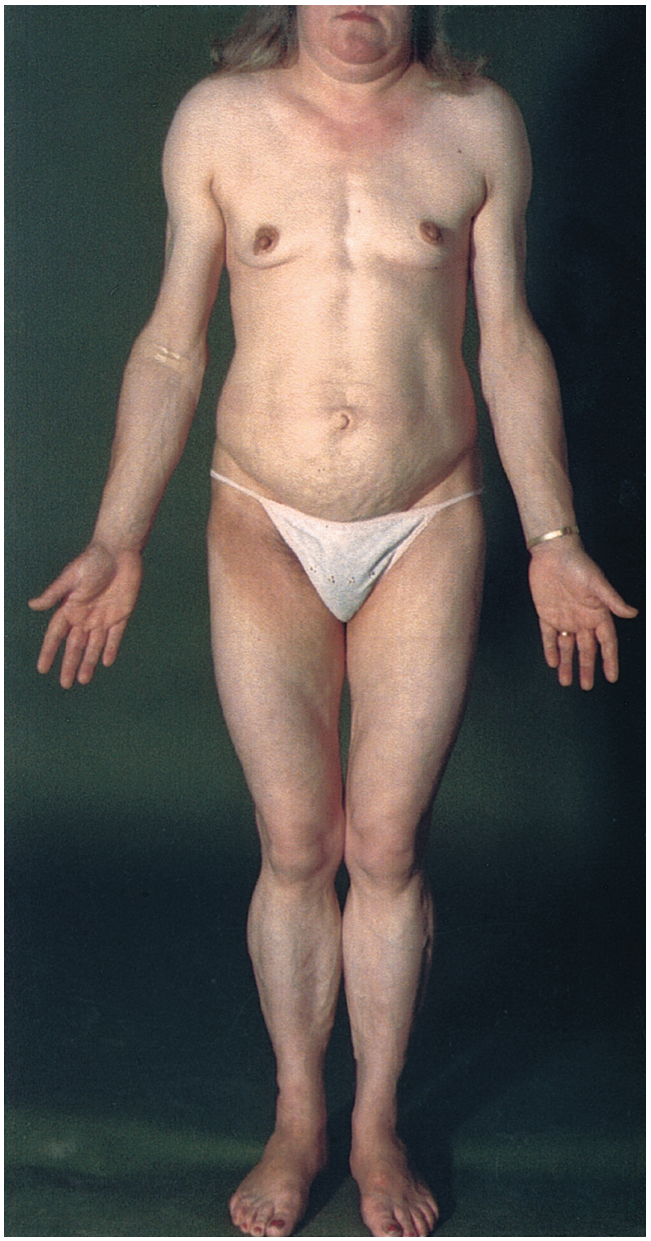

Figure 18.10 Familial partial lipodystrophy in a 46-year-old woman. There is truncal and limb lipodystrophy, preserved facial and neck adipose tissue, muscle hypertrophy and acanthosis apparent in the groin regions.

particularly in women [169]. Hypertriglyceridemia may be marked and associated with pancreatitis. Acanthosis and polycystic ovarian syndrome are relatively uncommon. Although hepatic steatosis may develop cirrhosis appears rare [170, 171]. Cardiovascular mortality is high.

Familial partial lipodystrophy associated with *PPARG* mutations appears to be phenotypically similar to that caused by *LMNA* mutations although hypertension is commoner [172–181].

Diagnosis may be obvious in women but more difficult in men where a muscular appearance of limbs is more usual. Early-onset diabetes in a non-obese individual with hypertriglyceridemia should raise suspicion of lipodystrophy particularly if there is marked peripheral fat loss [182].

Congenital generalized lipodystrophy (Berardinelli–Seip syndrome)

This is a rare (estimated prevalence 1 in 10 million) autosomal recessive disorder characterized by a near complete absence of subcutaneous fat from birth, giving a muscular appearance [166]. Because of the absence of functioning adipocytes, lipids are stored in metabolically active tissues. Those affected have features of severe insulin resistance including often widespread acanthosis, hypertriglyceridemia, and low HDL cholesterol [183]. Hepatic steatosis occurs early and may lead to cirrhosis; hepatomegaly is seen frequently [184–186]. Childhood growth is accelerated and bone age advanced. Diabetes commonly develops during adolescence. Other associated features include acromegaloid features, hypertrophic cardiomyopathy, skeletal muscle hypertrophy, bone cysts, and intellectual impairment [186]. Serum leptin and adiponectin levels are markedly reduced [187].

Three molecularly distinct forms have been identified: congenital generalized lipodystrophy types 1, 2 and 3 resulting from mutations in 1-acylglycerol 3-phosphate-O-acyltransferase 2 (*AGPAT2*), Berardinelli–Seip congenital lipodystrophy 2 (*BSCL2*), and Caveolin-1 (*CAV1*). *AGPAT2* and *BSCL2* account for the majority of cases and have some difference in phenotype. Some people with this phenotype do not have mutations in any of these genes and so it is likely there are further genetic etiologies to be discovered [166, 188, 189].

Other inherited forms of lipodystrophy

Rare subtypes of lipodystrophy associated with dysmorphic features include mandibuloacral dysplasia (lipodystrophy with characteristic skeletal abnormalities), SHORT syndrome (short stature, hyperextensibility of joints, ocular depression, Reiger anomaly, teething delay) and neonatal progeroid syndrome [156].

Management of lipodystrophy

Management should address insulin resistance and the main causes of morbidity and mortality in lipodystrophy which include diabetes and its complications, cardiovascular and cerebrovascular disease, recurrent pancreatitis (as a result of severe hypertriglyceridemia), cirrhosis, and psychologic distress related to appearance [166].

Lifestyle changes are important and should include an extremely low-fat diet (<15% total energy from fat) and increased physical activity. Hypertriglyceridemia that does not respond to lifestyle changes and control of hyperglycemia may require treatment with fibrates and high doses of fish oils. Estrogen replacement including contraceptive pills may exacerbate hypertriglyceridemia and is best avoided.

Glycemic control requires a combination of oral treatments and high-dose insulin in the majority. Metformin is commonly used to improve insulin sensitivity although there are no available trial data in inherited lipodystrophies [182]. Response to thiazolidinediones appears to vary with significant improvements in glycemic control and insulin resistance in some but not in all reported cases [181, 190–195]. Where insulin is required dose requirements may be very high and U500 insulin is appropriate. Where proteinuric renal disease develops the threshold for renal biopsy should be low as non-diabetic renal disease (e.g. membranoproliferative glomerulonephritis and focal segmental glomerulosclerosis) appears to be commoner than diabetic nephropathy [196].

Levels of the adipocytokine leptin are markedly reduced in severe lipodystrophies. Leptin replacement has been associated with marked improvements in glycemic control and hypertriglyceridemia in a number of cases of both generalized and partial inherited lipodystrophy [197–203] and may also improve hepatic steatosis [204, 205].

Other monogenic conditions associated with insulin resistance

Other monogenic conditions associated with insulin resistance either have marked obesity (e.g. Alström and Bardet–Biedl syndromes), neurologic disease including myotonic dystrophy and Friedreich ataxia or rapid aging (e.g. Werner syndrome) [206].

Conclusions

Monogenic diabetes results from single gene changes that affect β-cell function or insulin sensitivity. Correct diagnosis can help define prognosis and the best treatment and allow screening of family members. Diagnostic testing is now widely available and should be considered where presentation is atypical for T1DM or T2DM, where there is an autosomal dominant family history, where there are characteristic associated features and in all cases where diabetes has been diagnosed within the first 6 months of life.

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19 Drug-Induced Diabetes

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Key points

- Many commonly prescribed medications can contribute to hyperglycemia or cause overt diabetes in predisposed individuals.
- The main mechanism by which glucocorticoids cause hyperglycemia is by reducing insulin sensitivity in the liver, skeletal muscle and adipose tissue in a dose-dependent fashion.
- Second-generation antipsychotic use requires scheduled monitoring of glucose, lipids, blood pressure, and body mass index.
- Although combined oral contraceptives are associated with metabolic abnormalities, their use is still recommended for women with type 1 or type 2 diabetes without vascular complications and in women with a history of gestational diabetes.
- Postmenopausal women can safely take menopause hormone therapy without adversely affecting glucose homeostasis or triggering diabetes.
- Menopause hormone therapy has minimal impact upon established type 1 or type 2 diabetes in postmenopausal women. Continued surveillance of glycemic control is prudent in these women and appropriate adjustments should be made to their antidiabetes drug regimens as needed.
- Clinicians need to be aware that the thiazide diuretics can affect glucose homeostasis in a dose-dependent manner but the effect appears to be modest. Maintaining normokalemia is the best defense against this potential metabolic consequence of thiazide use.
- Whether beta-blockers affect glucose homeostasis or contribute to the development of overt diabetes is inconclusive. Beta-blockers with vasodilating properties, such as carvedilol and nebivolol, are the preferred choices for persons with diabetes or those at significant risk for diabetes, unless contraindicated by comorbidities such as asthma.
- Statins appear to increase insulin resistance and decrease insulin secretion, with small increases in HbA_{1c} and fasting glucose.
- Hyperglycemia and diabetes have been reported with the protease inhibitors and some of the nucleoside reverse-transcriptase inhibitors (zidovudine, stavudine, and didanosine). The nucleoside reverse-transcriptase inhibitors can cause insulin resistance, promote lipodystrophy, and pancreatitis.
- Fluoroquinolone-associated dysglycemia appears to be much more common with gatifloxacin compared to levofloxacin. Hyperglycemia tends to occur within 1 to 2 weeks of therapy initiation. Any changes in glycemic control can be managed with careful adjustment of the antidiabetes regimen and continued blood glucose monitoring.
- The calcineurin inhibitors, cyclosporine and tacrolimus, are associated with post-transplant diabetes. Risk factors include older age, obesity, corticosteroid use, non-Caucasian race, hepatitis C, and genetic determinants.
- Diazoxide is a long-known cause of drug-induced hyperglycemia and even diabetic ketoacidosis. Its hyperglycemic effects have been purported to result from impaired insulin secretion, increased glucose production, and decreased peripheral glucose utilization. Evidence suggests that insulin secretagogues (including the incretin mimetics) may be the drugs of choice to manage this condition.
- Whenever possible exposure to drugs that could affect glucose regulation or glycemic control should be limited. If a precipitant drug cannot be avoided, careful monitoring for the occurrence of hyperglycemia is warranted. If a morbid event occurs, the dose should be reduced or the drug discontinued.

Introduction

It has been notably recognized that drugs can do great good but the potential also exists for drugs to do great harm. Drug therapy can worsen an underlying disease state resulting in therapeutic challenges for the clinician. Diabetes is one such example where various drugs can worsen glycemic control and even contribute to hypoglycemic episodes. Importantly, a number of commonly used medications can also predispose the individual to the development of hyperglycemia and even overt diabetes. Corticosteroids, second-generation antipsychotics, diazoxide, statins, oral contraceptives, and niacin are just a few examples of drugs that have been associated with hyperglycemia or drug-induced diabetes. Various mechanisms have been proposed for drug-induced hyperglycemia and include insulin resistance, decreased insulin secretion, decreased glucose uptake, pancreatitis, weight gain, and increased hepatic gluconeogenesis. Whatever

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Table 19.1 Other medications that can induce hyperglycemia [1–5].

Antidepressants
Gonadotropin-releasing hormone agonists
Fish oil
Growth hormone
Interferons
L-asparaginase
Mammalian target of rapamycin (mTOR) inhibitors (everolimus, sirolimus, temsirolimus)
Megesterol acetate
Niacin
Phenytoin
Rifampin
Ritodrine
Somatostatin analogs—most significant with pasireotide
Terbutaline
Thalidomide

the cause, the clinician should be ever vigilant to the potential for drug-induced dysglycemia taking into consideration patient and drug factors and be prepared to manage its consequences in the appropriate manner.

This chapter will describe selected drug classes and individual drugs that have been associated with hyperglycemia or overt diabetes. Attention will be given to predisposing factors along with the attendant pathophysiologic characteristics utilizing the relevant literature and emerging evidence. The focus will be on medications that are commonly prescribed and those with clear and significant potential for the development of diabetes. Other medications that can induce hyperglycemia are listed in Table 19.1 [1–5]. The chapter will conclude with a discussion of strategies to prevent and manage drug-induced dysglycemia.

Glucocorticoids

Of all the medications that can potentially induce hyperglycemia, glucocorticoids are the drug class that most consistently leads to this effect. Glucocorticoids have been reported to increase blood glucose when administered via numerous routes. They most commonly induce hyperglycemia when administered intravenously or orally, at supraphysiologic doses because of the high bioavailability potential for these routes. They have also been reported to increase blood glucose when administered by the intra-articular and epidural routes [6, 7], and some, but not all, studies found that inhaled corticosteroid led to hyperglycemia [8, 9]. A case-control study of a large primary care registry in the United Kingdom found no association between inhaled, injected, ophthalmic, or topical glucocorticoids with incident diabetes but oral glucocorticoids are associated with up to 2% of cases of new-onset diabetes. The authors acknowledged the limitations of the database which may have provided an underestimation of the risk [10]. Other cohort studies have reported that the odds ratio for glucocorticoids-induced new-onset diabetes ranges from 1.36 to 2.31 [11].

The main mechanism by which glucocorticoids cause hyperglycemia is through reduction of insulin sensitivity in the liver, skeletal muscle and adipocyte, by approximately 50–70%, which appears to be dose-dependent [11–15]. Glucocorticoid administration leads to decreased glucose transport 4 (GLUT-4) expression and migration, decreased glycogen synthesis, and increased hepatic gluconeogenesis [16]. They have also been shown to decrease insulin production and secretion [17, 18].

The most common clinical presentation of glucocorticoid-induced hyperglycemia is a rise in the blood glucose starting in mid-morning and continuing throughout the day until bedtime [19]. Therefore, this adverse drug reaction may not be detected if only the fasting blood glucose is monitored. Oral glucocorticoids are typically administered so that they mimic the physiologic pattern of endogenous cortisol secretion, and once daily glucocorticoids such as prednisone and prednisolone are administered in the morning. Taking into account the peak effect of these medications after a dose (e.g. peak effect of prednisone at 4–6 hours), checking a 1– to 2-hour post-lunch or a pre-dinner blood glucose starting a few days after initiation of treatment will enable detection of any hyperglycemia [11, 18, 19]. An elevation in the fasting blood glucose can occur with higher doses of once-daily glucocorticoids (prednisone 40 mg or equivalent) and with twice-daily administration [19]. People with pre-existing diabetes should monitor their blood glucose more frequently during the course of glucocorticoid treatment and all patients should also be advised to monitor for symptoms of hyperglycemia. As of the time of this writing, there are no published guidelines on the treatment of glucocorticoid-induced hyperglycemia with diabetes medications although a number of strategies have been advocated by various authors [11, 19].

Oral agents that enhance insulin sensitivity (e.g. metformin, thiazolidinediones) or stimulate insulin secretion (e.g. sulfonylureas, non-sulfonylurea secretagogues) address the mechanisms underlying glucocorticoid-induced hyperglycemia. However, concerns about pre-existing renal impairment and other risk factors for lactic acidosis, long duration of action leading to hypoglycemia especially overnight, or slow onset of effect plus weight gain and edema, make the use of metformin, sulfonylureas, and thiazolidinediones, respectively, not an ideal option in some patients [11, 19]. The non-sulfonylurea secretagogues and dipeptidyl peptidase-4 inhibitors may be better choices given their quicker onset of action, effect on postprandial hyperglycemia, and lower potential for hypoglycemia [18]. Insulin therapy offers the flexibility of matching the onset, peak, and duration of action to the pattern and degree of hyperglycemia the individual is experiencing; furthermore the dose can be more easily adjusted when the glucocorticoid dose is changed. Neutral protamine Hagedorn (NPH) insulin or a premixed insulin containing NPH can be the best choice for those taking an intermediate-acting glucocorticoid (e.g. prednisone) in the morning [11, 18, 19]. When given once-daily at breakfast, NPH's peak effect starting at 4 hours after

administration and duration of 10–16 hours closely matches that of the peak effect and duration of prednisone. In individuals on a long-acting glucocorticoid such as dexamethasone, twice-daily dosing of intermediate-acting glucocorticoids, and higher doses (e.g. 40 mg or higher of prednisone or equivalent), fasting hyperglycemia will likely also be seen and a long-acting insulin (insulin glargine or insulin detemir), plus prandial insulin, will likely be needed [18, 19]. Because many courses of treatment with glucocorticoids consist of an initial high dose with a gradual taper to physiologic level and then discontinuation, careful monitoring of blood glucose and subsequent insulin dose adjustments may be necessary to avoid hypoglycemia as the medication is being withdrawn.

Table 19.2 Monitoring schedule for atypical antipsychotics.

Measurement	Baseline	6 weeks	12 weeks	At least annually
Weight and body mass index	X	Measure weekly in first 6 weeks	X	X
Waist circumference	X	X	X	X
Fasting glucose	X	X	X	X
Fasting lipid profile	X	X	X	X
Blood pressure	X	X	X	X

Source: NICE clinical guideline 178 [39].

Second-generation antipsychotics

The second-generation antipsychotics (SGA), also known as atypical antipsychotics, are another drug class with well-known hyperglycemic effects (see Chapter 57). Numerous case reports as well as studies of various SGAs worsening of existing diabetes, inducing new-onset diabetes, and hyperglycemic crises exist [20–23]. SGAs can cause blood glucose elevations both acutely and chronically [24–26]. Hyperglycemia has been reported for all currently marketed SGAs in the USA, although the degree of severity varies considerably [25, 27–29]. Olanzapine and clozapine appear to have the highest propensity for this adverse drug reaction [25, 26, 30]. SGAs with the lowest potential for hyperglycemia include the newer SGAs, specifically aripiprazole, ziprasidone, paliperidone, and lurasidone, although data and clinical experience with the newest agents (asenapine, iloperidone, lurasidone) are still limited [27–29, 31]. Quetiapine and risperidone appear to have moderate potential for hyperglycemia relative to the other SGAs [28].

The mechanism of SGA-induced hyperglycemia has yet to be fully elucidated but is likely multifactorial. SGA-induced weight gain is thought to be an important contributor, and SGAs with the highest potential for weight gain (olanzapine and clozapine) are also associated with the most clinically significant hyperglycemia. The binding of SGAs to histamine-1, serotonin, norepinephrine, and dopamine receptors, at different affinities depending on the agent, affects weight gain through regulation of hunger and satiety [28]. However, several studies also demonstrated that hyperglycemia and insulin resistance occur with some SGAs regardless of body weight and food intake [32, 33]. Animal studies also suggest that SGAs may induce hyperglycemia through inhibition of insulin secretion by antagonism of alpha-1 adrenergic, muscarinic (M_3), and serotonergic ($5HT_2$) receptors [34, 35].

Similar to glucocorticoids, SGA administration can lead to not only hyperglycemia but also weight gain and dyslipidemia, which further contribute to cardiovascular risks. These adverse drug reactions, along with the higher prevalence among people with psychiatric illness of being overweight or obese, physically inactive, and smoking, make monitoring and prompt treatment crucial [36]. A large meta-analysis encompassing 25,692 people with schizophrenia found an overall prevalence of 32.5% for metabolic syndrome, and 51.9%, 28.2%, 27.9%, and 20.2% for clozapine, olanzapine, risperidone, and un-medicated patients, respectively [37]. Recommendations for monitoring for the development of hyperglycemia, weight gain, and dyslipidemia were first published in 2004 by the American Diabetes Association, American Psychiatric Association, American Association of Clinical Endocrinologists, and the North American Association for the Study of Obesity [28] but other national and international guidelines have also emphasized the importance of regular screening for glucose and lipid abnormalities [38, 39]. In addition to obtaining personal and family history of diabetes, dyslipidemia, hypertension, obesity, and cardiovascular disease (CVD), these guidelines also recommend obtaining baseline measurement for glucose, lipids, blood pressure, and body mass index with periodic reassessment. A proposed monitoring schedule can be found in Table 19.2 [40]. Specific to fasting plasma glucose, this should be monitored at 12 weeks then annually. In addition, if the person gains 5% or more of their baseline weight during treatment, it is recommended that clinicians consider a switch to another SGA [28]. Several studies have shown an improvement in glucose control after switching from olanzapine to aripiprazole [41]. However, changing to another antipsychotic may not always result in equivalent control of the mental illness and other measures (therapeutic lifestyle changes, diabetes medications) may need to be employed.

Oral contraceptive agents

Combination oral contraceptive (COCs) preparations are used by more than 100 million women worldwide [42]. These products contain one of two estrogens, mestranol or ethinyl estradiol and a variety of progestins (e.g. norethindrone, norgestrel, norgestimate) in monophasic, biphasic, and triphasic formulations. Despite their proven efficacy, a number of adverse events have been ascribed to their use (especially the estrogen component) including metabolic abnormalities such as glucose intolerance

and overt diabetes. The causes of COC-induced dysglycemia have been historically associated with alterations in insulin sensitivity and insulin secretion. However, current evidence does not support a significant effect of COCs on glucose metabolism or homeostasis and the development of clinical diabetes [43]. Interestingly, a recent analysis of data from the Missouri Pregnancy Risk Assessment Monitoring System (PRAMS) in the United States suggested that women with gestational diabetes were nearly 1.5 times more likely to have used hormonal contraception before conception [44]. A recently published Cochrane Database systematic review sought to answer the question of whether COCs adversely affected carbohydrate metabolism in women without diabetes and in those who were overweight. In analyzing 31 trials that met inclusion criteria, there were no significant differences in carbohydrate metabolism among the different preparations. Surrogate endpoints used included fasting and 2-hour postprandial glucose, insulin and glucose area-under-the curve and glycated hemoglobin A_{1C} (HbA_{1c}) levels. Due to various study design deficiencies, the authors were unable to elucidate the metabolic risk of oral contraceptives in obese women [45].

Whereas the risk of dysglycemia from COCs in women without diabetes remains negligible, metabolic effects arising from the use of these drugs in women with type 1 or type 2 diabetes can be consequential. Similarly, unplanned pregnancy in this same population also has significant maternal and fetal consequences especially when glycemic control is poor. Thus contraceptive options must be chosen that do not contribute to an excess metabolic and cardiovascular risk for these women. Based upon the eligibility criteria for contraceptive use published by the World Health Organization (WHO) in 2009 (adapted by the USA in 2010), the use of COCs is favored in women with type 1 or type 2 diabetes without vascular complications and in women with gestational diabetes [43]. A 2013 Cochrane Database systematic review failed to show significant differences between progestin-only, combination hormonal and non-hormonal contraceptives on carbohydrate and lipid metabolism and vascular complications in women with type 1 or type 2 diabetes [46]. These results were ascribed to various methodological deficiencies making interpretation problematic.

Menopause hormone therapy

Menopause hormone therapy (MHT) or hormone replacement therapy (HRT) typically involves the administration of oral estrogens alone or in combination with an oral progestogen for the treatment of postmenopausal symptoms especially hot flashes, vaginal atrophy, and mood instability. Transdermal and intravaginal formulations are also prescribed. Given the potential for COCs to impact glucose homeostasis and glycemic control in women with diabetes, the use of MHT in postmenopausal women can be viewed with similar concerns, especially when the doses are administered by the oral route. The results of two published randomized placebo-controlled trials have dispelled the concern about whether MHT adversely impacts glucose metabolism or precipitates incident diabetes. The Heart and Estrogen/Progestin Replacement Therapy Study (HERS) studied nearly 2800 postmenopausal women with coronary heart disease who took MHT for approximately 4 years [47]. At the completion of the trial, there was no significant difference in the fasting blood glucose levels between women with and without diabetes and those with impaired fasting glucose. Importantly, women taking MHT had a 35% reduction in incident diabetes compared to those in the placebo arm of the trial (NNT = 30 over 4 years). Likewise, women enrolled in the Women's Health Initiative Hormone Trial and receiving conjugated equine estrogens plus medroxyprogesterone were found to have a 21% lower risk of diabetes ($p = 0.03$) at 1-year follow-up compared to placebo controls (NNT = 143 over 5.6 years) [48]. This difference in study results was ascribed to decreases in insulin resistance. The aforementioned findings suggest that postmenopausal women can safely take MHT without adversely affecting glucose homeostasis or triggering diabetes.

Whether women with diabetes can safely take MHT remains more uncertain and untested. A recently published Cochrane Database systematic review showed that glycemic control was not impacted by MHT in women with type 1 diabetes [49]. However, this finding was based upon only one underpowered placebo-controlled randomized clinical trial making the results questionable. Previous studies evaluating the effects of MHT on women with type 2 diabetes suggest improved glycemic control with its use [50, 51]. In a large observational study, investigators evaluated the impact of MHT (opposed and unopposed estrogen therapy) on HbA_{1C} in women with type 2 diabetes. HbA_{1c} was significantly lower in women taking MHT versus those not on MHT (age-adjusted mean ± SE: 7.9% ± 0.03% (63 mmol/mol) vs. 8.5% ± 0.02% (69 mmol/mol), respectively; $p = 0.0001$) [51]. Likewise, an assessment of data from the United States NHANES III (National Health and Nutrition Examination Survey, 1988–1994) indicated that postmenopausal women currently taking MHT had lower fasting blood glucose and HbA_{1c} levels versus women who had never taken MHT 112 versus 154 mg/dL (6.2 mmol/L vs. 8.5 mmol/L) and 6.0% versus 7.1% (42 mmol/mol vs. 54 mmol/mol), respectively. Whereas these aforementioned observational studies cannot support causation, the evidence does promote the notion that MHT has minimal impact upon established type 2 diabetes in postmenopausal women. Continued surveillance of glycemic control is prudent in these women and appropriate adjustments should be made to their antidiabetes drug regimens as needed.

Thiazide diuretics

The thiazide diuretics have been the mainstay for the management of hypertension for over 50 years [52]. Early on it was recognized that this drug class could negatively impact glycemic control in persons with diabetes [53]. Despite their widespread use and clinical utility, questions continue to be raised regarding their potential

effect on glucose homeostasis and glycemic control in those with established diabetes. The Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT), a very large landmark study in hypertension management, found significantly more new-onset diabetes (FBG $\geq$ 126 mg/dL; 7 mmol/L) with chlorthalidone compared to amlodipine and lisinopril at the 4-year follow-up period (11.6%, 9.8%, and 8.1%, respectively) [54]. In addition, participants with pre-existing diabetes or those who developed diabetes during the original Systolic Hypertension in the Elderly Program (SHEP) were evaluated as part of a long-term follow-up study (14.3 years) [55]. Investigators found that persons with diabetes assigned to chlorthalidone had lower cardiovascular and total mortality rates compared to placebo controls (HR 0.805; 95% CI: 0.680–0.952) [55]. These representative studies, whereas interesting in their findings, provide little resolution to the ongoing debate surrounding thiazide-induced dysglycemia.

Historically, thiazide-induced dysglycemia has been connected to alterations in potassium balance, namely hypokalemia. Since insulin secretion is linked, in part, to an accumulation of intracellular potassium within the pancreatic β cell, potassium loss would impair insulin release resulting in hyperglycemia. In an effort to substantiate this long-held belief, a group of investigators reviewed pertinent intervention trials using thiazides from 1966–2004 that measured serum potassium and glucose levels [56]. Fifty-nine trials met inclusion criteria. Analysis of the trial data supported an inverse relationship between potassium balance and blood glucose levels. However, the effects on blood glucose were modest with an average increase of 7.1 mg/dL ± 7.38; 0.4 mmol/L ± 0.4) [56]. In a subgroup analysis of the above-mentioned SHEP trial, for every 0.5 mEq/L decrease in serum potassium there was a corresponding 45% increase in incident diabetes risk (95% CI: 24–70%; p <0.001) [57]. This association was only evident during the first year of treatment with chlorthalidone. In a more recent subgroup analysis, no correlation was found between fasting serum glucose and serum potassium levels in people with hypertension receiving hydrochlorothiazide alone and when added to atenolol [58].

Clinicians need to be aware that the thiazide diuretics can affect glucose homeostasis in a dose-dependent manner but the effect appears to be modest at best. Maintaining normokalemia is the best defense against this potential metabolic consequence of thiazide use [57]. Any alteration in glycemic control can be managed with careful adjustment of the antidiabetes regimen and continued blood glucose monitoring.

Beta-adrenoceptor antagonists

Beta-blockers are widely used to treat a variety of conditions including hypertension, angina, arrhythmias, and congestive heart failure. Despite their benefits, these drugs can pose problems in persons with pre-established diabetes. Their propensity to mask the adrenergically mediated signs and symptoms of hypoglycemia and delay its recovery is well known. Theoretically, non-selective beta-blockers could also worsen peripheral vascular disease via unopposed alpha receptor stimulation of the vasculature. Whether beta-blockers affect glucose homeostasis or contribute to the development of overt diabetes is less certain. In an older prospective cohort study, the use of beta-blockers was associated with a 28% increased risk of new-onset diabetes (relative hazard, 1.28; 95% CI: 1.04–1.57) [59]. A more recent systematic literature review was undertaken to examine the effects of various beta-blockers on glucose homeostasis, insulin sensitivity, and diabetes risk [60]. Whereas the evidence supporting an association between the administration of selective and non-selective beta-blockers and diabetes-risk is inconclusive, beta-blockers with alpha-blocking properties (e.g. carvedilol) may have a reduced or no risk for diabetes [61]. This discrepancy has been attributed to differences in effects on insulin sensitivity compared to conventional beta-blockers. These findings warrant consideration of a beta-blocker with vasodilating properties, such as carvedilol and nebivolol, as the preferred choice for persons with diabetes or those at high risk for diabetes [60].

HMG CoA reductase inhibitors

The HMG CoA reductase inhibitors, commonly known as statins, have been the mainstay of hyperlipidemia and cardioprotection for over two decades but their hyperglycemic potential has only recently been reported. The FDA changed the product labeling of statin medications to include the findings of elevated fasting glucose and HbA_{1c} in early 2012 [62]. Statins appear to increase insulin resistance and decrease insulin secretion, with small increases in HbA_{1C} and fasting glucose [63]. A meta-analysis reported that the lowest risk for new-onset diabetes is with pravastatin at 40 mg/day (OR 1.07; 95% CI: 0.86–1.3), followed by atorvastatin 80 mg/day (OR 1.15; 95% CI: 0.9–1.5), and highest with rosuvatatin 20 mg/day (OR 1.25; 95% CI: 0.82–1.9) when compared to placebo [64]. Another meta-analysis found that the risk of incident diabetes is 9% (OR 1.09; 95% CI: 1.02–1.17) and that treatment of 255 people for 4 years would result in one additional case of diabetes [65]. The authors also reported that statin therapy would prevent 5.4 major coronary events (coronary heart disease death and non-fatal myocardial infarction) in these 255 individuals and that the potential benefit would be expected to be greater if prevention of strokes and revascularization was also taken into account [65]. The JUPITER trial reported that, for those with one or more diabetes risk factors, rosuvastatin was associated with a 28% increase in diabetes but 134 cardiovascular events or deaths were avoided for every 54 new cases of diabetes [66]. The 2015 American Diabetes Association Standards of Medical Care in Diabetes guideline noted that the absolute risk of rosuvastatin-induced diabetes is small (1.5% with rosuvastatin compared to 1.2% with placebo over 5 years) and recommends statin therapy for most people with diabetes with overt CVD or CVD risk factors [67].

Anti-retroviral therapy for human immunodeficiency virus (HIV)

The pharmacologic treatment of HIV-1 currently includes nucleoside reverse-transcriptase inhibitors (NRTI), non-nucleoside reverse-transcriptase inhibitors (NNRTI), protease inhibitors (PI), integrase strand transfer inhibitors, and entry inhibitors. Hyperglycemia and diabetes have been reported with the PI and some of the NRTIs (zidovudine, stavudine, and didanosine) [68]. These NRTIs can cause insulin resistance, promote lipodystrophy, and pancreatitis [1, 69, 70]. The PIs induce hyperglycemia through increasing insulin resistance and the development of lipodystrophy [71–77]. *In vitro* studies also demonstrated that some PIs can decrease insulin secretion [73, 77]. PI-induced lipodystrophy (Figure 19.1) is characterized by lipohypertrophy (resembling central obesity) with or without lipoatrophy, manifesting as peripheral fat loss (particularly in the extremities, face, and buttocks) [78]. Lipodystrophy, insulin resistance, hyperglycemia, and the dyslipidemia (elevated triglyceride and total cholesterol, reduced high-density lipoprotein cholesterol) associated with PIs can increase the risk of cardiovascular events in treated individuals [79, 80].

Pentamidine

Pentamidine is an antifungal/antiprotozoal agent which is FDA-approved for the treatment and prevention of *Pneumocystis jirovecii* pneumonia commonly associated with HIV-infection and

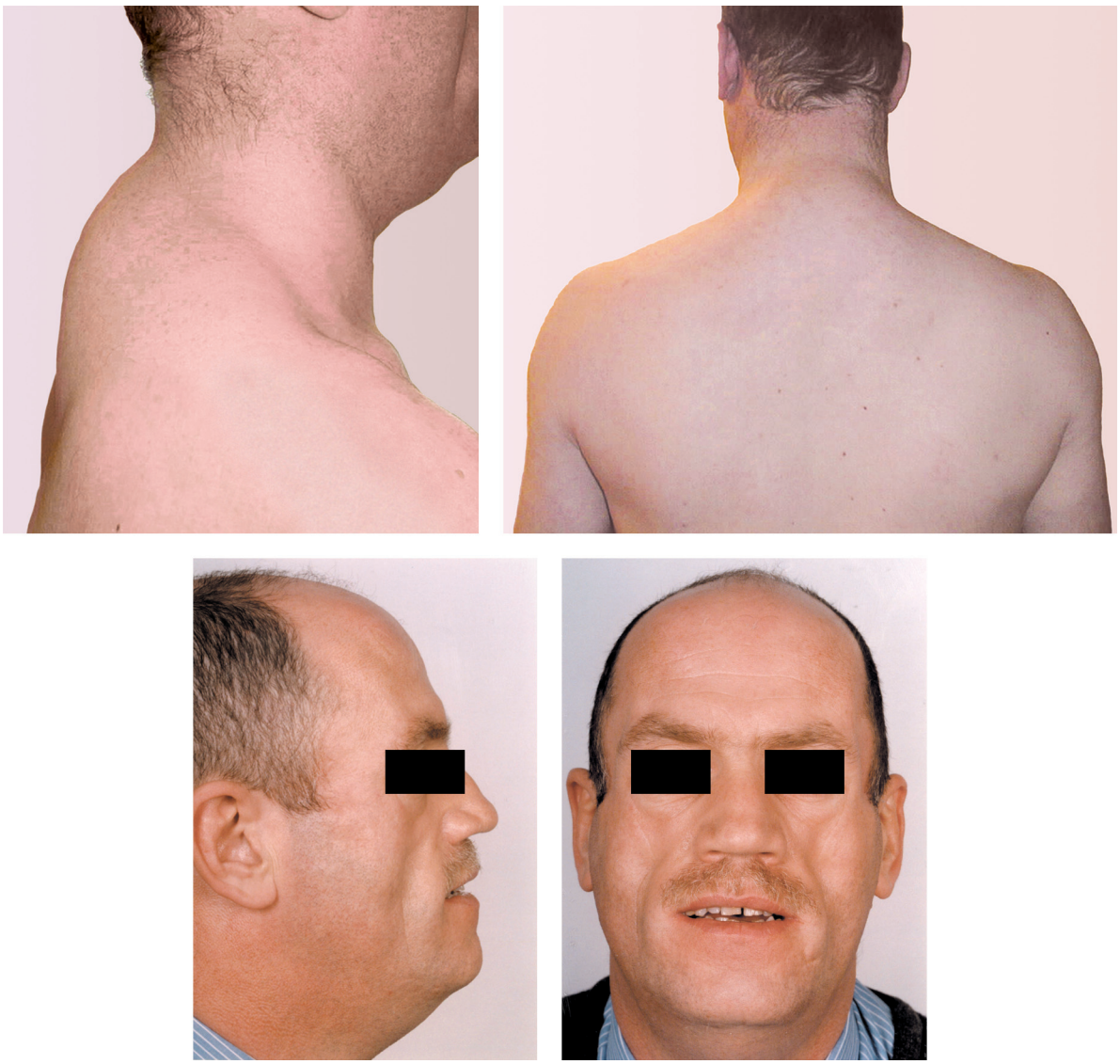

Figure 19.1 Protease inhibitor-induced lipodystrophy. (a,b) "Buffalo hump" caused by nuchal fat deposition. (c,d) Facial fat atrophy. Source: Courtesy of Professor Munir Pirmohamed, University of Liverpool, UK.

those with immunodeficiency or malignancy. The drug is usually administered intravenously or via inhalation for adults and children alike. Importantly, the drug has the propensity to cause both hypoglycemia and hyperglycemia. Its well-known dysglycemic effects are due to impaired insulin secretion and direct cytotoxicity and β-cell apoptosis. In 128 immunocompromised patients with *P. jirovecii* pneumonia, pentamidine was associated with seven cases of hypoglycemia, 23 cases of overt diabetes, and 18 cases of hypoglycemia followed by diabetes. Seventy-five percent of the patients received the drug parenterally. Hyperglycemia was noted within an average of 52 days (20–90) following pentamidine administration. Insulin was required in 63% of those with diabetes. Risk factors for the development of diabetes included high doses, impaired renal function, and poor clinical status of the patient [81]. In a retrospective chart review of pentamidine-associated adverse drug reactions in 106 HIV-infected persons, 9 persons experienced hyperglycemia with average blood glucose levels of 369 mg/dL (20.4 mmol/L) and a mean time of onset of 14 days [82]. Providers need to be aware of the development of hyperglycemia with pentamidine and monitor patients accordingly for this late-appearing adverse drug reaction.

Fluoroquinolones

The fluoroquinolone class of antimicrobial agents have been available for over 50 years. Despite their clinical utility, a variety of well-known adverse effects have been reported, most noteworthy being arthropathy and QT-prolongation [83]. In retrospective analyses, serious dysglycemia (both hypoglycemia and hyperglycemia) has also been associated with their use culminating in the voluntary removal of gatifloxacin from the US and Canadian markets in 2006 owing to a significant risk of hospitalization for hypoglycemic or hyperglycemic episodes [84, 85]. Although oral gatifloxacin is no longer available from many markets (United States, Canada, Japan, etc.), it is still sold around the world and is available via online distributors.

Whereas many drug adverse effects are a class effect, fluoroquinolone-associated dysglycemia appears to be much more common with gatifloxacin compared to levofloxacin. Ciprofloxacin poses little or no risk [85]. Of the currently available fluoroquinolones in the USA, moxifloxacin appears to have the highest likelihood for causing hyperglycemia compared to levofloxacin or ciprofloxacin [86]. The etiology of fluoroquinolone-induced hyperglycemia is unclear but possible contributing factors include a history of diabetes, failure to adjust doses in renal insufficiency, acute illness, and age. Recent animal studies suggest that hyperglycemia results from increased drug accumulation in the pancreas of individuals with diabetes, histamine-associated release of the counter-regulatory hormone epinephrine, and the prolonged secretion of GLP-1 which inhibits insulin secretion and production [87–89].

The risk of hyperglycemia from fluoroquinolone use (with and without diabetes) warrants careful surveillance by clinicians and patients alike. Hyperglycemia tends to occur within 1–2 weeks of therapy initiation. Any changes in glycemic control can be managed with careful adjustment of the antidiabetes regimen and continued blood glucose monitoring. Likewise, hypoglycemic signs and symptoms must be verified and managed accordingly. Adjustments of oral hypoglycemic and insulin therapy may be required.

Calcineurin inhibitors

There are various classes of drug that are used as immunomodulators to combat rejection following organ transplantation or to manage autoimmune diseases and other inflammatory conditions. One such class is the calcineurin inhibitors. Well-known representative examples include cyclosporine and tacrolimus. Calcineurin is a protein that is involved in the production of the cytokine interleukin-2 (IL-2) by T-helper cells. IL-2 is responsible for T-cell differentiation which is important in the maintenance of cellular immunity.

It had been recognized for many years that transplant recipients suffered from glucose intolerance and also developed type 2 diabetes [90]. At that time several associated risk factors were implicated in the development of post-transplant hyperglycemia or diabetes including the widespread use of corticosteroids in this patient population. In addition to the transplant itself, several immunosuppressant agents administered to counteract rejection were also implicated, namely cyclosporine and tacrolimus [90]. The prevailing belief that cyclosporine is less likely to impair glucose homeostasis versus tacrolimus has been questioned [91]. Alterations in insulin sensitivity and impaired β-cell function are cited as causative factors in the development of glucose intolerance. However, recent evidence corroborates findings that defective insulin secretion is the primary pathologic defect [92]. Whether cyclosporine has any advantages over tacrolimus in managing transplant recipients with pre-existing type 2 diabetes has recently come into question yet remains controversial [93, 94].

Risk factors for post-transplant diabetes (PTDM) include older age, obesity, corticosteroid use, non-Caucasian race, hepatitis C, and genetic determinants [95]. Glucose intolerance or overt diabetes tends to occur within 6 months of immunosuppressant therapy. Clinicians need to be aware of patient risk factors and aggressively manage dysglycemia when it occurs. Inattention to PTDM can result in graft failure and other diabetes-related complications [95]. The optimal therapeutic approach remains to be defined but emerging evidence suggests that insulin secretagogues (including the incretin-mimetics) may be the drugs of choice [95, 96].

Diazoxide

Diazoxide is a thiazide-like drug that had been in clinical use for over 40 years for the management of hypertensive emergencies and hyperinsulinemic hypoglycemia (secondary hypoglycemia). At present, the drug is only available as an oral suspension for

the treatment of secondary hypoglycemia (e.g. insulinoma, islet cell hyperplasias). Importantly, it has been long recognized as a cause of drug-induced hyperglycemia and even diabetic ketoacidosis [97]. Its hyperglycemic effects have been purported to result from impaired insulin secretion, increased glucose production, and decreased peripheral glucose utilization [98, 99]. Diazoxide's ability to inhibit insulin secretion results from "opening" the K_{ATP} channel in the β cell of the pancreas. This ability to inhibit insulin secretion may prove useful in the management of type 1 and type 2 diabetes by preserving β-cell function [100]. Likewise, diazoxide may improve hypoglycemic unawareness via opening SUR1 selective K_{ATP} channels in the central nervous system [100].

Prevention and treatment strategies

The old adage that an ounce of prevention is worth a pound of cure is germane to any discussion involving drug-induced dysglycemia. Clinicians need to be sensitized to the reality that drug therapy may precipitate hyperglycemia in predisposed individuals as well as lead to overt diabetes mellitus. It may be best to avoid precipitant drugs whenever possible and choose more appropriate alternatives. When evaluating a possible case of drug-induced dysglycemia, a careful review of prescription and non-prescription (over-the-counter) medications as well as herbal products and dietary supplements can reveal possible offenders. In addition to a thorough drug history, the clinician should also evaluate the patient's drug regimen and comorbid conditions that may affect the pharmacokinetics or pharmacodynamics of the suspected drug. When drug–drug interactions are suspected, a variety of resources are available to the clinician to facilitate their evaluation. These include various compendia, online references, smart phone applications, professional colleagues, and drug and health information centers. As with any reference tool, it is important to corroborate the information found using a second source. This ensures that the information is accurate and reliable.

Clinicians are often stymied when assessing non-prescription medication by the sheer number of products available for consumption by the patient. One can overcome this fact by employing a review of systems approach akin to asking patients about organ system-based complaints as part of a medical history. In this systematic approach, major product categories are captured and evaluated by asking "head-to-toe" questions. This method has been previously published if more information is needed [101].

Whenever possible limit a patient's exposure to drugs that could affect glucose regulation or glycemic control. Careful attention should be paid to limiting the numbers of drugs, as well as the doses and duration of therapy whenever possible. Baseline data such as weight and fasting blood glucose levels should be obtained when appropriate. This is especially important in people taking more than one medication with the potential for hyperglycemia, prescribed a high dose of the medication, taking concomitant drugs that can increase the concentration or duration of the medication, or those with other risk factors for diabetes (Table 19.3) [1, 67]. Importantly, prospective monitoring of high-risk individuals should be an ongoing process.

Table 19.3 Risk factors for diabetes according to the American Diabetes Association [67].

Age ≥ 45 years
Family history (first-degree relative) of diabetes
Race/ethnicity (e.g. African Americans, Latino, Native Americans, Asian Americans, and Pacific Islanders)
Physical inactivity
Overweight or obese (BMI ≥ 25 kg/m^2 or ≥ 23 kg/m^2 in Asians)
Hypertension (≥140/90 mmHg in adults)
High density lipoprotein cholesterol <35 mg/dL (0.90 mmol/L) and/or a triglyceride level >250 mg/dL (2.82 mmol/L)
History of cardiovascular disease
History of gestational diabetes mellitus or delivery of a baby weighing >9 lbs (>4.1 kg)
Polycystic ovary syndrome
Previously identified prediabetes based on laboratory values
Other clinical conditions associated with insulin resistance (e.g. acanthosis nigricans)

In the event that a precipitant drug cannot be avoided, prudence would dictate careful monitoring for the occurrence of dysglycemia. If a morbid event occurs, the dose of the offending agent can be reduced or the drug can be discontinued if suitable. If necessary, supportive care may be required for a time dependent upon the drug in question and the clinical status of the patient. Most importantly the clinician should learn from the incident and develop strategies to obviate such happenings in the future.

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20 Endocrine Disorders that Cause Diabetes

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Key points

- Endocrine causes of diabetes are mainly a result of an excess of hormones that are counter-regulatory to insulin, and act by inhibiting insulin secretion and/or action.
- Acromegaly is almost always secondary to growth hormone-secreting adenomas of the anterior pituitary somatotrophs and disturbs glucose homeostasis in up to approximately 50% of patients.
- Cushing syndrome is caused by excessive levels of glucocorticoids and disturbs glucose homeostasis to some degree in over 50% of cases.
- Pheochromocytoma is a tumor of the chromaffin cells, which in 90% of cases is located in the adrenal medulla and causes hyperglycemia in approximately 50% of cases.
- Glucagonoma and somatostatinoma are rare islet cell tumors that produce hormones that inhibit the secretion and action of insulin.
- Thyrotoxicosis commonly causes mild glucose intolerance, but overt diabetes only occurs in a tiny minority.
- Other endocrinopathies such as primary aldosteronism and primary hyperparathyroidism can disturb glucose homeostasis.
- Polycystic ovarian syndrome occurs in 5–10% of women of reproductive age and associates with some degree of glucose intolerance or diabetes resulting from insulin resistance in approximately 50% of cases.

Introduction

The primary focus of this chapter is on those endocrine disorders that cause hyperglycemia and where effective treatment of the endocrinopathy can be expected to normalize the blood glucose concentration. These conditions mostly reflect excessive secretion of "counter-regulatory" hormones, the metabolic actions of which oppose those of insulin by inhibiting its secretion, action, or both.

Acromegaly

Etiology, incidence, and clinical features of acromegaly

Acromegaly comprises a constellation of symptoms and signs caused by excessive growth hormone (GH) secretion that leads to bony and soft tissue overgrowth accompanied by cardiovascular and metabolic pathology (Figure 20.1; Table 20.1) [1]. Previous data suggested acromegaly affects approximately 60 people per million [2]; however, current evidence suggests the prevalence is much higher, between 86–240 people per million [1]. In 99% of cases, acromegaly is caused by a pituitary adenoma, most commonly larger than 1 cm in diameter (a "macroadenoma"; Figure 20.1). A tiny minority of cases are caused by excessive secretion of GH-releasing hormone (GHRH) from a hypothalamic gangliocytoma or a carcinoid tumor of the lung or pancreas [3]. A small percentage of acromegaly occurs within the wider endocrine syndrome of multiple endocrine neoplasia type 1 (MEN1) caused by mutations in the tumor suppressor gene, *MENIN* [4]. MEN1 can also include glucagonomas and somatostatinomas, both of which can independently cause secondary diabetes. Acromegaly can also rarely occur within the context of familial isolated pituitary adenomas, with germline mutations in the tumor suppressor gene encoding the aryl hydrocarbon receptor-interacting protein (*AIP*) implicated in the pathogenesis of some cases [5]. Commonly, acromegaly has been present for a decade prior to diagnosis [1]. This long-standing hypersecretion of GH provides the time necessary for the characteristic external features of the disorder to develop (Figure 20.1; Table 20.1). On occasion this timeline can stretch back prior to puberty. GH excess in this circumstance when exaggerated linear growth is still possible causes "gigantism" alongside the post-pubertal features of acromegaly.

Disturbance to glucose tolerance in acromegaly

Glucose intolerance or overt diabetes is common in acromegaly because of the direct hyperglycemic effects of GH excess (Figure 20.2). Diabetes and impaired glucose tolerance occurs in 15–38% of people with acromegaly [6–8]. Diabetes is most frequent in people with higher GH levels [9, 10]. There is also a correlation between serum insulin-like growth factor I (IGF-I) and both fasting and postprandial glucose. In fact, placing age-adjusted IGF-I values into rising quartiles correlated very accurately with

Textbook of Diabetes, Fifth Edition. Edited by R. Holt, C. Cockram, A. Flyvbjerg and B. Goldstein.

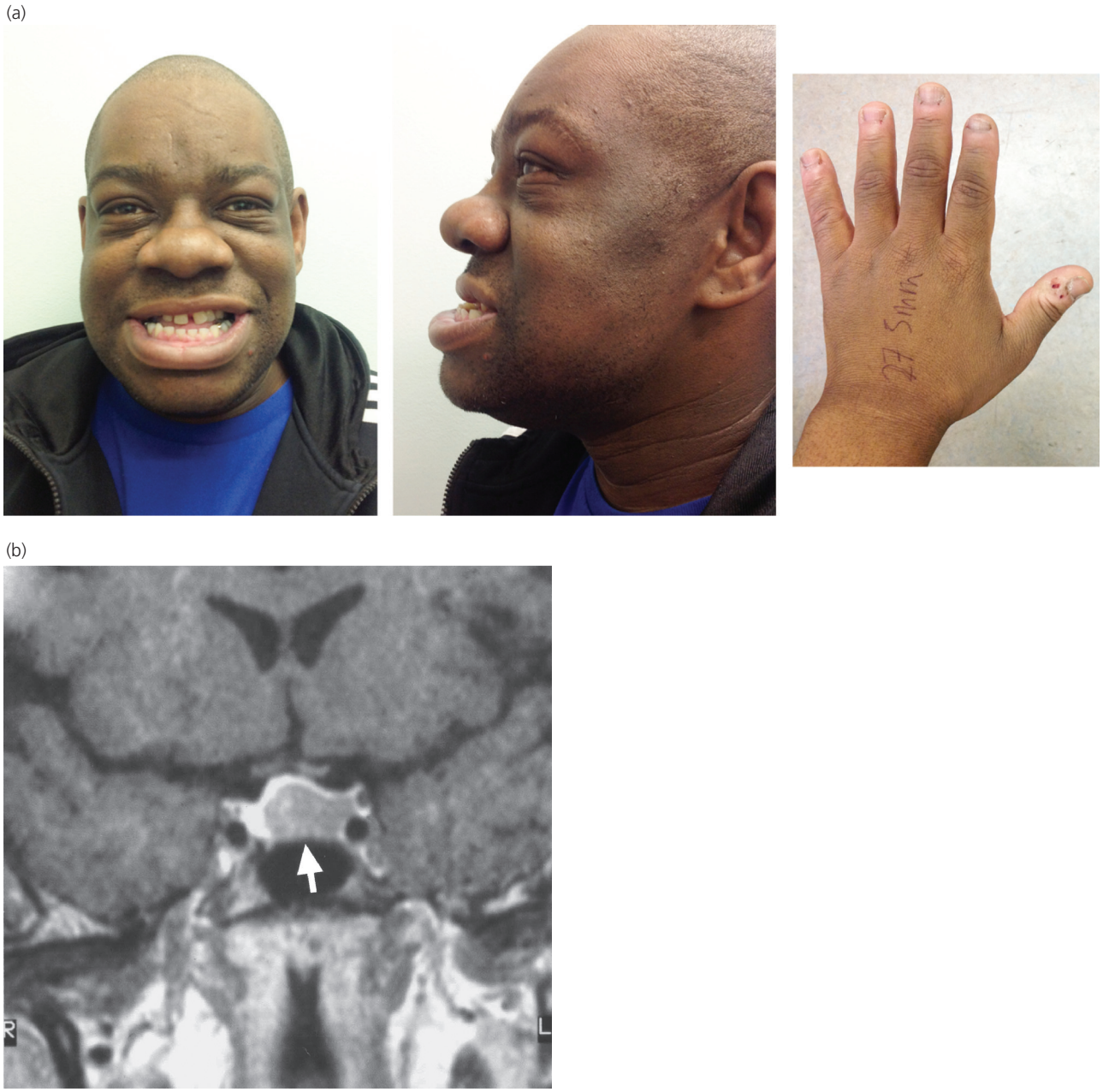


Figure 20.1 (a) Characteristic features of a man with untreated acromegaly. Note the teeth separation, particularly noticeable in the lower jaw and the associated underbite from the mandibular overgrowth. The hand illustrates soft tissue overgrowth and is often described as "spade-like." (b) MR imaging from a patient shows a large adenoma (arrow) in the pituitary extending up to but not in contact with the optic chiasm and also extending out into the left cavernous sinus. R, right; L, left.

decreasing insulin sensitivity such that serum IGF-I levels could predict insulin sensitivity more accurately than either random GH levels or the nadir value following glucose tolerance testing [11].

Clinically, diabetes in acromegaly usually resembles type 2 diabetes (T2DM), with most people not needing insulin therapy but being maintained with oral antidiabetes agents or diet alone [8]. GH can induce insulin resistance when infused into healthy volunteers [12, 13], and insulin resistance is a consistent feature of people with acromegaly [14, 15]. Insulin action is impaired in both the liver and extrahepatic tissues, with diminished suppression of hepatic glucose production and insulin-dependent glucose disposal [13, 15]. For instance, impairment of insulin-mediated activation of glycogen synthase has been demonstrated in skeletal muscle [16–18]. Insulin resistance may also be exacerbated by the lipolytic action of GH, generating non-esterified fatty acids (NEFAs), which act on the liver to increase glucose production and in muscle to inhibit glucose utilization (via the "glucose–fatty acid" cycle) (Figure 20.2). Where pancreatic compensation is

Table 20.1 Clinical features of acromegaly.

Musculoskeletal
Protruding mandible (prognathia) with lower teeth separation
Big tongue (macroglossia)
Enlarged forehead (frontal bossing)
Large hands and feet (carpal tunnel syndrome, tight rings, increasing shoe size)
Osteoarthritis from abnormal joint loading
Increased stature (gigantism; if GH excess occurs prior to epiphyseal closure)
Skin
Irritating, thickened, greasy (increased sebum production)
Excessive sweating
Cardiovascular
Dilated cardiomyopathy causing cardiomegaly and cardiac failure
Hypertension
Metabolic
Impaired glucose tolerance or potentially diabetes
General
Headaches
Tiredness, often very disabling and lowers quality of life and ability to work
Local tumor effects
Compression of the optic chiasm (superior tumor growth) or cranial nerves III, IV, and/ or VI (lateral tumor growth into cavernous sinus)

GH, growth hormone.

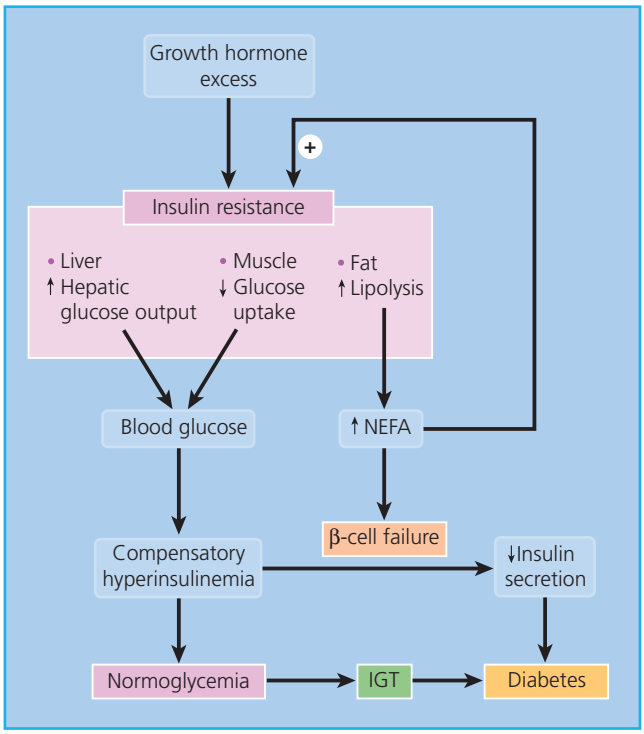


Figure 20.2 Mechanisms of hyperglycemia and diabetes in acromegaly. Diabetes develops if β cells fail to compensate for the increased demand for insulin. IGT, impaired glucose tolerance; NEFA, non-esterified fatty acid.

adequate, an exaggerated insulin secretory response creating hyperinsulinemia can counterbalance the insulin resistance and maintain euglycemia. Similar to the natural history of deteriorating blood glucose control in T2DM, eventually β-cell compensation fails, the insulin response is impaired and hyperglycemia ensues [14].

Diagnosis and treatment of acromegaly

GH release is normally pulsatile with intervening periods of low level or undetectable hormone, whereas secretion from pituitary adenomas is autonomous. Therefore, the diagnosis can be strongly suspected from a series of random serum measurements where GH is consistently detected. An alternative, better diagnostic test takes advantage of the negative feedback on GH secretion by glucose. A failure of serum GH to suppress to below 2 mU/L (approximately 1 μg/L) within 2 hours of 75 g oral glucose is diagnostic of acromegaly. A further option, particularly suited as the initial screening test for outpatients, is measurement of serum IGF-I, which if raised above sex- and age-matched reference ranges is diagnostic of acromegaly, unless there is a possibility of exogenous GH administration [3]. It is noteworthy that the diagnosis of acromegaly can be difficult in people with type 1 diabetes mellitus (T1DM) where GH hypersecretion is observed. Whereas this might compromise the use of serum GH as a diagnostic biomarker of a somatotroph adenoma, IGF-I values tend to be low in poorly controlled T1DM indicative of a state of GH resistance. Thus, raised serum IGF-I values remain a confident predictor for a diagnosis of acromegaly in people with T1DM. Having diagnosed acromegaly biochemically, magnetic resonance (MR) imaging of the anterior pituitary defines the extent of the adenoma (Figure 20.1).

Based on this investigation, symptoms, patient wishes, comorbidity, and GH levels, treatment can be either surgical, medical, or radiotherapy (Table 20.2) [3]. When the tumor is a macroadenoma, especially if it extends beyond the pituitary fossa, curative surgery becomes unlikely or impossible; however, surgery can be useful for "debulking" and rapid lowering of serum GH levels in patients who are highly symptomatic, or where the tumor has encroached upon the optic chiasm and affected visual fields. The standard approach is transsphenoidal, either via the nostril or from behind the upper lip. Once the sphenoid sinus has been traversed and midline access to the sella turcica gained, tumor is removed from the anteroinferior aspect causing the residual tissue to drop back down into or towards the pituitary fossa. Tumor beyond the fossa, in locations such as the cavernous sinus, cannot be approached directly, hence the reason why surgery for large tumors is not anticipated to be curative [19]. Conversely, cure can be commonly achieved for over 85% of microadenomas (<1 cm diameter) and 40–50% of macroadenomas [20–22]. The reported ranges vary widely according to expertise.

Medical therapy, most commonly using somatostatin analogs, is effective at both lowering GH levels and shrinking the tumor volume [1, 23, 24]. Approximately 60% of patients respond to somatostatin analogs because of the presence of somatostatin

Table 20.2 Treatment of acromegaly.

Advantages	Disadvantages
Transsphenoidal surgery	
Rapid effect	Invasive and requires general anesthetic
Can restore vision in optic nerve compression	Non-curative for large extrasellar tumors
Might be curative if complete resection	
Somatostatin analog drugs	
Non-invasive	Monthly intramuscular injection
May shrink tumor	Expensive
Decreases GH in ~60% of patients	Gastrointestinal side effects (commonly diarrhea)
	Unlikely to be curative (i.e. continuous therapy needed)
Pegvisomant	
Non-invasive	Expensive
Blocks GH action	GH concentrations remain elevated
Radiotherapy	
Non-invasive	Slow to act—may take up to 10 years
Likely to shrink tumor	Standard external three-beam radiotherapy likely to cause hypopituitarism by destroying other pituitary cell types
Likely to reduce GH levels	
Might be curative	

GH, growth hormone.
Source: Adapted from Holt and Hanley 2012 [149].

receptors (mostly type 2 and type 5) on the tumor cell surface [1, 24]. The analogs can be administered subcutaneously; however, once it is clear that they are tolerated, the most common formulation is month-long intramuscular depot preparations. They can be used either prior to surgery, with the goal of operating on a shrunken tumor, on a long-term basis in place of surgery, or post-surgery where GH levels have not been normalized.

Some GH-secreting adenomas co-express dopamine receptors more characteristic of prolactinomas [24]. Indeed, 25% of cases of acromegaly show raised levels of both prolactin and GH possibly indicating a tumor cell phenotype more consistent with the somatomammotroph from which it is thought that somatotrophs (GH secretion) and lactotrophs (prolactin secretion) terminally differentiate. In these instances, dopamine agonists, as used in hyperprolactinemia, can be useful, especially as they can be administered orally, and allow reduction in dosage of the more expensive intramuscular depot somatostatin analogs. This opportunity to use lower doses of somatostatin analogs may also lessen their side effects, such as gastrointestinal disturbance (most commonly diarrhea) and gallstones. It has been questioned whether commonly used ergot alkaloid-derived dopamine agonists, such as cabergoline, cause fibrotic side effects, especially involving heart valves [25, 26]. Despite concerns from regulatory agencies, the prevailing view from endocrinologists is that the doses of these agents used to treat endocrine disorders (compared with the therapeutic regimens in Parkinson disease) are not problematic. In any case, alternative non-ergot derived agents, such as quinagolide, are available. Bromocriptine is less commonly used because of the almost inevitable side effect of nausea. The role of dopamine in mood disorders and psychosis creates at least a theoretical concern over dopamine agonists in the treatment of endocrine disorders. While the practical significance remains disputed, it is prudent to inquire about mood in the past medical history and systemic inquiry and to encourage the patient to report symptoms if they commence dopamine agonist therapy. At the start of treatment, responsiveness to both dopamine and somatostatin analog therapy can be easily assessed by hourly measurement of serum GH over 8 hours following the administration of a test dose of each agent given sequentially on two consecutive days.

The last two decades has seen the appearance of a new clinical agent that blocks GH action. GH induces signal transduction via binding to its receptor as a dimer. Pegvisomant has been developed as a GH antagonist by preventing this dimerization and blocking downstream GH signaling. This leaves elevated GH levels from the somatotroph adenoma but, nevertheless, pegvisomant is effective at reversing the clinical features of acromegaly, with approximately 60% of patients sustaining normal IGF-I levels after 5 years of treatment [3, 27, 28]. The major problem with its use in many countries has been its prohibitive cost. Concern over tumor growth because of loss of negative feedback (a scenario similar to Nelson syndrome following bilateral adrenalectomy in Cushing disease) seems unfounded [27, 28].

Radiation therapy is most commonly administered as conventional three-field external beam radiotherapy [3]. It is effective at lowering GH and IGF-I levels [29]. This approach delivers approximately 4500 Gy to the pituitary region with the total dose calculated such that the optic chiasm receives less than 8 Gy. An alternative is stereotactic radiotherapy (also known as γ-knife therapy or radiosurgery), which by using more sources can focus a higher concentration of radiation to a defined area of tumor. Whereas the latter modality allows greater preservation of adjacent normal pituitary tissue, the former approach is a more all-encompassing strategy to ensure tumor destruction, albeit with a higher post-therapy incidence of hypopituitarism. The choice is important as there is evidence that pituitary radiotherapy is associated with increased morbidity and mortality from subsequent cerebrovascular disease meaning that repeat therapy is not undertaken lightly [30].

Outcome of acromegaly and the disturbance to glucose tolerance

Unless there are cogent reasons against, attempts should be made to normalize GH excess in acromegaly to decrease the morbidity and mortality associated with the disorder [3, 31]. Curative treatment is best defined by a nadir serum GH of less than 2 mU/L upon 75 g oral glucose challenge. Glucose tolerance improves

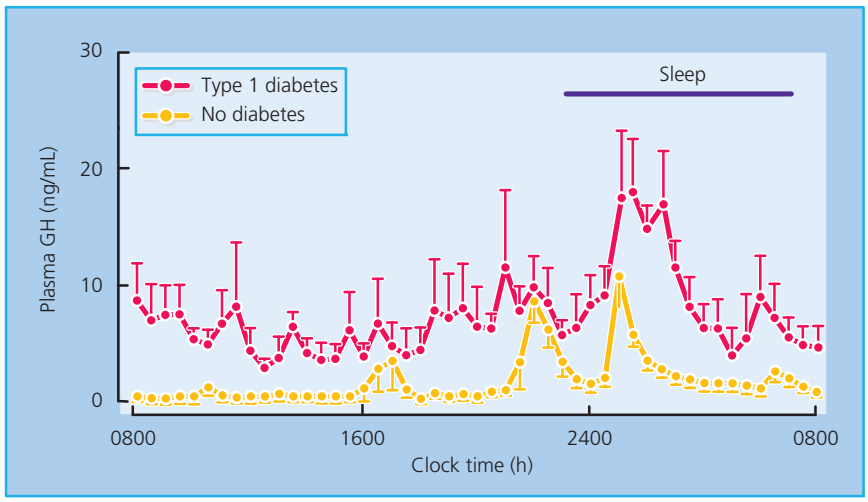


Figure 20.3 Increased growth hormone (GH) secretion in type 1 diabetes. Note the marked hypersecretion during sleep in the early hours of the morning. Source: Hansen et al. 1981 [147]. Reproduced with permission of John Wiley & Sons.

and insulin levels decrease after successful treatment by pituitary surgery and/or irradiation [32, 33]. Hyperglycemia may worsen in a few patients, presumably those with a stronger underlying tendency to T2DM, when GH excess is treated with somatostatin analogs because these drugs suppress insulin secretion [34, 35], similar to the normal effect of somatostatin from the pancreatic islet δ cell upon the adjacent β cell. In the longer term, by virtue of their effect on acromegaly somatostatin analogs tend to improve glucose tolerance [23, 36]. Insulin sensitivity is also improved with pegvisomant therapy in people with both glucose intolerance and diabetes [36–39]. If hyperglycemia persists after serum GH levels have been normalized then the individual should be considered as having T2DM. One caveat to this is the possibility of GH deficiency as part of hypopituitarism post-surgery or radiotherapy [14]. GH deficiency causes centripetal fat deposition, which could itself cause or accentuate insulin resistance and potential loss of euglycemia.

Generally, diabetic complications are rare in acromegaly. Nevertheless, it is worth considering GH action in the context of both macrovascular and microvascular diabetic complications. Untreated GH excess increases cardiovascular morbidity and mortality and, potentially, abnormalities of glucose metabolism occurring in acromegaly could contribute to hypertension which affects over 50% of people with acromegaly [40]. GH has been linked to proliferative diabetic retinopathy ever since resolution of diabetic retinopathy was noted in a woman who developed rapid-onset pan-hypopituitarism [41, 42]; this led to the use of hypophysectomy as a treatment of retinopathy prior to the advent of laser photocoagulation [41]. This view is supported by the observations that people with diabetes who are GH-deficient rarely develop retinopathy [43], and an experimental study in mice demonstrated that inhibition of GH secretion ameliorated diabetic retinopathy [44]. People with diabetes and acromegaly, however, do not show an increased incidence of diabetic retinopathy [45, 46]. Data on the progression of diabetic retinopathy treated with either pegvisomant or somatostatin analogs are contradictory, and the outcome of larger trials are awaited [41].

Effects of diabetes on GH–IGF-I axis

Dysregulation of the GH–IGF-I axis has been well documented in T1DM. The main disturbances include increased GH secretion (Figure 20.3), paradoxically associated with decreased serum IGF-I levels [47]. GH secretory pulses are larger and more frequent and total 24-hour serum and urinary GH levels are elevated. High circulating GH levels are most obvious during periods of poor diabetic control, and return towards normal with improved control. Pulses of GH secretion during sleep in the early hours of the morning lead to insulin resistance, which manifests itself before breakfast and is largely responsible for the "dawn phenomenon" of fasting hyperglycemia [48]. This physiologic effect, along with that caused by exercise and GHRH, is exaggerated in people with T1DM, especially those who have poor glycemic control. GH secretion accounts for much of the decreased insulin sensitivity observed during normal puberty, as well as the deterioration in glycemic control at this time in adolescents with T1DM. Despite GH hypersecretion, levels of IGF-I—the principal mediator of GH activity—are inappropriately low, indicating a state of GH resistance (Figure 20.4). Hepatic resistance to GH has been attributed both to decreased number of GH receptors and to post-receptor defects [47]. Circulating levels of GH-binding protein (GHBP) are also decreased in T1DM. Administration of recombinant human IGF-I (rhIGF-I) as an adjunct to insulin has been demonstrated to reverse GH hypersecretion and improve glycemic control, while reducing insulin requirements. Co-administration of IGF-binding protein 3 (IGFBP-3) with IGF-I has similar beneficial effects on carbohydrate metabolism, and also avoids side effects of IGF-I, notably edema, headache, retinal edema, and jaw pain, as well as reducing the risk of hypoglycemia [49]. Recombinant IGF-I has also been used to treat states of severe insulin resistance in which the insulin receptor is functionally impaired, such as the spectrum from Donohue to Rabson–Mendenhall syndrome (see Chapter 18) [50]. In such individuals, rhIGF-I can be used to treat ketoacidosis, which is the major cause of death and which may fail to respond to massive doses of insulin.

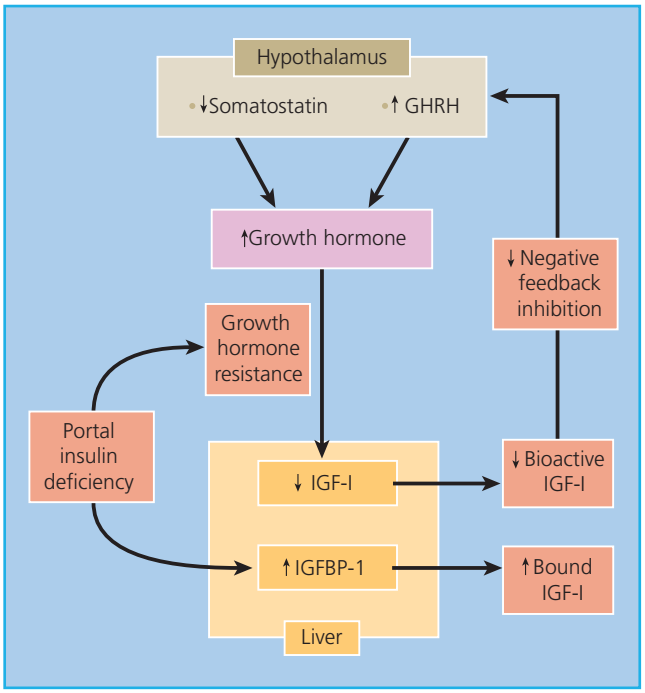


Figure 20.4 Mechanisms of growth hormone (GH) hypersecretion in diabetes. Insulin-like growth factor 1 binding protein 1 (IGFBP-1) binds and reduces the bioavailability of insulin-like growth factor I (IGF-I), which normally decreases GH secretion by negative feedback inhibition on the hypothalamus and pituitary; IGFBP-1 expression is inhibited by insulin.

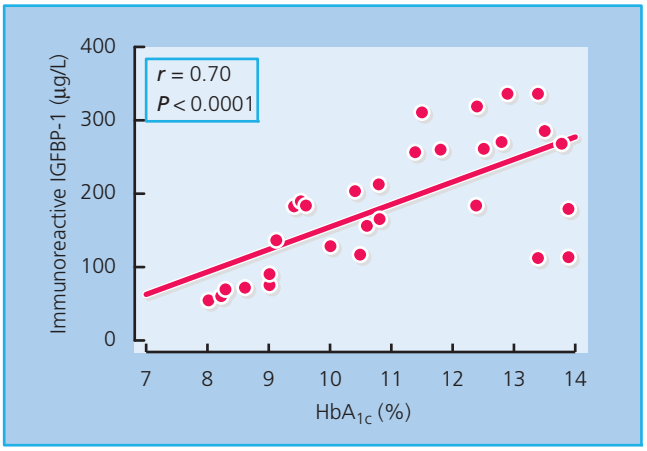


Figure 20.5 Correlation between serum immunoreactive insulin-like growth factor 1 binding protein 1 (IGFBP-1) and glycated hemoglobin (HbA_{1c}) concentrations in 48 people with type 1 diabetes mellitus. Source: Langford and Miell 1993 [148]. Reproduced with permission of John Wiley & Sons.

Abnormalities of IGFBPs may also alter the regulation of the GH–IGF-I axis in diabetes (Figure 20.4). Six IGFBPs have been identified in humans, the two most relevant being IGFBP-1 (molecular weight 25 kDa), whose synthesis by hepatocytes is inhibited by insulin but independently of GH, and IGFBP-3 (molecular weight 44 kDa), which is GH-dependent [51]. IGFBP-1 levels are increased in T1DM as a result of portal and hepatic insulin deficiency (Figure 20.4) [47], and increase with worsening insulin deficiency and rising HbA_{1c} concentrations (Figure 20.5). Increased IGFBP-1 levels have been shown to inhibit IGF-I bioactivity. Portal insulin deficiency in T1DM can thus account for GH resistance, through downregulation of hepatic GH receptors and increased IGFBP-1 levels, both reducing IGF-I production and bioactivity [52]. Decreased IGF-I levels in turn cause GH hypersecretion via reduced negative feedback at the hypothalamus and pituitary, and this exacerbates insulin resistance, thus establishing a vicious circle of raised GH and poor glycemic control (Figures 20.2 and 20.3).

Another consequence of IGF-I deficiency is impaired growth at puberty [52]. Paradoxically, children with new-onset diabetes tend to be taller, especially if the disease develops several years before puberty; increased GH and insulin levels during the preclinical evolution of the disease are a possible explanation. Once diabetes is established, growth may slow, particularly before the age of 10 years and if glycemia is poorly controlled (Figure 20.6). The pubertal growth spurt may be blunted and/or delayed, especially in girls, and this may lead to a reduction in final height [52]. Growth failure in adolescents with T1DM is rare nowadays, possibly because of improved management and monitoring of diabetes. Indeed, intensified insulin treatment has been shown to raise IGF-I levels, in parallel with an increase in growth velocity [52]. Finally, growth failure may be associated with truncal obesity, hepatomegaly (secondary to glycogen and/or triglyceride

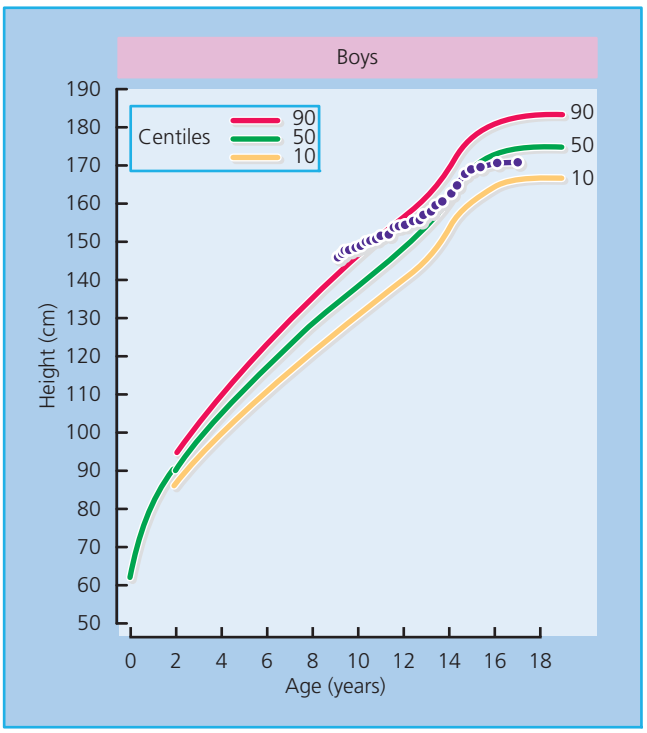


Figure 20.6 Growth failure in a boy with diabetes. Height fell progressively below the centiles (97th centile at diagnosis) and the pubertal growth spurt was delayed, resulting in a lower final height than predicted.

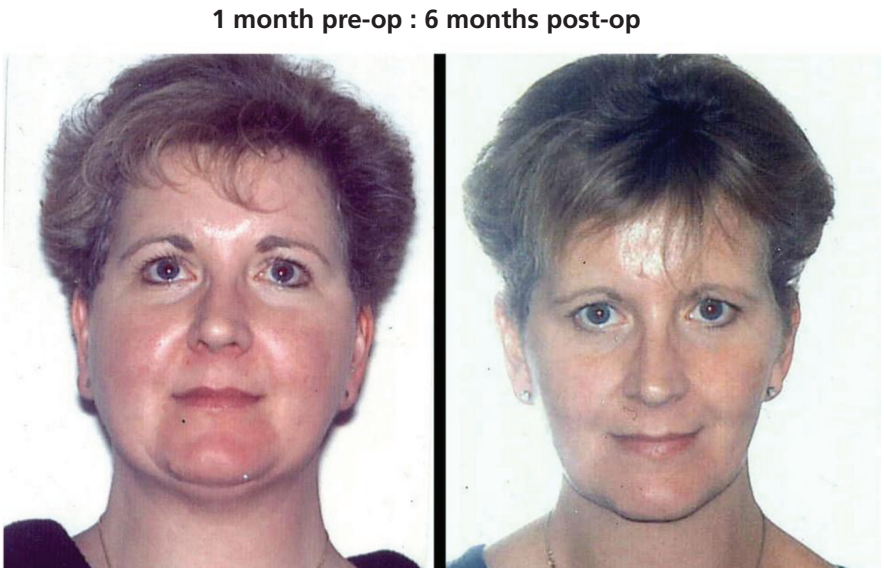


Figure 20.7 Cushing syndrome in a woman presenting with glucose intolerance, hypertension, and altered appearance. The original presentation related to subfertility misattributed as polycystic ovarian syndrome. The cause of the glucocorticoid excess was a small adenoma in the right adrenal gland. Six months following its removal by unilateral adrenalectomy the pronounced changes in physical appearance led to the woman being requested to renew her passport. Blood pressure and glucose homeostasis returned to normal.

deposition) and sexual infantilism in Mauriac syndrome [53]. This condition was reported in children with poor glycemic control and excessively high insulin dosages, but is now rare.

Cushing syndrome

Etiology, incidence, and clinical features of Cushing syndrome

Cushing syndrome comprises a constellation of symptoms and signs caused by excessive levels of glucocorticoid that leads to a characteristic appearance accompanied by metabolic and cardiovascular pathology (Figure 20.7; Table 20.3) [54–56]. It occurs most commonly as a side effect of synthetic glucocorticoids administered for conditions such as rheumatoid arthritis or reversible airways disease. Endogenous Cushing syndrome arises in approximately two-thirds of cases from adrenocorticotropin (ACTH)-secreting corticotroph adenomas of the anterior pituitary which affect 5–10 individuals per million. In one-fifth of cases, the cause is a glucocorticoid-secreting tumor of the adrenal cortex and in one-tenth of cases is secondary to syndromes of ectopic ACTH secretion, most commonly from small cell carcinoma of the lung or, more rarely, carcinoid tumors [54–57]. Cushing syndrome is more common in women than men, with a greater predilection for corticotroph adenomas as the underlying pathology. Prolonged excessive levels of cortisol, the major glucocorticoid in humans, either directly from an adrenocortical tumor or from inappropriate amounts of ACTH causing bilateral hyperfunctional adrenal cortices, cause the characteristic external features of the disorder to develop and results in excess cardiovascular morbidity and mortality (Figure 20.7; Table 20.3) [54–57].

Table 20.3 Clinical features of Cushing syndrome.

Easily bruised, thin skin; poor wound healing
Striae (purple or "violaceous" rather than white)
Thin (osteoporotic) bones that easily fracture
Glucose intolerance/diabetes mellitus
Central obesity, characteristic rounded facies, "buffalo" hump
Susceptibility to infection
Predisposition to gastric ulcer
Hypertension
Disturbance of menstrual cycle; symptoms overlap with PCOS
Mood disturbance (depression, psychosis)

PCOS, polycystic ovarian syndrome.

Disturbance to glucose tolerance in Cushing syndrome

Impairment of glucose tolerance is observed in 30–70% of cases [56, 58, 59]. Overt diabetes occurs in 20–50%, arguably in people predisposed to diabetes (e.g. those with a family history [56, 58, 59]). It resembles T2DM because glucocorticoid excess causes hyperglycemia primarily by inducing insulin resistance, reflected by hyperinsulinemia [58]. Insulin-stimulated glucose uptake and utilization by peripheral tissues are both reduced, while hepatic glucose production is greatly increased through stimulation of gluconeogenesis [56, 60, 61]. This results from the direct activation of hepatic gluconeogenic enzymes such as phosphoenolpyruvate carboxykinase (PEPCK), and an increasing supply of glucogenic substrates (amino acids and glycerol) generated by muscle proteolysis and peripheral adipose tissue lipolysis (Figure 20.8) [61, 62]. Glucocorticoids also have permissive effects on the gluconeogenesis induced by epinephrine (adrenaline) and glucagon. Besides enhancing hepatic gluconeogenesis, glucocorticoids also increase hepatic glycogen storage [62].

With endogenous causes of Cushing syndrome, the hyperglycemia can sometimes be treated effectively with sulfonylureas, but many cases require insulin therapy [61]. For Cushing syndrome caused by exogenous drugs, treatment can be tailored from

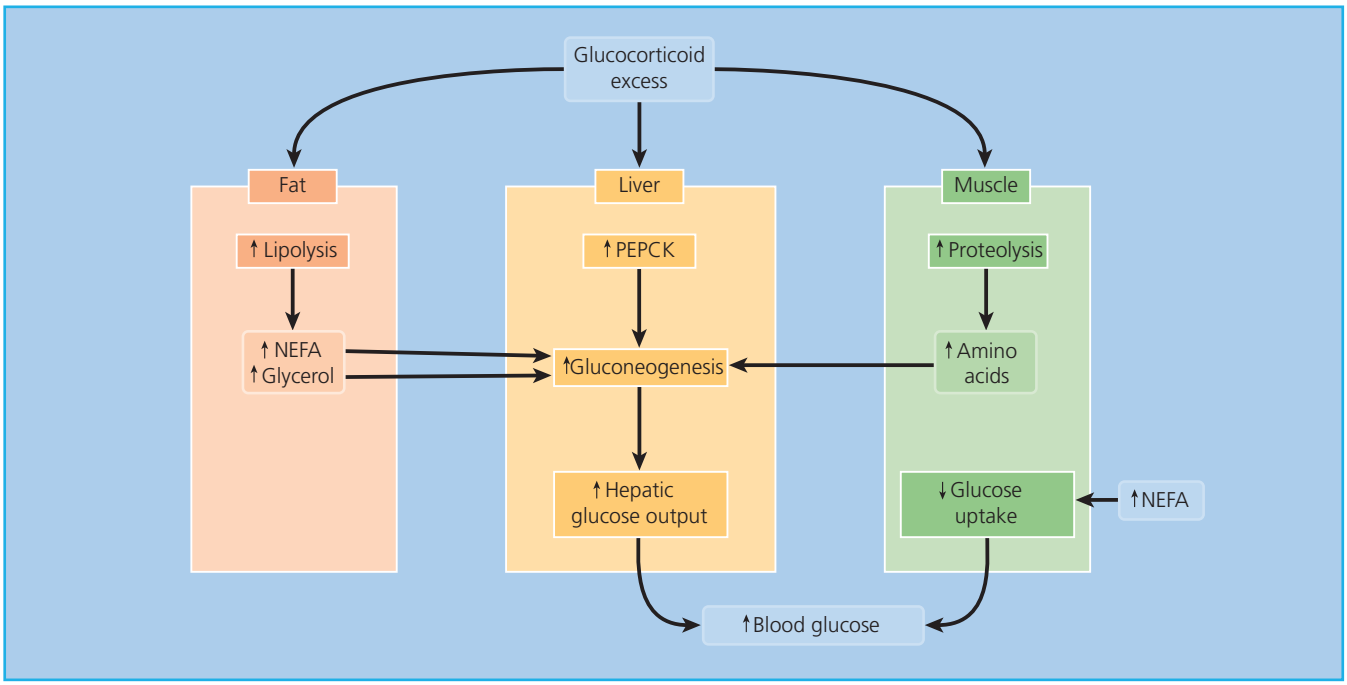


Figure 20.8 Mechanisms of hyperglycemia and diabetes in Cushing syndrome. NEFA, non-esterified fatty acids; PEPCK, phosphoenolpyruvate carboxykinase.

knowledge of the timing and half-life of the glucocorticoid drug as a predictable period of hyperglycemia follows. For instance, prednisolone administered for reversible airways disease at breakfast will generate elevated glucocorticoid levels throughout the remainder of the day with levels falling in the evening. This profile makes the choice of an intermediate-acting insulin administered at breakfast appropriate (see Chapter 19).

Diagnosis and treatment of Cushing syndrome

For exogenously administered glucocorticoids, the diagnosis and treatment of Cushing syndrome are straightforward: wherever possible remove or reduce the offending medication. The major challenge in diagnosing Cushing syndrome resulting from endogenous causes is frequently one of simply considering the condition as the underlying cause of otherwise very common symptoms such as tiredness and weight gain. Avoiding this pitfall is aided by thorough clinical examination when more specific signs may be detected, for instance violaceous stretch marks (called "striae") or proximal myopathy [54–56]. This issue may be particularly pertinent to the diabetes clinic, with some evidence that occult Cushing syndrome may affect up to 2% of people with T2DM [63].

The first goal is to establish the presence of either autonomous secretion or excessive levels of cortisol [54–56]. Several screening tests with high sensitivity have been designed (Table 20.4). Normally, circulating cortisol is relatively high during the day and low at bedtime. Maintained daytime levels at night are abnormal and imply glucocorticoid excess. This can be tested by measuring midnight serum cortisol, although this requires prior acclimatization of inpatients for at least 24 hours and quiet surroundings as cortisol levels rise with minimal stress. Where assays have been validated, bedtime salivary cortisol measurement can now be very useful as patients can post samples to the laboratory from home. Salivary levels are approximately 10% of those in serum and so care must be taken to avoid contamination with blood (e.g. from brushing teeth). The "low dose" dexamethasone suppression tests interrogate the potential loss of physiologic negative feedback at the corticotroph leading to autonomous ACTH secretion. The formal 48-hour test is marginally more specific [54]; however, it is also less convenient to perform in the outpatient setting compared with the overnight 1 mg suppression test. Caution needs to be exercised in patients where dexamethasone metabolism is enhanced (e.g. by antiepileptic medication) as this can lead to false-positive results. In addition, women need to avoid taking the combined oral contraceptive pill for the preceding month or so to avoid elevations in cortisol-binding globulin giving spuriously high total cortisol results. An alternative screening test examines total excretion of cortisol in a 24-hour urine collection, commonly on several occasions, as an integrated assessment of one day's adrenocortical function. It is commonplace for endocrinologists to apply more than one of these various screening tests, which, if failed, provides evidence of glucocorticoid excess and a diagnosis of Cushing syndrome.

Several endocrine tests have been developed to differentiate the various etiologies of endogenous Cushing syndrome (Table 20.4) [54–56]. Undetectable serum ACTH indicates an adrenocortical source of excessive cortisol causing suppression of ACTH secretion by the anterior pituitary. It can be particularly challenging to distinguish between anterior pituitary and ectopic sources of ACTH causing Cushing syndrome. Corticotroph adenomas,

Table 20.4 Diagnosis of Cushing syndrome from endogenous causes.

Test	Interpretation
Screening tests to diagnose Cushing syndrome	
Midnight serum cortisol measurement or bedtime salivary cortisol assay	Maintained daytime levels at night-time indicates autonomous cortisol production of Cushing syndrome
1 mg overnight DST. Oral dexamethasone taken at midnight	Serum cortisol >50 nmol/L at following 9 a.m. consistent with Cushing syndrome
Formal low-dose DST (0.5 mg × 8 doses 6-hourly ending at 3 a.m.)	Serum cortisol >50 nmol/L at following 9 a.m. consistent with Cushing syndrome
24-hour urinary free cortisol measurement	Elevated values support diagnosis of Cushing syndrome
Tests to localize cause of cortisol excess	
Serum ACTH measurement	If suppressed, indicates autonomous adrenocortical overproduction of cortisol (e.g. an adrenocortical adenoma)
If serum ACTH detectable:	
High-dose dexamethasone suppression test (2 mg × 8 doses 6-hourly ending at 3 a.m.)*	>50% suppression of 9 a.m. serum cortisol from pre- to post-test indicates anterior pituitary source; <50% suppression indicates extrapituitary "ectopic" source of ACTH
Bilateral IPSS*	Gradient from IPS to periphery of >2 : 1 supports anterior pituitary source (test can also incorporate CRH administration; see text)
MRI (can include gadolinium enhancement)	Should only be considered once biochemical evidence of pituitary source obtained. Helpful for surgeon in planning transsphenoidal surgery

ACTH, adrenocorticotropic hormone; CRH, corticotropin releasing hormone; DST, dexamethasone suppression test; IPSS, inferior petrosal sinus sampling; MRI, magnetic resonance imaging. *, larger centers commonly tend to progress straight to bilateral IPSS if available and conducted by experienced operators rather than perform high-dose dexamethasone suppression test.

especially intrasellar ones, usually retain a partial capacity for negative feedback. Historically, the "high dose" dexamethasone suppression test, administered as eight 2-mg doses every 6 hours, has exploited this feature with the expectation that cortisol levels reduce pre-test to post-test by at least 50%. As this cause underlies the original description of the disorder by Harvey Cushing in 1912, pituitary-driven glucocorticoid excess is called "Cushing's disease." Extrapituitary tumors secreting ectopic ACTH less commonly display this degree of negative feedback such that ACTH levels and consequently cortisol levels are likely to be higher. Although these tumors may be relatively indolent carcinoids, more commonly they are aggressive carcinomas of the bronchus characterized by a rapid onset of symptoms within a few months, marked hypokalemia, and weight loss. The high level of ACTH also binds to the type 1 melanocortin receptor (MC1R) resulting in skin pigmentation. Clinically, these features are usually obvious. In recent years, the high-dose dexamethasone test has become less prevalent because in settings with appropriate experience and expertise venous sampling of the bilateral inferior petrosal sinuses can distinguish between ectopic or anterior pituitary sources of excessive ACTH with greater sensitivity and specificity. For pituitary sources, a gradient in ACTH levels of at least 2 : 1 (or 3 : 1 after the injection of 100 μg corticotropin-releasing hormone (CRH) intravenously) should be found between central and peripheral samples. However, bilateral inferior petrosal sinus sampling (IPSS) carries the risk of thrombosis in approximately 1% of cases such that some endocrinologists feel the test is not always warranted, especially where preceding biochemical tests have been conclusive and MR imaging shows clear evidence for a tumor. Where biochemistry is supportive of a pituitary source of ACTH excess, but the MR scan is equivocal, even after gadolinium enhancement, IPSS can help to lateralize a corticotroph adenoma by detecting a clear gradient between the right and left sinuses or vice versa. Sources of ectopic ACTH, most commonly in the chest, can be imaged with fine-cut computerized tomography (CT), MRI, or by using isotope-labeled scintigraphy to detect somatostatin receptors present on approximately two-thirds of ectopic ACTH-secreting carcinoid tumors. Autonomous cortisol-secreting tumors of the adrenal cortex can be imaged satisfactorily by CT or MRI when it can be possible to make assessment of functionality according to lipid content. Features of high lipid content imply a tumor with active steroidogenesis.

Wherever possible, curative approaches are undertaken to normalize cortisol secretion as Cushing syndrome carries a high morbidity and markedly increases mortality from cardiovascular causes [54–56, 64]. For adrenocortical sources, unilateral adrenalectomy is performed. For ectopic ACTH-secreting tumors, excision of carcinoids is potentially curative, whereas the natural history of carcinoma of the bronchus with ectopic hormone secretion usually makes palliative care more appropriate. Frontline treatment of corticotroph adenomas is commonly by transsphenoidal surgery. The indications and complications for radiotherapy are largely the same as for those described in the section on acromegaly. The fact that ACTH-secreting adenomas are commonly microadenomas can increase the chances of curative surgery, although this remains heavily operator-dependent. If surgery is delayed, suppressants of adrenocortical steroidogenesis such as ketoconazole or metyrapone can be used temporarily where patients are highly symptomatic and can improve glycemic control [54, 55, 65]. Direct medical therapy against corticotroph adenomas remains suboptimal. Treatment with the somatostatin analog pasireotide takes advantage of the fact that corticotroph adenomas express the somatostatin receptor subtype 5 (in addition to subtypes 1–3). Initial trials demonstrated positive results, with a reduction in urinary free cortisol levels after 12 months of treatment [66]. Approximately three-quarters of patients have

shown a reduction in urinary free cortisol excretion [67]. However, over 70% of patients treated with pasireotide developed glucose intolerance, due to the drug's effects on reducing incretin and insulin secretion [66, 68].

In extremis, bilateral adrenalectomy provides a rapid resolution of excessive cortisol secretion, although the total loss of negative feedback to a corticotroph adenoma can result in dangerous pituitary tumor growth that becomes refractory to further treatment, a scenario called Nelson syndrome. In patients where ACTH levels continue to rise, concomitant radiotherapy to the anterior pituitary can help reduce the risk of this problem arising.

Outcome of Cushing syndrome and the disturbance to glucose tolerance

After successful transsphenoidal surgery, the patient is reliant in the short term on external glucocorticoid administered as oral hydrocortisone. However, a return of cortisol secretion from the adrenal gland(s) can be anticipated over ensuing weeks or months. Commonly, a physiologic return of diurnal rhythm is never achieved postoperatively [69]. For some, the extensiveness of anterior pituitary surgery, or the long-term suppression either of normal corticotrophs (pituitary or ectopic ACTH-secreting tumors) or normal adrenocortical cells (cortisol-secreting tumors) causes a permanent state of hypocortisolism because of inadequacy of the remaining tissue. This can require continued hydrocortisone administration as for those with Addison disease, except that mineralocorticoid replacement should not be required.

With successful treatment of Cushing syndrome (Figure 20.7), glucose intolerance may resolve. In such instances, when the patient might be entirely dependent on replacement doses of hydrocortisone, care needs to be taken not to cause hypoglycemia by continued antidiabetes medication. By contrast, persisting abnormalities are relatively common, most likely associated with persistent visceral obesity and metabolic syndrome [7, 61]. On close analysis in one case series, there was a marked persistence of visceral obesity and glucose intolerance in approximately 60% of those who fulfilled criteria for remission of Cushing syndrome [70].

Effects of diabetes on hypothalamic–anterior pituitary–adrenal cortex axis

Evidence of overactivity of the hypothalamic–pituitary–adrenal (HPA) axis has been reported in children, adolescents, and adults with diabetes, including moderate increases in urinary free cortisol excretion, plasma cortisol and ACTH concentrations [71–74]. These abnormalities have been related to the duration of diabetes [72, 73] and to the presence of diabetic neuropathy [74]. Serum cortisol levels fall as metabolic control improves [75].

The role of 11βHSD1 in diabetes

The similarities between Cushing syndrome and the metabolic syndrome have led researchers into investigating a potential role for the HPA axis and cortisol metabolism in obesity and its metabolic complications. The inactive form of cortisol, cortisone, can be converted back into active cortisol via catalysis by the enzyme 11β-hydroxysteroid dehydrogenase type 1 (11βHSD1), present in the liver as well as peripheral tissues, including adipose tissue [76]. The activity of 11βHSD1 is potentially dysregulated in obese people, with increased activity in adipose tissue and reduced hepatic activity [77]. Whilst circulating cortisol levels are not increased in obese people, the local adipose-generated cortisol may contribute to some metabolic complications of obesity, such as impaired glucose tolerance. In addition, levels of 11βHSD1 seem increased in those with obesity and T2DM [78]. These findings have resulted in 11βHSD1 becoming a potential therapeutic target for diabetes, with pharmacological inhibitors in development [76].

Pheochromocytoma and paraganglioma

Etiology, incidence, and clinical features of pheochromocytoma and paragangliomas

Catecholamine-secreting pheochromocytomas and paragangliomas are tumors arising from the neural crest-derived chromaffin cells of the adrenal medulla (pheochromocytoma, 80–85%) (Figure 20.9) [79, 80] or the paravertebral sympathetic chains in the chest, abdomen, or pelvis (paragangliomas). Approximately, 10% of pheochromocytomas are bilateral. They can secrete epinephrine, norepinephrine, dopamine, or various combinations thereof. Although most pheochromocytomas are sporadic, advances in molecular genetics have demonstrated a hereditary basis underlying approximately one-third of diagnoses, not just in well-known syndromes, such as MEN2, von Recklinghausen neurofibromatosis, and von Hippel–Lindau disease [81]. In fact, there are now at least 10 genes associated with pheochromocytomas and paragangliomas linked to particular tumor phenotypes [79] (Table 20.5). For instance, succinate dehydrogenase subunit B (*SDHB*) and succinate dehydrogenase subunit D (*SDHD*) mutations are more frequent in extra-adrenal tumors [81]. Mutations in *SDHB* are more commonly associated with a malignant phenotype [81]. The risk of malignancy also increases with tumor size [81].

The clinical symptoms of catecholamine-secreting pheochromocytomas and paragangliomas are classically described as a triad: headaches, sweating, and tachycardia [82]. Hypertension is the most common clinical finding and occurs in 80–90% of cases. It can be paroxysmal or sustained, the latter occurring especially in children and in norepinephrine-secreting tumors [83]. Other symptoms may be secondary to the co-secretion of various other peptide hormones such as vasoactive intestinal peptide (VIP), substance P, atrial natriuretic factor, endothelin-1, CRH, and GHRH [84]. The normal adrenal medulla predominantly secretes epinephrine, converted from norepinephrine by methylation. This reaction is governed by the enzyme phenylethanolamine-*N*-methyltransferase (PNMT), the expression of which is dependent on high concentrations of cortisol draining centripetally from the

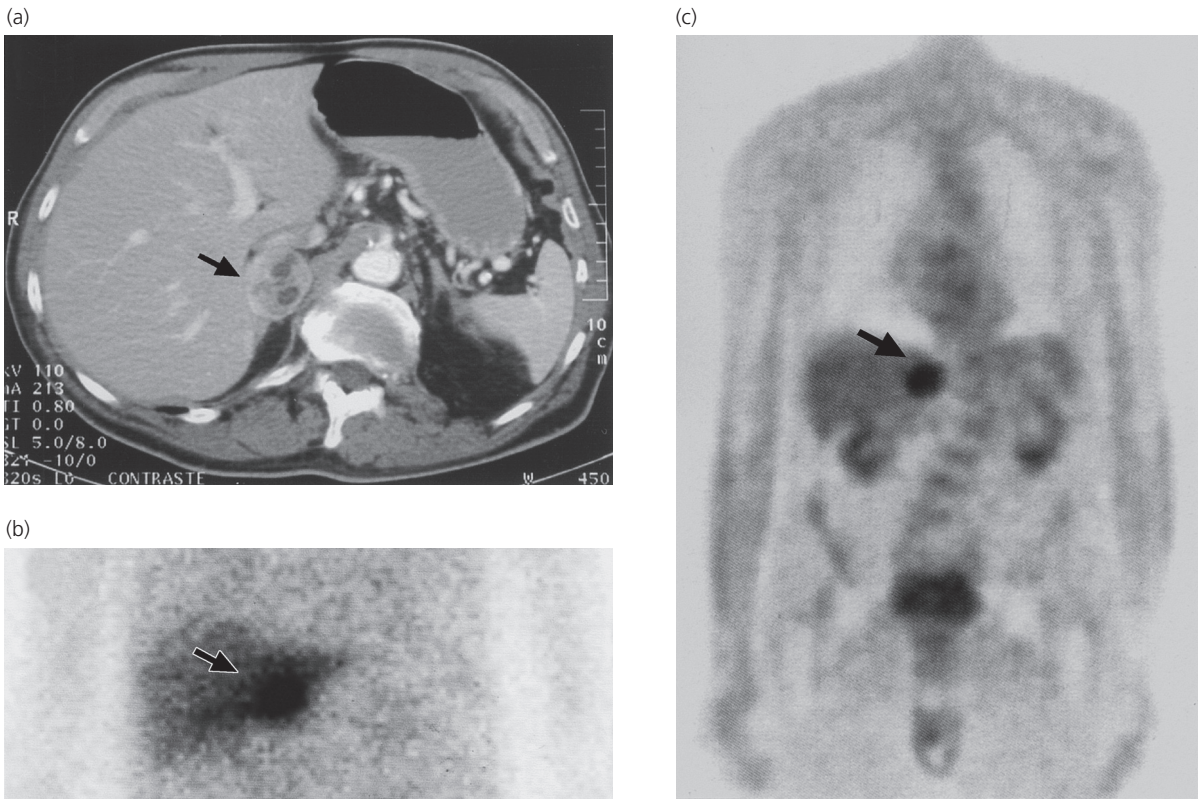


Figure 20.9 Pheochromocytoma in a 75-year-old man with recent-onset type 2 diabetes treated with a sulfonylurea, who was admitted on an emergency basis with severe chest pain and hypertension (blood pressure 240/130 mmHg). Blood glucose on admission was 27 mmol/L. Urinary catecholamine excretion was greatly increased, and a pheochromocytoma of the right adrenal was demonstrated by: (a) computed tomography; (b) scanning with ^{131}I-metaiodobenzylguanidine, which is taken up by catecholamine-synthesizing tissues; and (c) positron emission tomography with ^{18}F-fluorodeoxyglucose. After laparoscopic removal of the tumor, diabetes and hypertension both resolved.

Table 20.5 Genes associated with catecholamine-secreting pheochromocytomas and paragangliomas.

Gene	Germline mutation rate (% detected in all PPGL)	Key characteristics and associations
SDHB	10.3	Extra-adrenal tumors; malignant phenotype
SDHD	8.9	Extra-adrenal tumors; paternal inheritance
SDHC	*1*	Head and neck PGL
SDHA	<2	Extra-adrenal tumors
SDHAF2	*ND*	Head and neck PGL
VHL	7.3	von Hippel-Lindau disease
RET	6.3	Multiple endocrine neoplasia type 2
NF1	*3.3*	Neurofibromatosis type 1
TMEM127	<2	Adrenal tumors
MAX	<2	Malignant phenotype

PPGL, pheochromocytoma and paraganglioma.

outer adrenal cortex towards the adrenal vein [82]. For this reason, larger tumors with more marked disturbance of the normal anatomy or paragangliomas along the sympathetic chain are notable for predominantly secreting norepinephrine as conversion to epinephrine is compromised.

Disturbance to glucose tolerance in pheochromocytomas and paragangliomas

Hyperglycemia occurs in up to approximately 50% of people with pheochromocytomas and paragangliomas, mostly pheochromocytomas. The prevalence of diabetes is approximately 35% [85]. Its presence in a young hypertensive person of normal body weight should raise suspicion of pheochromocytomas and paragangliomas. The predominant mechanism is catecholamine-mediated reduction in insulin sensitivity and insulin secretion, predominantly caused by epinephrine rather than norepinephrine (Figure 20.10) [86–88]. Epinephrine inhibits β-cell insulin secretion via stimulation of α_2-adrenergic receptors [89]. In the liver, epinephrine activates β_2-adrenoceptors to enhance glycogenolysis transiently and gluconeogenesis in a more sustained fashion [90–92]. This hepatic gluconeogenesis is fueled by the precursors,

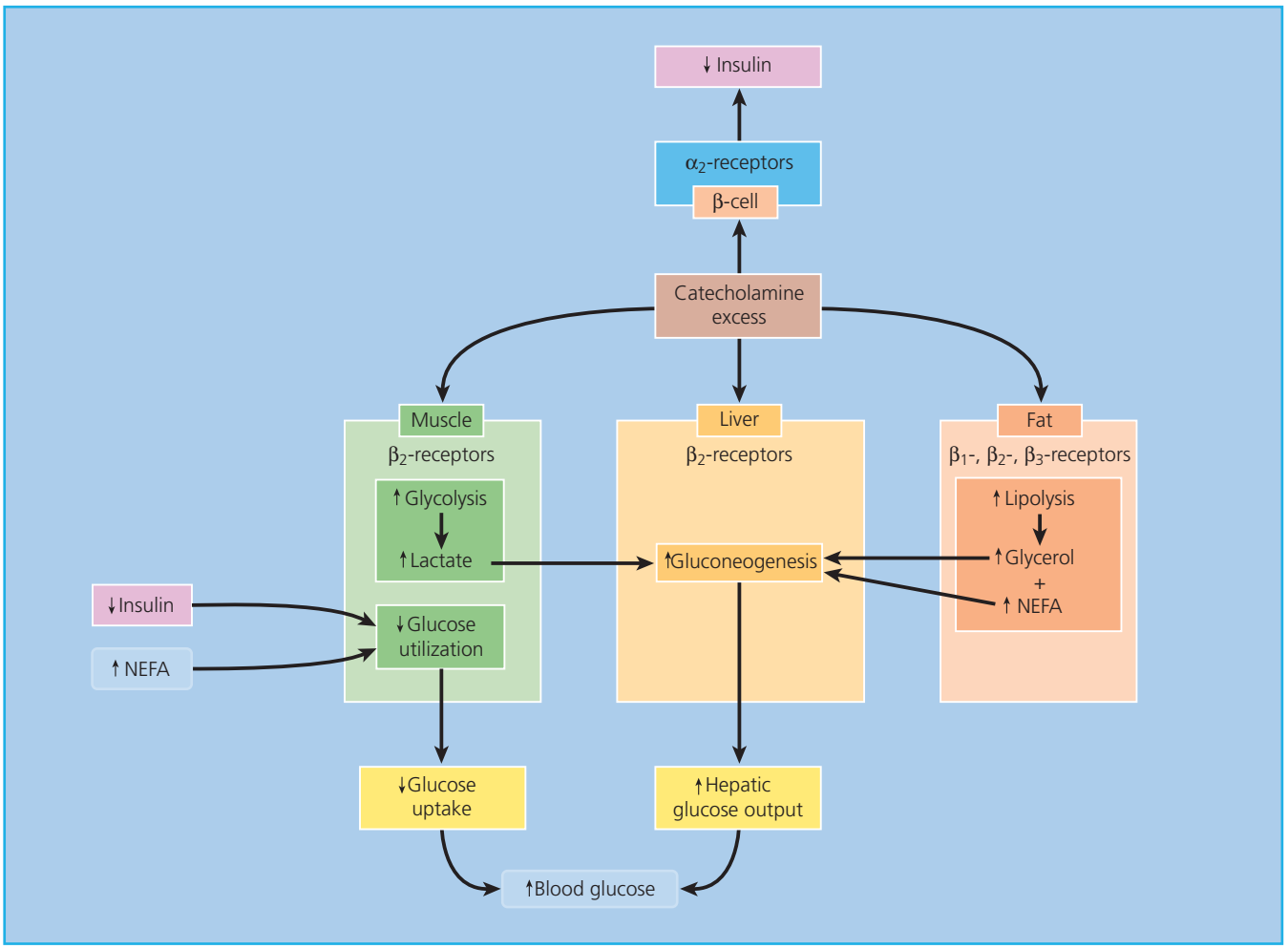


Figure 20.10 Mechanisms of hyperglycemia in pheochromocytoma. NEFA, non-esterified fatty acid.

lactate, alanine, and glycerol, generated by β_2-adrenergic stimulation of muscle glycolysis and adipose tissue lipolysis. Lipolysis in adipose tissue is also stimulated via the β_1- and β_3-adrenoceptors. In addition, epinephrine can impair glucose utilization in muscle through direct β_2-adrenergic effects. The predominance of these β_2-adrenergic effects probably explains why epinephrine, with its higher affinity for β_2-receptors, is more potent than norepinephrine in producing hyperglycemia [90–92]. All these effects are potent mechanisms that raise blood glucose, explaining why epinephrine release is an important component in correcting hypoglycemia after inhibition of insulin and increased glucagon secretion in the hierarchy of counter-regulatory responses (see Chapter 35).

Diagnosis and treatment of pheochromocytomas and paragangliomas

Pheochromocytomas and paragangliomas are diagnosed by demonstrating an excess of circulating catecholamines. This is most accurately achieved by measuring their metabolites, metanephrines, derived by the enzymatic action of catechol-O-methyl transferase in the urine over 24 h and in the plasma [79]. These measures are superior to historical measurement of the metabolite, vanylmandelic acid, and the catecholamines themselves in terms of sensitivity and specificity [79]. Imaging the tumor can be performed by either MRI or CT. Treatment is surgical removal of the tumor as an adrenalectomy, increasingly performed laparoscopically unless malignancy is suspected [79]. Preoperative preparation must be meticulous to prevent both a hypertensive crisis during manipulation of the tumor and cardiovascular collapse after its removal. This is achieved by initial α-receptor blockade, most commonly using the irreversible agent phenoxybenzamine, followed by a beta-blocker if needed. The order of implementation is important to prevent a hypertensive crisis from unopposed α-adrenoceptor stimulation. The preoperative α-adrenergic blockade often controls hypertension, but has less effect on glucose intolerance [90, 93]. In malignant pheochromocytoma where surgery is not possible, adrenolytic drugs, such as mitotane, can be used palliatively.

Outcome of pheochromocytomas and paragangliomas and the disturbance to glucose tolerance

Removal of the tumor corrects the metabolic abnormalities. If presentation, diagnosis, and treatment have occurred without undue delay, it also resolves the hypertension [90, 93–95]. Greater understanding of the molecular genetics of pheochromocytomas and paragangliomas makes clinical genetics input very important which can direct the order of genetic testing, even in seemingly isolated tumors [79, 81]. It is also straightforward to exclude hyperparathyroidism by measuring serum calcium as this simple test, if normal, goes a long way to excluding MEN1. Annual follow-up to exclude recurrent pheochromocytomas and paragangliomas is by measurement of plasma metanephrines. People with pheochromocytomas and paragangliomas due to identified genetic disorders should be followed up at least annually in dedicated services combining the skills of endocrinology and clinical genetics.

Effects of diabetes on adrenal medulla function

Function of the adrenal medulla may be selectively impaired in people with long-standing diabetes and hypoglycemia unawareness; attenuation of the epinephrine response to hypoglycemia can delay the restoration of normal serum glucose levels. Epinephrine responses can remain normal to other stimuli, indicating failure of sympathetic activation at a specific, possibly hypothalamic level (see Chapter 35).

Other endocrine conditions causing disturbance of glucose tolerance

Three tumor types derived from the gastroenteropancreatic endocrine system can cause disturbance of glucose tolerance: glucagonoma, somatostatinoma, and tumors secreting vasoactive intestinal polypeptide (VIPoma). While these tumors are still referred to as "neuroendocrine tumors (NETs)" the term is misleading as their embryological origin is from the gut endoderm; they are not related to neural development.

Glucagonoma

Glucagonoma is a rare tumor of the α cell of the pancreatic islet. The first clear-cut case was reported in 1942, but the "glucagonoma syndrome" (in a series of nine patients with similar symptoms) was not described until 1974 [96, 97]. It may form part of MEN1 caused by mutations in the tumor suppressor gene, *MENIN* [98]. In a series of 21 patients, the syndrome's most striking clinical features were weight loss (71%), necrolytic migratory erythema (67%) (Figure 20.11a), diabetes (38%), cheilosis or stomatitis (29%), and diarrhea (29%) [99]. In this report, patients with the combination of necrolytic migratory erythema and diabetes mellitus were diagnosed more rapidly (after a mean of 7 months), but some cases remain undetected for years. Glucagonoma should be considered particularly in people with diabetes and unexplained weight loss or a chronic blistering skin rash.

Necrolytic migratory erythema (Figure 20.11a) is described in full in Chapter 52. It usually involves the buttocks, groin, thighs, and distal extremities, and characteristically remits and relapses [96, 97]. Hyperglucagonemia may contribute to the rash, as also may hypoaminoacidemia through glucagon's enhancement of amino acid uptake by the liver and zinc deficiency [97]. The glucagonoma syndrome is also characterized by a normochromic normocytic anemia, a tendency to thrombosis (pulmonary embolism is a common cause of death) and neuropsychiatric disturbances [96]. Reporting of the prevalence of diabetes in glucagonoma has been variable but it probably affects approximately three-quarters of individuals [96]. In cohorts with this detection rate, the hyperglycemia has most commonly been mild and may respond to oral antidiabetes agents. In studies with lower rates of diagnosis, 75% of people required insulin [96]. The hyperglycemia is largely brought about by the effects of glucagon on stimulating hepatic gluconeogenesis and, in adequately fed individuals, glycogenolysis [97].

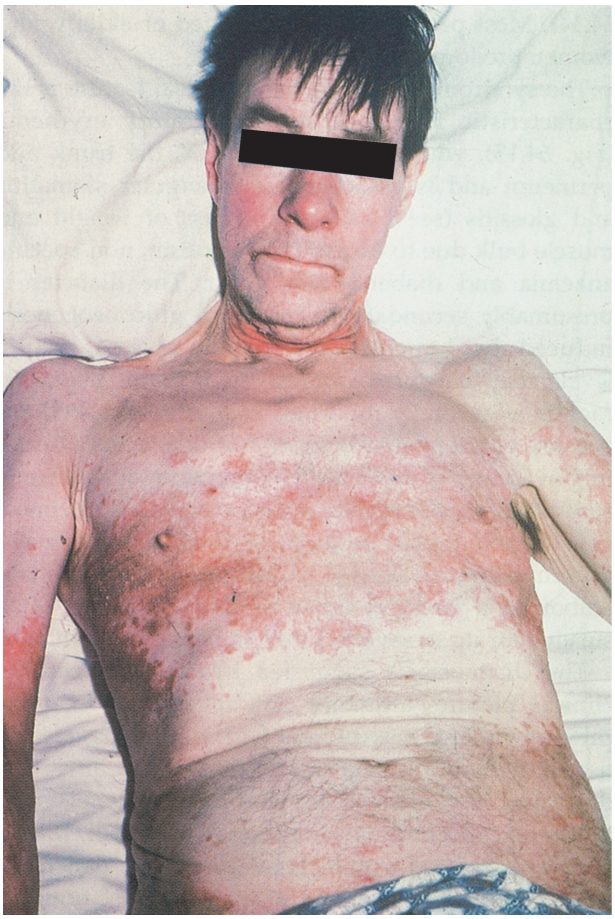
The diagnosis is suggested by finding a pancreatic mass and high fasting plasma glucagon concentration in the absence of other causes of hyperglucagonemia (e.g. severe stress, hepatic and renal failure, poorly controlled diabetes, small-bowel malabsorption, and synthetic androgenic drugs) [96, 97, 100]. Surgical removal of the tumor is the treatment of choice, but 50% of tumors have metastasized to the liver by the time of diagnosis (Figure 20.11b) [99]. Treatment can then be completed by hepatic artery embolization and/or chemotherapy; somatostatin analogs can also suppress glucagon secretion. The rash may respond to normalization of glucagon levels following removal of the tumor or by the use of somatostatin analogs. The administration of zinc, a high-protein diet and control of the diabetes with insulin may also help [96, 97, 99, 100].

Somatostatinoma

Somatostatinomas are extremely rare tumors arising in 1 in 40 million individuals from δ-cells of the pancreatic islet or enteroendocrine cells of the duodenum and ampulla of Vater [101]. They may be sporadic or as part of genetic syndromes, such as MEN1 [101]. The first two somatostatinomas were found incidentally during cholecystectomy [102, 103], but a subsequent case was diagnosed preoperatively and extensively investigated [104]. The diagnosis was suggested by the triad of diabetes, steatorrhea and gallstones, associated with a tumor of the duodenum [104]. These features, together with hypochlorhydria, are attributable to the widespread inhibitory effects of somatostatin on endocrine and exocrine secretions [101]. Consistent with inhibition of both insulin and glucagon by somatostatin, hyperglycemia is mild, non-ketotic and satisfactorily controlled without insulin [104].

Diagnosis is made by clinical presentation, measuring elevated fasting levels of circulating somatostatin and imaging by CT or MRI. Octreotide scintigraphy can also be used to localize

(a)



(b)

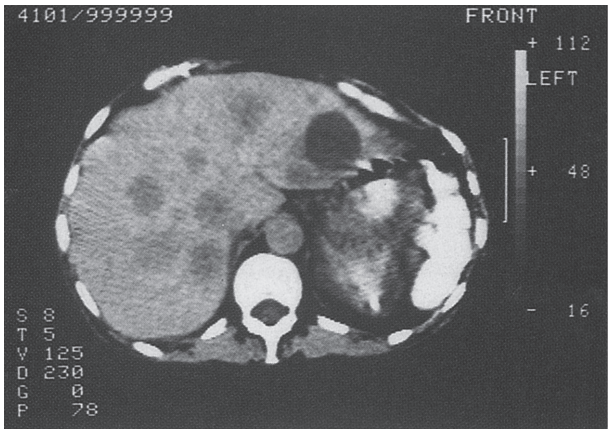


Figure 20.11 Glucagonoma showing characteristic necrolytic migratory erythema (a) and multiple hepatic metastases (b). This man had non-ketotic diabetes, controlled with low dosages of insulin; the rash recurred many times despite treatment with somatostatin analog. He died from pulmonary embolus. Source: Courtesy of Professor Stephen Bloom, Imperial College School of Medicine, London, UK.

the tumor. Surgical resection is the treatment of choice and can be curative. Where tumors are large and malignant with metastases at the time of diagnosis, debulking, embolization, and chemotherapy (including radiolabeled somatostatin analogs) are appropriate [101].

Vasoactive intestinal peptide-producing tumor (VIPoma)

The first VIP-secreting tumor was recognized by Verner and Morrison in 1958 [105]. Classic features are caused by elevated circulating VIP levels and include watery diarrhea (pancreatic cholera), hypokalemia, and achlorhydria [100, 106]. Hypercalcemia and glucose intolerance occur in half of the patients, but overt diabetes is unusual; hyperglycemia is probably secondary to the glycogenolytic effect of VIP and/or to hypokalemia, which can impair both insulin secretion and insulin sensitivity. Diagnosis is aided by serum assay for fasting VIP levels. The tumors are usually large and have metastasized from the pancreatic tail by the time of diagnosis. Debulking surgery forms the mainstay of treatment and 10-year survival is approximately 40% [106].

Hyperthyroidism

Hyperthyroidism is defined by overproduction of thyroid hormones. Hyperthyroidism leads to thyrotoxicosis, the manifestations of increased circulating thyroid hormones (Table 20.6) [107]. Ignoring the association of autoimmune hyperthyroidism (Graves' disease) with T1DM, thyrotoxicosis per se can disturb glucose tolerance in approximately one-third of individuals, with diabetes occurring in a further 8% of patients [108]. There is evidence for insulin resistance as the primary defect [107, 108], especially in those who are overweight [109], although insulin secretion may also be impaired [108, 110]. Glucose production and expression of the hepatocyte glucose transporter 2 (GLUT-2) protein are enhanced by thyroid hormone excess [111–113]. The insulin resistance is improved with restoration of euthyroidism even if body mass index (BMI) rises [108]. When hyperthyroidism develops in people with insulin-treated diabetes, glucose control deteriorates and insulin requirements increase in approximately half the patients; these changes are reversed following treatment of hyperthyroidism [114]. In addition to these alterations in insulin secretion and

Table 20.6 Clinical features of thyrotoxicosis plus features associated with Graves' disease.

Clinical features of thyrotoxicosis
Weight loss despite full, possibly increased, appetite
Tremor
Heat intolerance and sweating
Agitation and nervousness
Palpitations, shortness of breath/tachycardia ± atrial fibrillation
Glucose intolerance
Amenorrhea/oligomenorrhea and consequent subfertility
Diarrhea
Hair loss
Easy fatigability, muscle weakness and loss of muscle mass
Rapid growth rate and accelerated bone maturation (children)
Specific features associated with Graves' disease
Bruit in a diffuse, firm goiter
Thyroid eye disease, also called Graves' orbitopathy
Pretibial myxedema—thickened skin over the lower tibia
Thyroid acropachy (clubbing of the fingers)
Other autoimmune features (e.g. vitiligo)

action, the response to oral glucose tolerance testing is also altered in hyperthyroidism because of faster intestinal absorption [88].

Hypothyroidism

Hypothyroidism is defined by insufficient production of thyroid hormones. Similar to hyperthyroidism, hypothyroidism (both overt and subclinical) is associated with impaired glucose tolerance. Although the underlying mechanism is less well characterized compared with hyperthyroidism, raised insulin levels suggest insulin resistance as the metabolic disturbance in hypothyroidism [113]. Glucose transport and uptake into myocytes via GLUT-5 transporters is decreased, potentially due to reduced blood flow to muscle tissue [115]. Insulin clearance is also reduced [113]. Together these physiological changes result in increased circulating glucose levels [113].

Primary hyperaldosteronism

Primary hyperaldosteronism was originally described by Conn in 1955 in a patient with hypertension, hypokalemia, and neuromuscular symptoms associated with an adrenocortical adenoma secreting aldosterone [82]. A benign adenoma is the most common primary cause (65%) with bilateral hyperplasia accounting for 30% of cases. A handful of cases are brought about by a genetic recombination event between the genes encoding two closely related steroidogenic enzymes (cytochrome P450 11β-hydroxylase and aldosterone synthase) called familial type 1 hyperaldosteronism or glucocorticoid-remediable hyperaldosteronism. This causes aldosterone secretion under the regulation of ACTH, which is suppressible by glucocorticoids [82]. Although debate is active over the extent to which more subtle normokalemic aldosterone excess causes hypertension, the relevance of primary hyperaldosteronism to glucose tolerance relates largely to the hypokalemia that is part of the classic Conn syndrome. Low serum potassium impairs insulin secretion [94]. Others have questioned whether aldosterone might exert other diabetogenic effects on glucose metabolism, although this remains unclear [116]. Glucose intolerance has been reported in approximately 50% of patients [117]. This is generally mild and overt diabetes is unusual. Defective insulin release has been implicated with delayed or reduced insulin responses following oral glucose challenge. Removal of the adenoma or potassium loading can correct these defects [117].

Primary hyperparathyroidism

Primary hyperparathyroidism is secondary to hypersecretion of parathyroid hormone, usually by a parathyroid adenoma and less commonly by parathyroid hyperplasia [118]. The prevalence of diabetes in primary hyperparathyroidism is approximately threefold higher than in the general population [119–121], with some people requiring insulin therapy. Insulin resistance with hyperinsulinemia is generally held responsible, with raised intracellular calcium limiting cellular glucose uptake [121]. It has been debated whether treatment by parathyroidectomy improves glucose homeostasis; some reports argue that it is beneficial for both diabetes and impaired glucose tolerance [122, 123] while others find less effect [124, 125]. Possibly this relates to duration and severity of the calcium disturbance. With the widespread availability of serum biochemistry, hyperparathyroidism is shifting from a symptomatic disorder to an asymptomatic one where serum calcium tends to be only marginally elevated. In the latter scenario, glucose tolerance appears less affected [126].

Hypopituitarism with growth hormone deficiency

In children, lack of GH increases insulin sensitivity such that young children with GH-deficiency tend to develop fasting and readily provoked hypoglycemia [127, 128]. Using insulin tolerance tests, children with GH-deficiency were more insulin-sensitive than short children with normal GH secretion [127]. This exaggerated insulin sensitivity attenuates with age and puberty, possibly following increased gonadal steroid production [127] and changes in body composition, characterized by increased abdominal fat, such that adults with GH deficiency demonstrate insulin resistance [12]. Given that GH excess is diabetogenic and acute GH administration raises fasting glucose and fasting insulin levels, and reduces insulin sensitivity [14, 17], the value of GH replacement to improve glucose tolerance is likely to be related to whether it can be administered physiologically.

Given this challenge, it is not surprising that the long-term results of GH replacement are somewhat conflicting [12]: a 30-month study showed a deterioration in glucose tolerance and insulin sensitivity despite an increase in lean body tissue and a reduction of fat mass [129]; another study of 6 months' duration found rises in fasting glucose and HbA_{1c} without effects on peripheral or hepatic sensitivity [130]; however, a 5-year trial concluded that GH replacement decreased HbA_{1c} levels [131]. Another study, evaluating the impact of GH therapy in people with GH-deficiency during transition from childhood to adulthood, showed that the beneficial effects of chronic treatment on body

composition did not overcome the direct antagonistic effects on insulin action [132]. Insulin secretion may also deteriorate during GH administration [129]. Thus, the replacement of GH in hypopituitary patients with diabetes is contentious: long-term treatment with GH may improve insulin sensitivity via improvements in body composition; however, such individuals need to be monitored regularly and overtreatment that might lead to the development of diabetes should be avoided [12, 133].

Endocrine disorders that associate with diabetes

Several endocrine disorders are associated with T1DM because of a common etiology and similar pathology (e.g. autoimmune adrenalitis [Addison disease] or autoimmune thyroid disease). Attention for the onset of new autoimmune pathologies is warranted in people with these disorders. In people with T1DM, screening can be justified to exclude hyperthyroidism or hypothyroidism by measuring serum thyroid stimulating hormone (TSH) annually. The development of Addison disease in people with T1DM markedly increases sensitivity to insulin such that unanticipated hypoglycemic reactions occur as dose requirements fall. Even in the absence of diabetes and insulin therapy, Addison disease can cause hypoglycemia, especially in children. Rare conditions resembling T1DM with associated endocrinopathies, such as the autoimmune polyglandular syndromes or POEMS syndrome may occur. Monogenic causes of diabetes that affect other endocrine organs are covered in Chapter 18. Examples (and their respective endocrine disorder) include the various types of hemochromatosis (primary hypogonadism, Chapter 21), Wolfram syndrome (diabetes insipidus) and Kearns–Sayre syndrome (hypoparathyroidism, hypogonadism, and hypopituitarism). Here, polycystic ovarian syndrome (PCOS) is addressed as a complex endocrine disorder that includes insulin resistance. The hormonal alterations in PCOS share relevance with some of the mechanisms underlying glucose homeostasis in pregnancy and obesity, covered in Chapters 61 and 16, respectively.

Polycystic ovarian syndrome

PCOS is defined as clinical or biochemical hyperandrogenism with oligo- or anovulation where other definable causes have been excluded [134–139]. Some definitions incorporate the detection of multiple ovarian cysts into the diagnosis [138, 139], although these occur in approximately half of women with Cushing syndrome and are non-discriminatory (Figure 20.12) [140, 141]. PCOS occurs in 5–10% of women of reproductive age and is characterized primarily by insulin resistance although there is also evidence of β-cell dysfunction [136, 142]. Impaired glucose tolerance and T2DM are present in nearly 40% and 7.5–10%, respectively, of women with PCOS, with the former having a tendency to progress to T2DM and being associated with an approximate threefold higher risk of gestational diabetes [142]. These data are confounded to some degree by the effect of obesity, but the incidence of PCOS remains increased across ethnicities whereas obesity rates vary [136]. Indeed, it can be argued that PCOS in women with normal BMI represents the most severe form of the disorder where genetic screening programs are most likely to identify PCOS susceptibility genes.

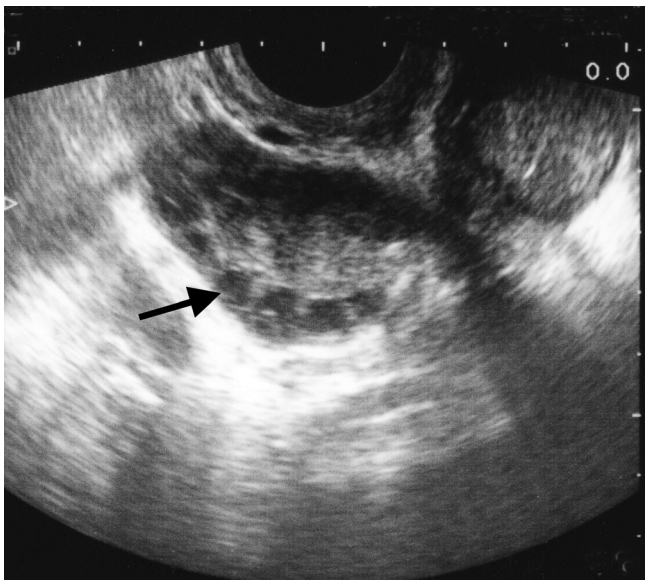


Figure 20.12 Polycystic ovary syndrome, showing characteristic ultrasonographic appearance of large, mainly peripheral cysts (arrow).

The source of the androgens is both the adrenal cortex and the ovary [143]. The raised insulin levels can stimulate androgen production by the ovary and interfere with other aspects of ovarian function. Within the adrenal cortex, where insulin receptors are expressed in the zona fasciculata of the adrenal cortex [144], there is some evidence that insulin can influence glucocorticoid versus sex steroid precursor production [143].

The diagnosis of PCOS is one of exclusion, meaning that clinical and biochemical findings are only supportive of the condition [145]. Serum estradiol is detectable and usually >200 pmol/L. Endocrine abnormalities include increases in serum luteinizing hormone (LH) leading to a raised LH : FSH (follicle stimulating hormone) ratio, androstenedione and testosterone concentrations. Serum sex hormone-binding globulin (SHBG) levels are commonly low. Ovarian ultrasound is useful to help exclude the presence of a tumor underlying the androgen excess [145].

Further evidence that the condition is caused by insulin resistance comes from its amelioration with exercise and agents that improve insulin sensitivity such as metformin or thiazolidinediones [146]. As well as lowering blood glucose, these agents improve menstrual regularity and increase the chance of ovulatory cycles [146].

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21 Pancreatic Diseases and Diabetes

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Key points

- Pancreatic disease is a rare cause of diabetes.
- Acute pancreatitis is associated with transient hyperglycemia which rarely persists.
- Chronic pancreatitis secondary to any cause can lead to permanent diabetes which is typically difficult to control; imaging studies reveal dilated ducts and pancreatic calculi.
- Tropical calcific pancreatitis is a disease of unknown etiology found in low- and middle-income countries associated with large pancreatic calculi and diabetes (fibrocalculous pancreatic diabetes).
- Hereditary hemochromatosis is an inherited disorder that produces diabetes secondary to iron deposition in the pancreatic islets and subsequent islet cell damage.
- Pancreatic carcinoma may complicate type 2 diabetes, diabetes secondary to chronic pancreatitis and, most commonly, fibrocalculous pancreatic diabetes. It is important to suspect malignancy in any patient who complains of back pain, jaundice, or weight loss in spite of good glycemic control.
- Pancreatic surgery can lead to diabetes that is insulin-requiring and often difficult to control.
- Cystic fibrosis is a relatively common genetic disorder affecting the lung, pancreas, and other organs. Up to 75% of adults with cystic fibrosis have some degree of glucose intolerance.

Introduction

The pancreas plays an important role in carbohydrate metabolism and is a key player in the pathophysiology of different types of diabetes. It is therefore surprising that pancreatic disease is a rare cause of diabetes, accounting for less than 0.5% of all cases of diabetes. The prevalence of undiagnosed disease, however, may be much higher [1]. The rarity of diabetes in pancreatic disease may be explained, in part, by the presence of considerable β-cell reserve in most individuals. It has been estimated that nearly 80–90% of the pancreas has to be destroyed or removed for diabetes to develop in otherwise healthy individuals.

A number of disease processes affecting the pancreas can lead to diabetes; some of these are listed in Table 21.1. Most of these conditions damage the exocrine as well as endocrine components of the pancreas. The exocrine parenchyma and islet tissue lie in intimate contact with each other and are functionally related. This may explain why parenchymal disease can impair β-cell function [2].

Acute pancreatitis

Acute pancreatitis varies considerably in its impact on the gland and its metabolism. Pathologic findings vary from mild edema to hemorrhagic necrosis, and the clinical presentation spans a wide spectrum from mild to fulminating or fatal illness.

The most common causes of acute pancreatitis are alcoholism and gallstone disease. Table 21.2 sets out the causes of acute pancreatitis. It is of interest that diabetes, in itself, is a risk factor for acute pancreatitis, and that use of certain classes of oral antidiabetes agents (particularly the glucagon-like peptide-1 receptor agonists and the dipeptidyl peptidase-4 inhibitors) has been reported to be associated with acute pancreatitis [3, 4]. A recent review by the U.S. Food and Drug Administration and the European Medicines Agency has concluded. However, that the currently available data do not support a causal relationship between incretin-based drugs and pancreatitis [5].

Classically, the disease presents with sudden onset of epigastric pain, associated with nausea and vomiting, aggravated by

Textbook of Diabetes, Fifth Edition. Edited by R. Holt, C. Cockram, A. Flyvbjerg and B. Goldstein.

Table 21.1 Pancreatic diseases associated with glucose intolerance and diabetes.

Inflammatory
Acute
Chronic, including fibrocalculous pancreatic diabetes
Infiltration
Hereditary hemochromatosis
Secondary hemochromatosis
Very rare causes: sarcoidosis, amyloidosis, cystinosis
Neoplasia
Adenocarcinoma of the pancreas
Glucagonoma
Surgical resection or trauma
Cystic fibrosis

food and partially relieved by sitting up and leaning forward. Physical examination reveals low-grade fever, tachycardia, and hypotension. Jaundice may also be found infrequently. Cullen sign (periumbilical discoloration) and Grey Turner sign (flank discoloration) indicate severe necrotizing pancreatitis.

Commonly found metabolic abnormalities include hyperglycemia, hypocalcemia, hyperlipidemia, hypoalbuminemia, and coagulation disorders [6]. Serum levels of amylase and lipase are elevated, but these are neither sensitive nor specific. Computed tomography (CT) or magnetic resonance imaging (MRI) shows edema of the pancreas. Loss of the normal enhancement on dynamic CT scanning indicates pancreatic necrosis.

Most patients with acute pancreatitis develop transient hyperglycemia, which mostly results from a rise in glucagon levels rather than from β-cell injury [7]. Hyperglycemia is usually mild and resolves within days to weeks without needing insulin treatment. Permanent diabetes is rare and occurs mostly in cases with fulminant disease and multiorgan failure, in whom the incidence approaches 25% [8]. Blood glucose levels exceeding 11.1 mmol/L (200 mg/dL) during the first 24 hours indicate a poor prognosis [9].

Non-specific elevations of serum amylase and lipase may also be found in diabetic ketoacidosis [10]. Acute pancreatitis, however, may affect up to 11% of patients with ketoacidosis, usually with mild or even no abdominal pain [9].

Table 21.2 Causes of acute pancreatitis.

Common (75% of cases)	Uncommon
Alcohol abuse	**Drugs**
Gallstone disease	Sulfonamides
Idiopathic	Tetracyclines
	Valproate
	Didanosine
	Estrogens
	Metabolic disorders
	Hypertriglyceridemia
	Hypercalcemia
	Diabetic ketoacidosis
	Infections
	Mumps, Coxsackie, and HIV viruses
	Mycoplasma pneumoniae
	Trauma
	Abdominal injury
	Surgery, including ERCP
	Miscellaneous
	Hereditary relapsing pancreatitis
	Pancreatic cancer
	Connective tissue diseases
	Pancreas divisum

ERCP, endoscopic retrograde cholangiopancreatography.

Chronic pancreatitis

This condition is characterized by progressive and irreversible destruction of the exocrine pancreatic tissue, leading to exocrine pancreatic insufficiency and varying degrees of glucose intolerance which often require insulin. The causes of chronic pancreatitis vary according to the geographic location (Table 21.3).

Alcohol abuse accounts for most of the cases (>85%) in European and North American populations. Alcohol alters the composition of pancreatic secretions, leading to the formation of proteinaceous plugs that block the ducts and act as foci for calculi formation. Tropical chronic pancreatitis is a distinct form of the disease that is not associated with excessive alcohol intake and is prevalent in low- and middle-income countries [11].

Hereditary chronic pancreatitis is a rare entity, inherited in an autosomal dominant fashion. Mutations in a number of genes have been implicated including *PRSS1* (encoding cationic trypsinogen), *SPINK1* (serine protease inhibitor, Kazal type 1), and *CFTR* (cystic fibrosis transmembrane conductance regulator) [12–15].

Obstructive chronic pancreatitis is a rare condition that follows occlusion of pancreatic ducts by tumors, scarring, pseudocysts, or congenital anomalies. Stones are not seen. Surgery or endoscopic dilatation may occasionally be curative.

Idiopathic pancreatitis, which accounts for 10–20% of all cases, affects two distinct age groups, one with onset at 15–25 years and the other at 55–65 years [16]. Cigarette smoking is a risk factor and mutations in specific genes have also been postulated [15, 17, 18].

Table 21.3 Causes of chronic pancreatitis.

Common (90% of cases)	Rare
Alcohol abuse	Hereditary relapsing pancreatitis
Idiopathic	Obstructive chronic pancreatitis
Tropical chronic pancreatitis	

Epidemiology

Chronic pancreatitis is prevalent worldwide. In Europe and North America, the incidence is about four cases per year per 100,000 population [19, 20]. Tropical chronic pancreatitis is confined to tropical and subtropical regions of the world, with the highest prevalence rates reported in southern India.

Pathologic features

The term chronic calcific pancreatitis accurately describes the pathologic changes in over 95% of cases of chronic pancreatitis in European and North American countries. The ductal and acinar lumina are filled with proteinaceous plugs which later calcify, forming small stones composed chiefly of calcium carbonate or calcite. Huge stones can occur but these are more characteristic of tropical pancreatitis. The stones are found diffusely throughout the affected organ. Microscopically, there is atrophy of the ductal epithelium and stenosis of the ducts, associated with patchy fibrosis. There may also be foci of necrosis, with infiltration by lymphocytes, plasma cells, and histiocytes [21]. Ultimately, the pancreas shrivels and develops an opaque capsule that may adhere to surrounding organs.

As fibrosis progresses, the acini atrophy and eventually disappear, leaving clusters of islets surrounded by sclerosed parenchyma. Neoformation of islet cells from ductal tissue can occur (nesidioblastosis) (Figure 21.1). Immunohistochemistry studies reveal generalized decrease in the number of islets, accompanied by overall reduction in β-cell density and insulin immunoreactivity which correspond to disease duration and C-peptide levels (Figure 21.2; Table 21.4) [22, 23].

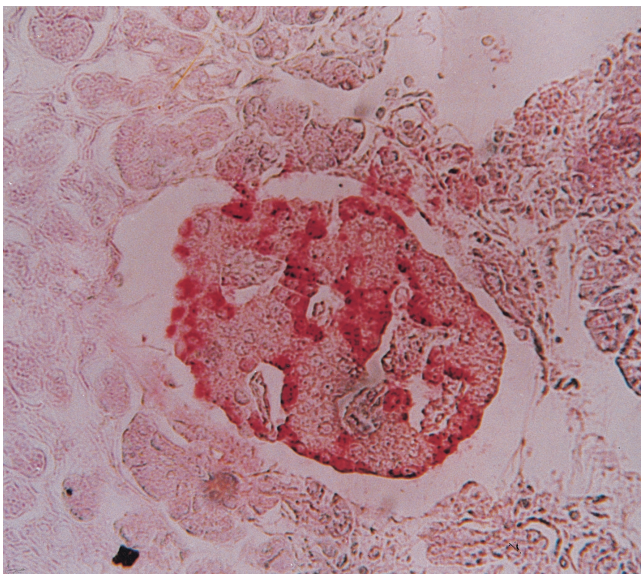

Figure 21.1 Nesidioblastosis, from a case of fibrocalculous pancreatic diabetes, showing islet tissue arising from ductal remnants. Stain aminoethylcarbazole; magnification ×40.

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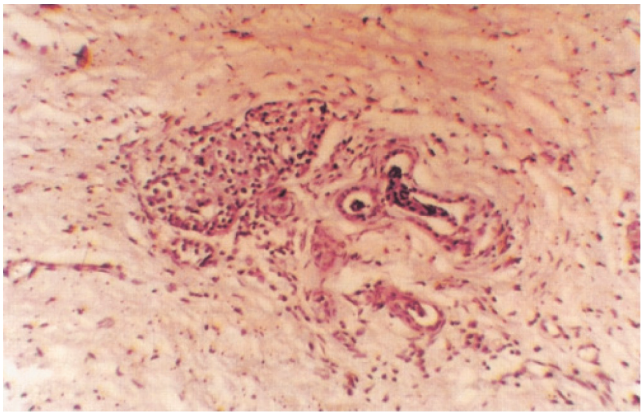

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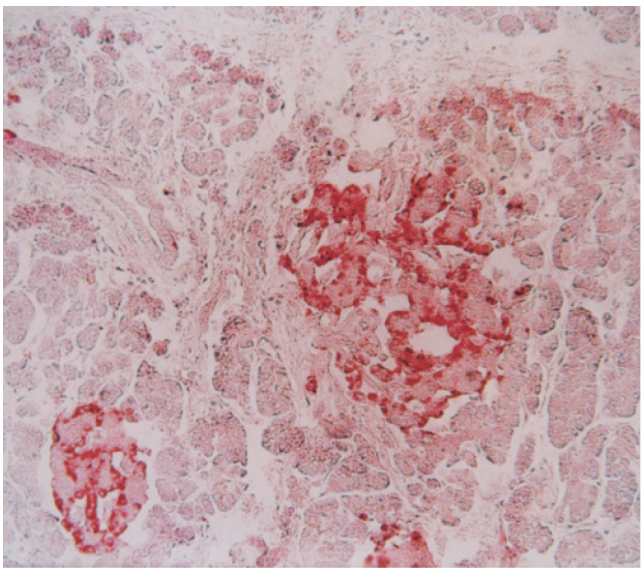


Figure 21.2 Histologic features of chronic pancreatitis, from cases of fibrocalculous pancreatic diabetes. (a) Exocrine tissue is entirely replaced by dense fibrosis that spares the islets. Hematoxylin and eosin stain; magnification ×40. (b) A hyperplastic islet. Section immunostained for insulin; magnification ×40.

Clinical features and diagnosis

Abdominal pain is the predominant symptom and the usual reason for seeking medical care. The pain is usually steady, boring and agonizing, and located in the epigastrium or left hypochondrium with radiation to the dorsal spine or the left

Table 21.4 Islet cell changes in chronic pancreatitis [28].

Cell type	Changes observed
β cells	Decreased numbers (40% below controls)
α cells	Increased numbers
β-cell : α-cell ratio	0.6–2.5 (controls, 3.0–3.5)
PP cells	Increased numbers
δ (D) cells	Unchanged

shoulder. Bending forward or assuming the knee–chest position relieves the pain. The cause of the pain is unknown, but may relate to increased intrapancreatic or intraductal pressure, or to ischemia of the pancreas. It tends to remit and relapse and follows an unpredictable course. The development of end-stage pancreatic disease is associated with disappearance of the pain in many cases.

Exocrine pancreatic insufficiency may manifest with steatorrhea and features of fat-soluble vitamin deficiency, although steatorrhea may not be apparent on a low-fat diet. The combination of oily and greasy stools with diabetes should raise the suspicion of chronic pancreatitis.

Investigations

Demonstration of pancreatic calculi on a plain X-ray of the abdomen is diagnostic (Figure 21.3). In cases where obvious calculi cannot be found, ultrasonography, CT scanning or endoscopic retrograde cholangiopancreatography (ERCP) will help to confirm the diagnosis. ERCP is considered the gold standard and usually reveals irregular dilatation of the pancreatic ducts with filling defects caused by stones (Figure 21.4). CT scanning shows patchy increases in parenchymal density and, ultimately, atrophy of the gland.

Exocrine pancreatic function can be assessed by measuring the urinary excretion of compounds that are liberated in the gut by pancreatic enzyme action on orally ingested precursors such as NBT-PABA (para-aminobenzoic acid) or fluorescein dilaurate (pancreolauryl). Screening tests of pancreatic enzymes (fecal chymotrypsin, fecal elastase) are also used as they are simpler to perform but are less specific. Measurement of pancreatic output (via a tube placed in the duodenum) following ingestion of the Lundh test meal may also be helpful. Serum amylase is usually normal, except during acute attacks.

Diabetes in chronic pancreatitis

Abnormal glucose tolerance and diabetes complicate around 40–50% of cases of chronic pancreatitis. Unlike acute pancreatitis, the cause here is damage to the β cells, owing to loss of trophic signals from the exocrine tissue [2, 24]. The diabetes is of insidious onset and usually occurs several years after the onset of pain. The prevalence has been assessed at 60% after 20 years [25]. Half or more of patients require insulin for optimal glycemic control [26, 27], but ketoacidosis is rare, even if insulin is withdrawn. Possible explanations include better preservation of β-cell function (compared with type 1 diabetes [T1DM]) [28], reduced glucagon secretion and lower body stores of triglyceride, the major substrate for ketogenesis [28, 29]. On account of the lower glucagon reserve, these people are also prone to severe and prolonged hypoglycemia, and often diabetes is difficult to control with wide fluctuations of blood glucose levels.

Chronic diabetic complications

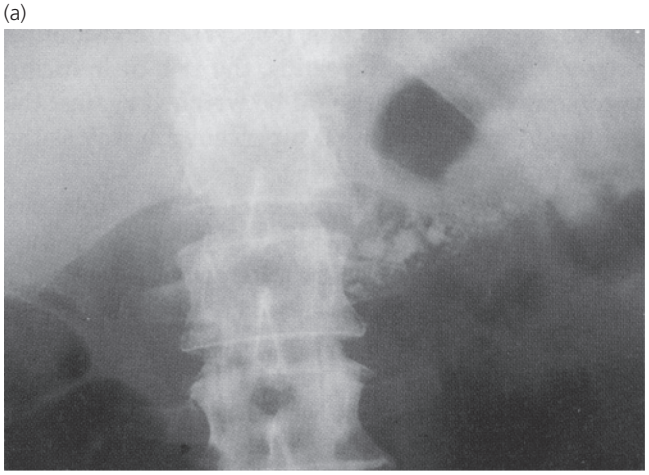
It was originally thought that people with pancreatic diabetes were not at increased risk of microvascular complications; however, it has now been shown that retinopathy [30], nephropathy [31], and neuropathy [32] occur in these individuals at frequencies similar to those with type 2 diabetes (T2DM). The risks of macrovascular complications, however, are relatively low. This may partly be explained by the favorable blood lipid profile that often accompanies the malnutrition commonly seen in these people [33].

Management of diabetes in chronic pancreatitis

Removal of obvious causes, such as alcohol and hypertriglyceridemia, will help to prevent progression of the damage to the gland.

Pain can be very difficult to manage. Measures include total abstinence from alcohol, dietary modification (small frequent

(a)



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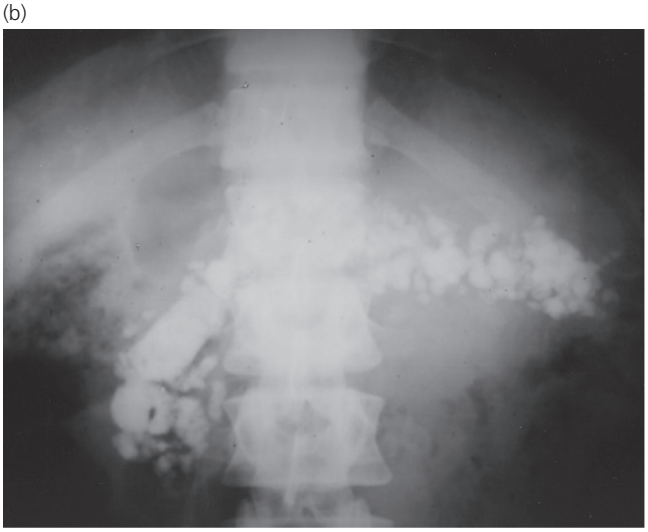
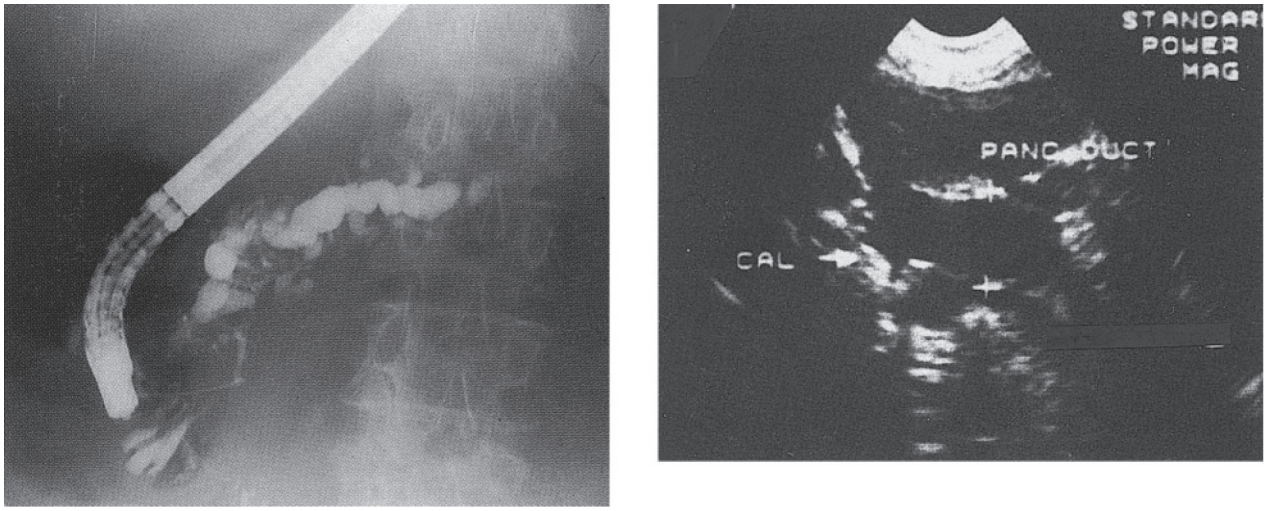


Figure 21.3 Pancreatic calculi, showing characteristic patterns in (a) alcoholic chronic pancreatitis, and (b) fibrocalculous pancreatic diabetes.

(a)



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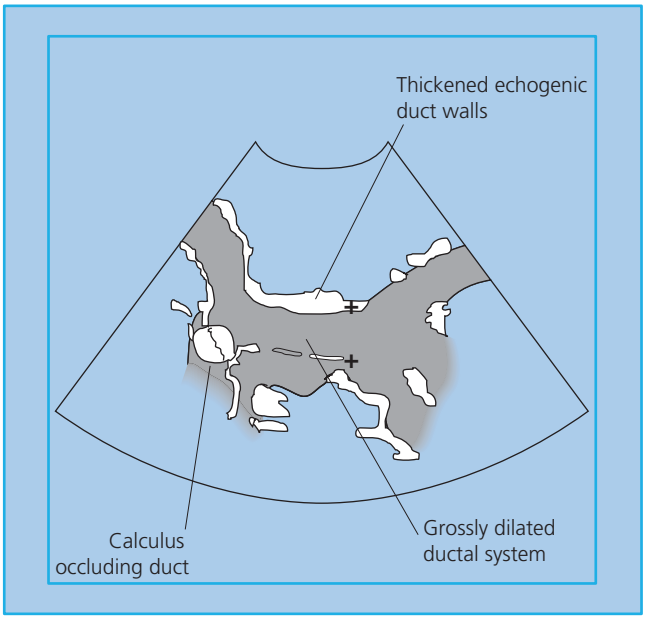

Figure 21.4 Investigations in chronic pancreatitis. (a) Endoscopic retrograde cholangiopancreatogram, showing dilatation and irregularity of the pancreatic ductal system in a patient with alcoholic chronic pancreatitis. Source: Courtesy of Professor Jonathan Rhodes, Liverpool. (b) Ultrasound scan of the pancreas from a patient with fibrocalculous pancreatic diabetes, demonstrating highly echogenic parenchyma and duct walls (fibrosis), grossly dilated ducts and calculi. Source: Courtesy of Dr. S. Suresh, Chennai, India.

meals with low fat content), analgesics, and the somatostatin analog, octreotide, which suppresses pancreatic exocrine secretion. In a subgroup of patients, massive doses of non-enteric-coated preparations of pancreatic enzymes have been shown to reduce pain. Surgical interventions include sphincterotomy, internal drainage of pancreatic cysts, endoscopic removal of calculi (via ERCP), insertion of duct stents, and denervation procedures. Total resection of the pancreas followed by whole pancreas or islet cell transplantation may be an option for intractable cases.

Malabsorption can be effectively treated with a low-fat diet with pancreatic enzyme supplements (along with histamine H_2 blocker or proton pump inhibitor to block gastric acid secretion) taken at meal times.

Diabetes can be managed along conventional lines, with a few caveats. High carbohydrate and protein intakes are encouraged along with fat restriction in order to prevent steatorrhea whilst preventing weight loss. Over 80% of patients require insulin; however, the required doses are typically low, around 30–40 units/day [26, 27]. Diabetic control is often difficult to achieve, with frequent and severe hypoglycemia; reduced glucagon secretion may be responsible.

It is of interest that individuals with T2DM also exhibit evidence of reduced exocrine pancreatic function, albeit not to the

degree found in "pancreatic" diabetes. In a study from India, it was found that the prevalence of exocrine pancreatic insufficiency (measured by the fecal chymotrypsin assay) was 4.5% in T2DM, as compared to 87.5% and 23.5% in fibrocalculous pancreatic diabetes and T1DM, respectively [34]. Pancreatic insufficiency has been postulated to occur as a result of loss of trophic action of insulin on the exocrine tissue; however, some authors also contend that autonomic neuropathy affecting the enteropancreatic reflexes plays a role in the pathogenesis [35]. However, routine screening of people with T2DM for exocrine pancreatic insufficiency in the absence of symptoms is not recommended.

Tropical chronic pancreatitis

This is a distinct variety of chronic pancreatitis seen predominantly in low- and middle-income countries in the tropical and subtropical regions of the world [36, 37]. This entity was first reported in 1959 by Zuidema [37] in people from Indonesia but the disease was subsequently reported in several countries in Africa and Asia. The highest prevalence appears to be in southern India, particularly in the states of Kerala and Tamil Nadu [38]; however, the prevalence seems to be declining even in these areas.

The disease usually starts in childhood with recurrent abdominal pain and during adolescence progresses to large pancreatic calculi and ductal dilatation (Figures 21.3 and 21.5). By adulthood, frank diabetes is found in more than 90% of patients [39]. Nevertheless, it remains a rare cause of diabetes, constituting less than 1% of all cases of diabetes even in regions where it is most prevalent [40]. A recent study in urban southern India reported a prevalence of 0.36% among people with self-reported diabetes and 0.019% among the general population [41].

The term "tropical chronic pancreatitis" is used to denote the prediabetes stage of the disease whereas the term fibrocalculous pancreatic diabetes is used to describe the clinical picture once diabetes has supervened (Figure 21.6).

The etiology of this condition remains unknown. Poor nutrition has been implicated as a possible factor; however, this may be the consequence rather than a cause of the pancreatopathy. The condition can also affect well-nourished individuals [42]. In the past, attention was also focused on the role of dietary toxins such as cyanogens (found in cassava), but this link has not been substantiated. Cases have been found to cluster in families, which may suggest a genetic etiology for the disease [43–46]. A number of studies have reported an association between the *SPINK1* gene and tropical chronic pancreatitis [47–53]. A role has also been suggested for oxidant stress and free radical-mediated injury but this has not been proven conclusively [54].

Figure 21.5 Calcite stones of various sizes removed from the pancreas of a person with fibrocalculous pancreatic diabetes.

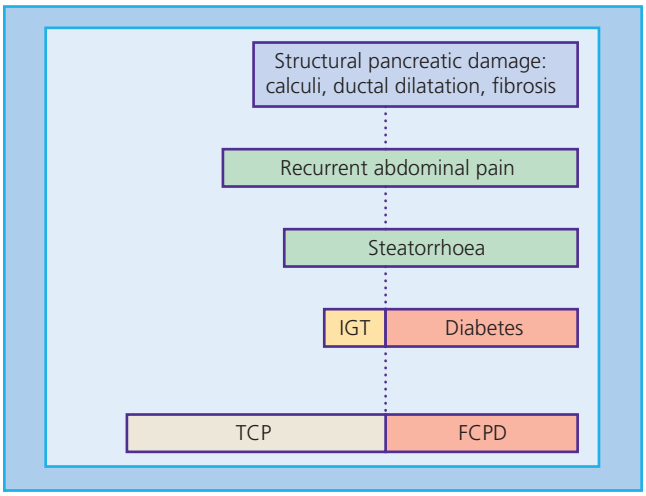

Figure 21.6 Natural history of tropical calcific pancreatitis (TCP) and fibrocalculous pancreatic diabetes (FCPD). IGT: impaired glucose tolerance.

Salient differences between alcoholic chronic pancreatitis and tropical chronic pancreatitis are summarized in Table 21.5. The classic clinical triad of tropical chronic pancreatitis consists of abdominal pain, steatorrhea, and eventually diabetes. The disease often progresses steadily from euglycemia through impaired glucose tolerance to frank diabetes. Most patients require insulin but

Table 21.5 Differences between tropical chronic pancreatitis and alcoholic chronic pancreatitis.

	Tropical chronic pancreatitis	Alcoholic chronic pancreatitis
Demographic features		
Male : female	70 : 30	90 : 10
Peak age at onset (years)	20–30	30–50
Socioeconomic status	Poor > affluent	All groups
Alcohol abuse	Absent	Present
Pancreatic morphology		
Prevalence of calculi	>90%	50–60%
Features of calculi	Large; in large ducts	Small, speckled; in small ducts
Ductal dilatation	Usually marked	Usually moderate
Fibrosis	Heavy	Variable
Risk of pancreatic cancer	Markedly increased	Increased
Diabetes		
Prevalence	>90%	50%
Time course	Faster evolution	Slower evolution

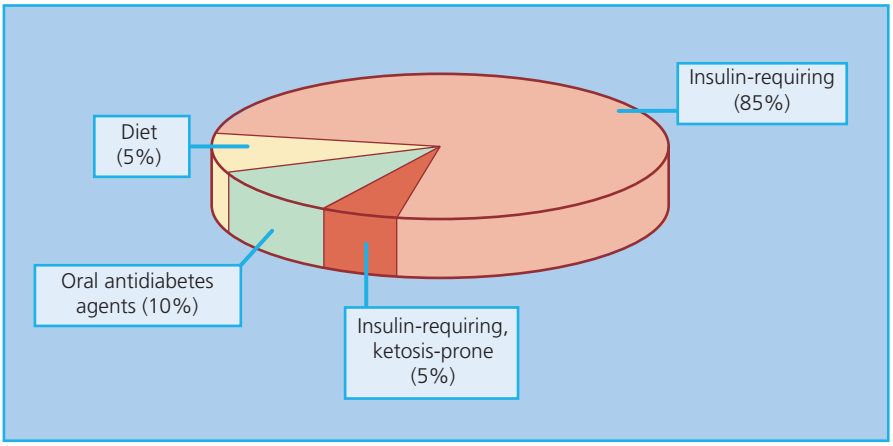

Figure 21.7 The spectrum of diabetes in fibrocalculous pancreatic diabetes. Source: Data from Mohan et al. [29].

are generally not prone to ketosis; some can be managed with oral antidiabetes agents (Figure 21.7). Studies have shown that the risk of developing pancreatic carcinoma in tropical chronic pancreatitis is 100-fold greater than in those without the disease and is much higher than in other forms of chronic pancreatitis [55]. Pancreatic malignancy should be suspected in individuals with tropical chronic pancreatitis if they complain of intractable pain or significant weight loss even after attaining good glycemic control.

Management of tropical chronic pancreatitis and fibrocalculous pancreatic diabetes is similar to that outlined for chronic pancreatitis.

Hereditary hemochromatosis

This condition, also called idiopathic or primary hemochromatosis, is the most common autosomal recessive genetic disorder in people of Northern European ancestry, with a prevalence of 4–5 per 1000 [56, 57]. The classic triad of diabetes, cirrhosis, and bronzed hyperpigmentation of the skin was first described by Trousseau in 1865 and called "hemochromatosis" by von Recklinghausen in 1889 [58].

Etiology and pathology

Genetic basis

Most cases of primary hemochromatosis arise from mutations in the hemochromatosis gene (*HFE*), located on the short arm of chromosome 6, close to the major histocompatibility complex (MHC), which explains the linkage with HLA A3 [59]. The HFE protein encoded by this gene is expressed on the cell surface of various tissues, including the enterocytes of the duodenal brush border, where iron is chiefly absorbed. The *HFE* gene modulates iron absorption by binding to the transferrin receptor. In two-thirds of cases, a C282Y mutation (substitution of cysteine by tyrosine at position 282) in the *HFE* gene is responsible [56]. Another mutation, H63D, seems to act synergistically with C282Y [60]. These mutations inhibit the binding of HFE to transferrin, leading to an excessive and inappropriate increase in intestinal iron absorption and greatly increased body iron stores. Non-*HFE* mutations are also rarely found to be responsible in some cases.

Pathophysiology

The primary defect is excessive iron absorption across the mucosa of the proximal small intestine, which continues even in the setting of greatly increased total body iron stores (often 15–20 g: cf. normal adult iron stores of 1–2 g). Excess iron is deposited preferentially in the liver, pancreas (exocrine tissue as well as islets), pituitary, heart, and parathyroids (Figure 21.8). Tissue injury is postulated to occur as a result of rupture of iron-laden lysosomes, generation of free radicals (by decomposition of hydrogen peroxide catalyzed by the ferrous and ferric ions—the Fenton reaction) and by the stimulation of collagen synthesis by activated stellate cells.

Clinical features

The classic clinical features are hepatic cirrhosis, diabetes, and skin hyperpigmentation ("bronzed diabetes") (Figure 21.9). Hepatic fibrosis and cirrhosis usually only develop in those aged over 40 years, unless other factors such as alcoholism are present. Portal hypertension, hepatic failure, and hepatocellular carcinoma (in 15% of cases) are late sequelae [61]. Bronzing of the skin, which occurs in 70% of cases but may be less evident in darker-skinned races, is caused by both iron deposition in the subcutaneous tissue and increased melanin in the basal dermis. Hypopituitarism, hypogonadism, hypoparathyroidism, and chondrocalcinosis with pseudogout are less common features.

Presenting symptoms include weakness, weight loss, diabetic symptoms, arthralgia, erectile dysfunction, and skin pigmentation. Signs include hepatosplenomegaly, heart failure, skin pigmentation, testicular atrophy, arthropathy, hypogonadism, and occasionally hypothyroidism. Many people with hemochromatosis, however, are asymptomatic and may be detected during investigation for unrelated reasons or through genetic screening of family members of those with hemochromatosis.

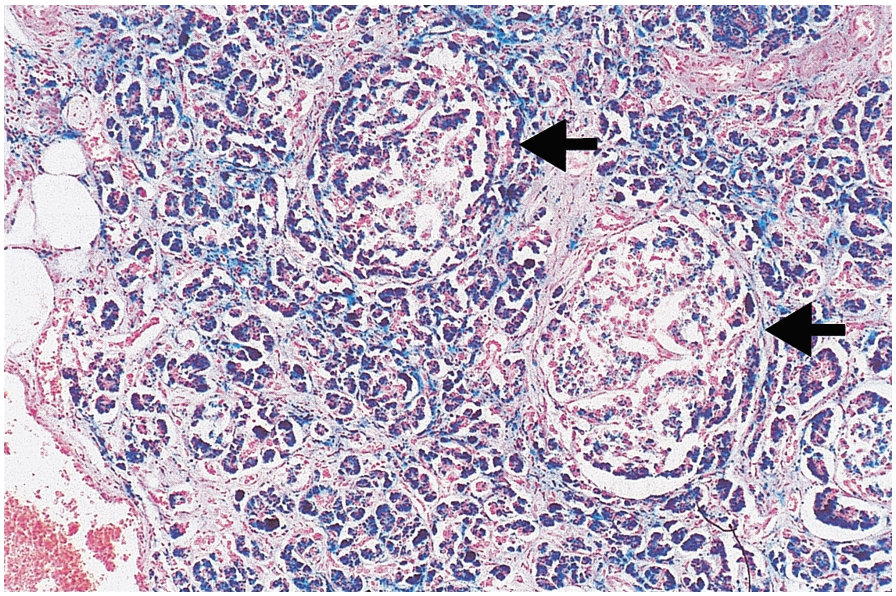

Figure 21.8 Hereditary hemochromatosis. Perls' stain shows heavy iron deposition (blue) in exocrine and islet tissue in the pancreas (arrows). Original magnification ×375. Source: Courtesy of Dr. A. Clark, Wirral Hospital, UK.

Diabetes in primary hemochromatosis

The prevalence of diabetes depends on the severity of iron overload and presence of cirrhosis [62]. Up to 50% of patients have glucose intolerance and 25% have overt diabetes [63], although the disease is an extremely rare cause of diabetes in the general population. The prevalence is steadily declining as the diagnosis is being made earlier, before significant pancreatic damage has occurred. Both insulin resistance and β-cell failure contribute to the development of diabetes, and most people eventually require insulin. These individuals are prone to both microvascular and macrovascular complications [64], the risk of nephropathy being particularly high in those carrying the H63D mutation [65].

Investigations and diagnosis

The diagnosis should be suspected in any person with diabetes, hepatomegaly or liver disease, skin pigmentation, arthritis, and hypogonadism. A high index of suspicion is required to make an early diagnosis, because significant iron overload can exist with few or none of these clinical manifestations.

The total-body iron stores can be assessed using measurement of serum ferritin and percent saturation of transferrin. Serum ferritin is a useful screening test for relatives of affected individuals, but because ferritin is an acute phase reactant, the levels of which can be elevated in inflammatory states, abnormally high results should be confirmed by other tests (Table 21.6) [66]. Serum iron and percent saturation of transferrin are elevated early in the

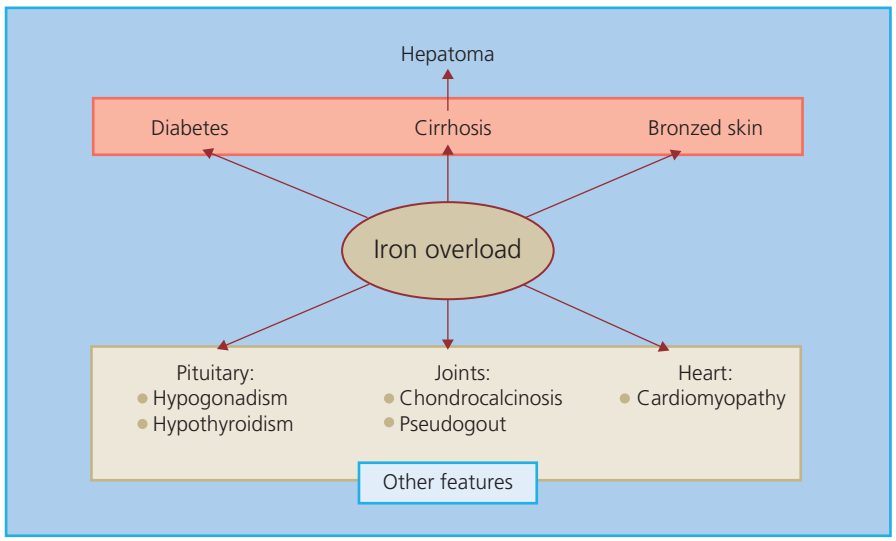

Figure 21.9 Clinical features of hereditary hemochromatosis. The classic triad comprises diabetes, cirrhosis, and hyperpigmentation of the skin ("bronzed diabetes").

Table 21.6 Diagnostic tests in hereditary hemochromatosis [63].

	Hemochromatosis	Normal
Serum iron (μg/dL)	180–300	50–150
Transferrin saturation (%)	80–100	20–50
Total iron-binding capacity (μg/dL)	200–300	250–370
Serum ferritin (μg/dL)		
Men	500–6000	20–300
Women	500–6000	15–250
Hepatic iron concentration (μg/g dry weight)	10,000–30,000	300–1800

course of the disease, but lack specificity. A combined measurement of the percent transferrin saturation and serum ferritin levels provide a simple and reliable screening test for hemochromatosis. A positive test mandates genetic testing.

The role of liver biopsy in diagnosis and management of hemochromatosis has significantly diminished following the development of genetic testing for the C282Y mutation. The major role of liver biopsy at the present time is in excluding the presence of cirrhosis, which is a major risk factor in the development of hepatocellular carcinoma. Hepatic iron overload can also be detected using imaging techniques such as CT or MRI scanning.

All first-degree adult relatives of individuals with hemochromatosis should be tested for C282Y and H63D mutations, in an attempt to detect disease in the early precirrhotic phase at which stage treatment can prevent further progression.

Treatment

Treatment of hereditary hemochromatosis is by repeated venesection, which must be started as early as possible. Removal of excess iron by venesection prevents diabetes and cirrhosis and prolongs survival [61]. Chelating agents such as desferrioxamine are more expensive, less safe, and less effective than venesection. Diabetes may be improved by venesection, but usually requires insulin treatment. Management is often complicated by hypoglycemia caused by concomitant α-cell damage and glucagon deficiency. Hepatic transplantation for hereditary hemochromatosis was previously associated with a poor prognosis, but survival rates have improved of late. Diabetes tends to worsen after transplantation because of the use of immunosuppressant drugs [67]. Hepatocellular carcinoma is a late complication and may be an indication for transplantation if the disease remains localized.

Secondary hemochromatosis

Iron overload can also occur as a consequence of repeated blood transfusion and disorders of erythropoiesis such as thalassemia and sickle cell anemia, in which case the condition is termed secondary hemochromatosis or hemosiderosis. Pancreatic damage and diabetes frequently result. The duration of disease and number of transfusions correlate well with the degree of glucose intolerance. It has been postulated that iron overload may induce an autoimmune attack against the β cells, thereby contributing to development of diabetes [68].

Pancreatic neoplasia

Adenocarcinoma of the pancreas is the fifth most common cause of cancer death and is increasing in its incidence [69]. It has a poor prognosis, with a 5-year survival rate of less than 3%.

Although diabetes has long been associated with pancreatic adenocarcinoma, the nature and strength of the association remain controversial. A meta-analysis of 20 epidemiologic studies showed a twofold increased risk of pancreatic cancer among people with diabetes of more than 5 years' duration [70], suggesting that diabetes is a risk factor for the neoplasm. Other studies, however, have concluded that the cancer preceded and caused the diabetes [71], a view supported by observations that diabetes may improve after resection of the tumor. Some studies have even suggested that diabetes protects against pancreatic cancer [72]. Tropical chronic pancreatitis is associated with a 100-fold increase in the risk of developing pancreatic carcinoma [56]. The association of incretin-based therapies with pancreatic carcinoma remains controversial [73, 74]; the U.S. Food and Drug Administration and the European Medicines Agency have recently concluded in a review that assertions regarding a causal association between incretin-based diabetes therapies and pancreatitis or pancreatic cancer are inconsistent with the current data [5].

The diagnosis of pancreatic carcinoma must be suspected in any person with T2DM who complains of unexplained weight loss (despite insulin therapy and apparently good control of diabetes), back pain, or jaundice.

Pancreatic surgery and diabetes

Diabetes is a frequent complication of pancreatic resection performed for various indications. The incidence and severity of diabetes depends on the extent of resection of the distal segment, where the islets are most abundant. In one study, diabetes developed in 56% of cases following distal resection [75].

Diabetes is more likely to follow subtotal pancreatectomy than procedures such as lateral pancreaticojejunostomy and pancreaticoduodenoctomy (Whipple procedure). Diabetes is obviously inevitable following total pancreatectomy.

Management of diabetes caused by pancreatic surgery

The diabetes is usually difficult to control, with wide excursions in blood glucose levels. Patients are exquisitely insulin-sensitive and prone to hypoglycemia as a result of the loss of glucagon function. Frequent small meals and multiple small doses of insulin can minimize these problems to an extent. Use of a subcutaneous insulin infusion pump may be beneficial in some cases. People with diabetes following pancreatectomy are ideal candidates for whole pancreas or islet cell transplantation.

Associated exocrine pancreatic insufficiency should also be addressed. Meals should be low in fat and high in carbohydrate and protein. Pancreatic enzyme therapy will help in controlling steatorrhea and stabilizing blood glucose [76].

Cystic fibrosis

Cystic fibrosis is a multisystem disease characterized by recurrent airway infection leading to bronchiectasis, pancreatic insufficiency, abnormal sweat gland function, and urogenital dysfunction. It is an autosomal recessive disorder caused by mutations in the *CFTR* gene located on chromosome 7q22. This gene encodes a protein, cystic fibrosis transmembrane conductance regulator (CFTR), which regulates the chloride secretion across epithelial surfaces. Various mutations have been described of which deletion of the phenylalanine residue at position 508 (Δ508) is the most common [77]. The defect produces unusually viscid secretions which lead to pancreatic ductular obstruction, dilatation, and pancreatic insufficiency. The incidence is 1 in 2500 live births in white European populations, but the disease is much less common in Africans and Asians [78].

The most common clinical features are steatorrhea, failure to thrive and growth retardation, recurrent lung infections, hepatobiliary complications, osteoporosis, and symptoms of fat-soluble vitamin deficiency such as night blindness. The diagnosis is confirmed by the presence of an elevated sweat chloride concentration in excess of 60 mmol/L.

Diabetes in cystic fibrosis

The incidence of diabetes in children with cystic fibrosis is 2–3% (about 20 times higher than in the general population). The incidence rises steadily through adolescence, with up to 25% of individuals in their twenties developing diabetes and a further 50% having glucose intolerance [79]. Occasionally, diabetes is the first manifestation of cystic fibrosis.

As the treatment of the lung disease in cystic fibrosis has improved, more and more people are surviving into adulthood, leading to an increase in the prevalence of diabetes in cystic fibrosis.

The major factor in the pathogenesis of diabetes is damage to the pancreatic β cells secondary to exocrine pancreatic degeneration. Other postulated mechanisms include enhanced absorption of glucose [80] and autoimmune attack against the β cell, which may explain why T1DM is more common in relatives of people with cystic fibrosis [81]. The physiologic insulin resistance of normal puberty may also contribute. Interestingly, diabetes develops more commonly in people homozygous for Δ508 than in heterozygotes [82].

Diabetes is usually insidious in onset and characterized by a delayed, flattened, and prolonged insulin secretory response to glucose [83]. Ketoacidosis is rare, although insulin treatment is usually required. As patients now survive longer [77], chronic microvascular complications are also frequently seen, although macrovascular disease is virtually unknown. Hyperglycemia predisposes to chest infections in these individuals and may be an important, often overlooked, cause of weight loss.

Management

The International Society for Pediatric and Adolescent Diabetes (ISPAD) recommends that all children with cystic fibrosis be screened for diabetes with an oral glucose tolerance test (OGTT), starting from 10 years of age [84]. Although there is debate about the optimal glucose needed to prevent pulmonary exacerbations, current guidance recommend the diagnostic criteria are the same as for other forms of diabetes. The OGTT should not be performed during acute exacerbations of pulmonary disease, particularly if the treatment includes glucocorticoids. Although some patients initially respond to sulfonylureas, most ultimately need insulin and this is reflected in the guidelines for treatment which recommend insulin as the treatment of choice [85]. In addition to controlling diabetes, insulin also improves body weight and pulmonary and pancreatic function [79, 86, 87]. Annual monitoring for complications of diabetes is recommended, starting 5 years after the diagnosis of diabetes [88, 89].

Dietary modification in people with cystic fibrosis who also have diabetes presents much the same difficulties as in people with chronic pancreatitis. A diet rich in carbohydrates and protein but restricted in fat is recommended. Oral pancreatic enzyme therapy helps to improve nutrient digestion and absorption. Enteric-coated preparations of lipase can control steatorrhea. Fibrosing colonopathy is a concern in patients receiving higher strengths of lipase [84].

Conclusions

Although rare, diabetes secondary to pancreatic disease is potentially important. The underlying pancreatic disease may need treatment in its own right, while disorders with a genetic basis must be identified so that other family members can be screened. Diagnosis of pancreatic diabetes requires a high index of suspicion. Suggestive symptoms include features of pancreatic disease (steatorrhea, unexplained weight loss, or back pain) and severe and brittle diabetes in the absence of a family history of diabetes.

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5 Managing the Patient with Diabetes

22 Clinical Presentations of Diabetes

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Key points

- People with type 1 diabetes (T1DM) usually present with classic symptoms and occasionally diabetic ketoacidosis.
- People with type 2 diabetes mellitus (T2DM) may be asymptomatic or present with classic symptoms.
- In the context of thirst, polydipsia, and polyuria, the presence or absence of weight loss is an important diagnostic feature
- The mode of presentation of slow onset T1DM, monogenic, and pancreatic diabetes is helpful in diagnosis.
- With advancing age, the renal threshold for glucose increases and thirst perception diminishes.
- Consideration of the impact of the initial consultation upon the individual is important.
- T2DM may present with complications of diabetes which may be either microvascular or macrovascular.
- Initial diagnosis of T2DM during acute myocardial infarction or stroke is common.
- Presentation may be asymptomatic and discovered on routine examination or laboratory test.
- Diabetes of onset in pregnancy is important and ideally detected by an effective screening program.

Introduction

Diabetes has long since taken over from syphilis as the great imitator, and nowhere is this more apparent than in the wide variation of possible modes of initial presentation. The classic triad of thirst, polydipsia, and polyuria accounts for only a modest proportion of new diagnoses of diabetes. The relatively acute onset of such symptoms associated with loss of weight is the hallmark of type 1 diabetes mellitus (T1DM). Ketoacidosis or hyperosmolar hyperglycemic syndrome may precipitate a dramatic presentation of T1DM or type 2 diabetes mellitus (T2DM) to emergency services. Non-specific symptoms including tiredness, general malaise, and repeated or persistent skin infections may lead to a biochemical diagnosis of diabetes. Screening of at-risk groups or individuals allows early diagnosis. Regrettably, the nature of the condition is such as to allow it to remain asymptomatic for years, allowing the clinical presentation to be a long-term complication of diabetes. This could be in the form of macrovascular disease (myocardial infarction, stroke, black toe) or in the form of microvascular disease (loss of visual acuity, neuropathy). Pregnancy may cause gestational diabetes (GDM), which, although it may remit after delivery, does indicate a high risk for future T2DM.

Clinical considerations at presentation

At the heart of any consultation involving the presentation of diabetes there is a patient. Depending upon prior knowledge, "diabetes" may be associated in their mind with blindness and amputation, disability and premature death. Alternatively, it may be associated with vague concepts of malaise along with lumbago or fibrositis. The patient's beliefs and thoughts on diabetes need to be established if the diagnostic consultation is to be a therapeutic consultation. In an era of medicine by numbers, often traduced as "evidence-based medicine," it is easy to overlook the impact of the consultation itself upon the person who will live with diabetes. "Where were you when JFK was shot?" "What was it like when you were told you have diabetes?" The moment is likely to be memorable and influential.

The therapeutic consultation will involve listening, a process that need not be unduly time-consuming. "Do you know of anyone with diabetes?" "What do you know of diabetes just now?" The information received will allow the patient's likely type of diabetes and immediate prognosis to be put into perspective. Together with other aspects of sound clinical history-taking, it will also transform that person's view of the consultation. Patients list

Textbook of Diabetes, Fifth Edition. Edited by R. Holt, C. Cockram, A. Flyvbjerg and B. Goldstein.

"listening" as the most valued attribute of a doctor. Although others may listen too, this cannot be delegated to the healthcare team.

At what stage of diabetes is the person in front of you? The implications for the individual who was identified on routine screening are quite different from those for the person presenting with a black toe. The former is likely to be at an early stage of a long process with a good chance of modifying disease progression, whereas the latter is likely to have other tissue complications already established. Clearly, genetic susceptibility to develop complications plays a part as well as natural history time course. The former patient may never develop more than microaneurysms in the eye and be resistant to diabetic nephropathy. Even if they are to be susceptible to complications, these are amenable to intervention over a period of many years. The latter patient, however, requires clear explanation of what can be done and how future trouble can be avoided. Hippocrates summed it up nicely: "Cure sometimes, relieve often, comfort always."

The possibility of cure should not be overlooked. Diabetes has long been regarded as incurable. However, this is not always true. At the beginning of the 21st century and with further advances in our understanding, the number of circumstances where diabetes can be cured will increase. Look out for the slatey grey person with large liver and hemoglobin level of 19 gm/dL. Hemochromatosis is rare as a cause of diabetes but it is treatable and therefore important (Chapter 21). The person taking a combination of thiazide diuretic and beta-blocker will be pleased to have hyperglycemia at least ameliorated by use of alternative agents (see Chapter 19). Cushing syndrome may include curable diabetes (see Chapter 20). Few people on systemic steroid therapy can be taken off treatment just because of the development of diabetes, but knowledge is cheering that the diabetes will go away or become much more easily controllable when the steroid course finishes. Cure of short-duration T2DM by substantial and sustained weight loss is possible for those who have the determination and willpower to change long-standing behavior patterns [1]. For such people, this knowledge is life-changing and normoglycemia continues as long as weight regain is avoided [2, 3]. Only 50% of individuals with diabetes of duration longer than 8 years can reverse their diabetes, compared with around 90% of those with diabetes for less than 4 years [4]. Bariatric surgery produces dramatic and long-term cure of T2DM in the early years of the condition by enforced calorie restriction [5, 6].

Types of diabetes

The classification of diabetes will remain the cause of much debate until the exact etiology of each subtype has been established. Currently, the paradigm is to group together those people who appear to have primary β-cell destruction as T1DM, and those who are not slim and who can be controlled at least in the early years with diet and oral agents as T2DM. The monogenic causes of diabetes are capable of precise genetic description and are clearly separate (see Chapter 18). Similarly, pancreatic disease such as chronic pancreatitis, pancreatic carcinoma, and hemochromatosis is capable of precise diagnosis (see Chapter 21). T2DM, however, is a term used to describe conditions that do not fit into the other, more easily defined categories. It is clear that more subtypes will be identified in due course.

The important practical question at the initial presentation of a person with diabetes is whether insulin therapy is necessary. In some circumstances there is no doubt, such as diabetic ketoacidosis or severe weight loss with ketonuria and glycosuria in a child (Figure 22.1). More usually in adult practice the question must be asked. Table 22.1 lays out the common and distinguishing features from the clinical history, examination and urinalysis to help the clinician come to the answer. The subsequent sections consider the separate features in context.

Thirst, polydipsia, and polyuria

These symptoms result from an osmotic diuresis as a consequence of hyperglycemia. The symptoms are common to all types of diabetes although the time course is likely to be shorter and the symptoms more severe in T1DM. Not infrequently, sugar-containing carbonated drinks are selected to slake thirst with resulting worsening of symptoms. A careful history documenting the time course of symptoms and any change in intake of specific drinks is important. Remembering how many times per day urine is passed is not easy, but nocturia is more clear-cut and the number of times urine is passed at night should be quantified. "Do you need to drink water when you get up at night?" is a reasonably objective measure of thirst.

For glucose to escape into the urine, plasma glucose concentration must exceed the renal threshold for tubular reabsorption of glucose and the absolute amount of glucose delivered to the renal tubules must exceed the maximum absorptive capacity. The renal threshold averages 11 mmol/L but displays a wide individual variation of around 6–14 mmol/L [7]. Additionally, the maximum absorptive capacity varies with age such that older people exhibit glycosuria at higher plasma glucose levels [8].

The rise in maximum renal tubular absorptive capacity with increasing age is clinically significant as older people will only develop osmotic symptoms at higher plasma glucose levels. Conversely, a negative urine test is even less likely to exclude a diagnosis of diabetes than in younger people. In addition to the need for higher plasma glucose levels in older people to produce osmotic symptoms, the threshold for triggering the sensation of thirst rises with advancing years [9]. This is important because, once the maximum renal absorptive capacity has been exceeded, dehydration will become considerably more advanced before thirst is sensed. These age-related changes are highly relevant to development of severe hyperosmolar states.

The presence of chronic hyperglycemia itself changes the renal sensitivity to vasopressin such that thirst is not appreciated despite rising plasma osmolarity [10]. Hence, the combination of undiagnosed diabetes and advanced age is particularly potent in

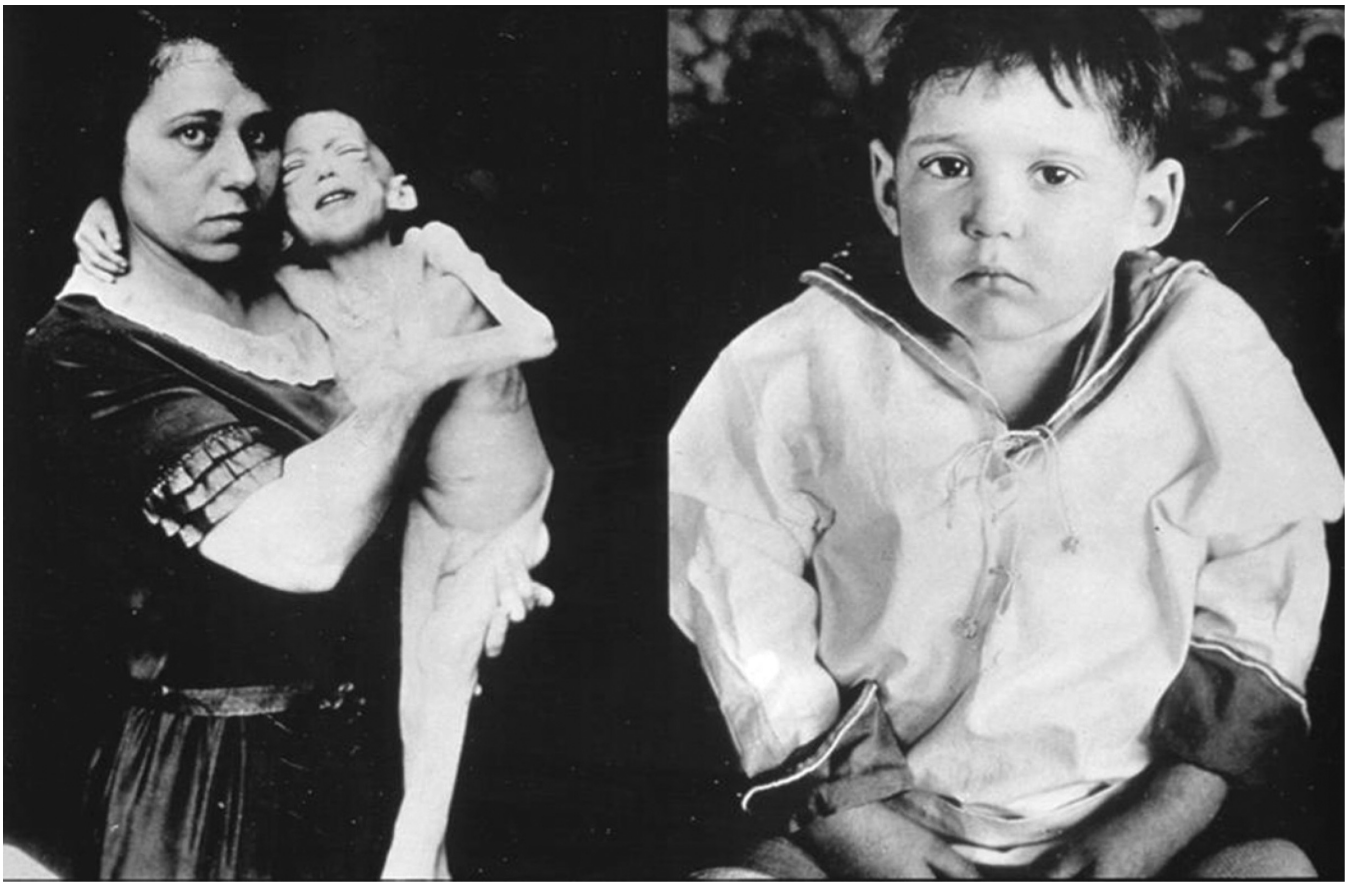

Figure 22.1 A 3-year-old boy before and after 3 months of insulin therapy (1922). The severe wasting of muscle and adipose tissue due to the insulin deficiency of type 1 diabetes is painfully evident in the left-hand panel. There is no more dramatic reminder of weight loss as a prominent presenting feature of type 1 diabetes especially if presentation is delayed. The speed of restoration of body mass on replacing insulin (right-hand panel) is impressive. Source: Eli Lilly & Co. Reproduced with permission.

Table 22.1 Clinical features at presentation of type 1, type 2, and monogenic diabetes. This is a diagnostic guide with exceptions because of specific circumstances. It is not exhaustive and does not include rarer forms of diabetes, including syndromic diabetes.

	Type 1	Type 2	Monogenic	Pancreatic
Weight loss	Yes (not essential e.g. in slow onset T1DM)	Usually, no	No	Possible. If marked consider pancreatic carcinoma
Ketonuria	Yes (not essential in slow onset T1DM)	No unless recent fasting	No unless recent fasting	Yes, but not necessary for diagnosis
Time course of symptoms	Weeks or days	Months	Months	Weeks or months
Severity of symptoms (e.g. nocturia >3)	Can be marked	Variable but not usually extreme unless fueled by sugary drinks to assuage thirst	Not usually severe	Depends on clinical situation
Family history	Possibly of insulin dependence at a young age	Present in 30% with onset in adult life	Present in almost all with onset in childhood or adult life	Only by chance except in association with hemochromatosis
Age	Peak age in preschool and teenage years but can present at any age	Typically after the age of 20 years	Childhood, adolescence or adult	Usually middle aged and older

delaying appropriate action to increase oral fluid intake as dehydration progresses. The clinical features identified from the history at presentation will vary in relation to the above factors. In older people, thirst may not be experienced despite an osmotic diuresis and polydipsia will be absent. The most reliably quantitated feature of an osmotic presentation is therefore frequency of nocturia, and specifically an increase from habitual levels.

In children, enuresis may be the first symptom of polyuria. Sudden onset of enuresis should always prompt testing of urine for glucose. It must be noted that a urine test is entirely appropriate as an initial screen in this situation, as the absence of glucose from the urine absolutely excludes hyperglycemia as a potential cause of polyuria.

Weight loss

Establishing whether significant weight loss has occurred is the most important aspect of history-taking in those with newly presenting diabetes. Unless secondary to concurrent disease, the symptom strongly suggests insulin deficiency and hence newly presenting T1DM. Its absence does not exclude T1DM as the speed of onset of insulin deficiency and the presence of intercurrent illness, which may have exacerbated osmotic symptoms, may mean that weight loss has not yet commenced.

Weight loss at presentation of T2DM may occur as a result of dietary restriction often undertaken because of suspicion of impending health problems. Such deliberate changes in eating habit are readily established from the history. Typically, weight does not change, or even continues to rise, prior to the symptomatic onset of T2DM.

The weight loss reflects mainly the relative loss of the anabolic actions of insulin. Muscle wasting may be prominent, especially in young men. Associated loss of muscle strength may be reported. As an anabolic hormone, insulin acts principally to inhibit protein degradation [11]. Its relative absence allows the balance between continuous protein synthesis and breakdown to be disturbed. There is an additional effect of insulin deficiency in the failure of normal promotion of lipogenesis and inhibition of lipolysis. Excess non-esterified fatty acids accumulate in plasma, forming substrate for ketogenesis. If the clinical presentation of diabetes is acute, a component of the weight loss will reflect the loss of both intracellular and extracellular water.

Blurred vision

Major changes in plasma glucose will be followed over a period of days and weeks by blurring of vision. The symptom is typically present after a relatively acute change, usually in the context of presentation of T1DM or in the specific circumstance of a hyperosmolar presentation of T2DM. It is most important to explain to the patient that the visual blurring will become worse following the relatively rapid correction of gross hyperglycemia. This explanation is vital to avoid the supposition that diabetic blindness is already progressing with consequent unnecessary worry. It is also important to prevent the unnecessary purchase of spectacles that will be redundant after the hyperglycemia is treated.

It is reasonably assumed that shifts in osmotic pressure between plasma and inside the eyeball accounts for the visual change. Certainly, this provides a practical and immediately understandable explanation. Detailed tests, however, have not to date tied down any identifiable refractive change [12].

Infections

Exposure of leukocytes to glucose concentrations above 11 mmol/L produces paralysis of phagocytic and other functions [13]. This effect, together with other possible effects upon immune function, explains the impaired ability to fight off bacterial and fungal infections. Susceptibility to viral infections appears to be little changed although clear data are lacking.

Recurrent or refractory yeast infections may draw attention to previously undiagnosed diabetes. Most frequently this involves vaginal candidiasis in women or balanitis in men. Initial control of blood glucose levels will permit clearance of the infection with continued antifungal application. Staphylococcal pustules, boils, and carbuncles may be present at the diagnosis of diabetes, especially T1DM. This clinical observation was supported by a prospective study of 482 people with skin or mucous membrane sepsis presenting to an accident and emergency department who were found to have over a threefold increased incidence of capillary blood glucose >7.8 mmol/L compared with a background population [14].

Very rare but serious infective presentations of diabetes must be considered. Necrotizing fasciitis is considerably more common in people with diagnosed and undiagnosed diabetes [15]. Fournier gangrene (gangrene of the perineum and genitalia) is associated with diabetes in almost 50% of cases [16]. The rare and often fatal facial and/or maxillary sinus fungal infection mucormycosis is most often associated with diabetes [17].

Diabetic ketoacidosis

Diabetic ketoacidosis (DKA) occurs as a result of marked insulin deficiency associated with an increase in circulating levels of counter-regulatory hormones. It is characterized by hyperglycemia, acidosis, and ketonuria. It mainly occurs in people with T1DM, but it is not uncommon in some people with T2DM. There is a wide geographic variation in the reported incidence of DKA. For example, EURODIAB, a cross-sectional survey of 3250 people with T1DM in 29 centers in Europe, reported that 8.6% of participants had been admitted with a diagnosis of DKA in the previous 12 months [18]. In 25% of cases, DKA is the presenting feature of

T1DM [19]. The overall mortality rate from DKA ranges 2–5%, but is higher in the elderly.

DKA typically presents with the symptoms of hyperglycemia (i.e. thirst, polyuria, and polydipsia). Patients may also complain of malaise or lethargy and muscle cramps. Abdominal pain and vomiting may be sufficiently severe as to mimic an acute surgical problem. It is critically important to recognize this, as the administration of an anesthetic is almost invariably fatal. All doctors dealing with emergencies should be aware of the potential pitfall of missing this tell-tale sign of DKA.

Clinical signs include dehydration, deep, sighing respirations (air hunger or Kussmaul respiration), and a sweet-smelling fetor (like nail varnish remover) caused by the ketones on the breath. As the ability to detect the smell of ketones is genetically determined, and approximately one-third of people are unable to do this, it is important that individual doctors are aware if they are not equipped with this additional diagnostic tool. Consciousness may be clouded. If the condition has progressed to the stage of coma, the associated signs of dehydration must lead to urgent checking of blood glucose and ketones and arterial blood pH in order to expedite definitive treatment. If bedside blood ketone testing is not available then the semi-quantitative urine test to detect ketonuria is entirely satisfactory.

The marked deficiency or absence of insulin in this condition means that insulin-mediated glucose uptake into tissues such as muscle, fat, and liver cannot occur and hepatic glucose output is unrestrained. In the meantime, the dysregulated secretion of counter-regulatory hormones (glucagon, growth hormone, and catecholamines) enhances the breakdown of triglyceride into free fatty acids and increases the rate of gluconeogenesis, which is the main cause for the high blood glucose level in diabetic ketoacidosis. Beta-oxidation of these free fatty acids leads to formation of ketone bodies (β-hydroxybutyrate, acetoacetate, and acetone). Acetone is volatile and is released from the lungs, giving the characteristic sweet smell to the breath. Metabolic acidosis ensues when the ketone bodies are released into circulation and deplete the acid buffers.

The hyperglycemia-induced osmotic diuresis further depletes sodium, potassium, phosphates, and water. Patients are often profoundly dehydrated and have a significantly depleted total body potassium at presentation. Sometimes, a normal or even elevated serum potassium level is seen as a result of the extracellular shift of potassium with severe acidosis. Great care must be taken to monitor serum potassium levels repeatedly once insulin treatment is started as the concentration can drop precipitously (see Chapter 36).

Hyperosmolar hyperglycemic syndrome

Hyperosmolar hyperglycemic syndrome (HSS) occurs exclusively in people with T2DM. Often there is a history of several days of ill health. The principal clinical feature is profound dehydration. Confusion is usual, and focal neurologic symptoms such as weakness on one side or hemi-sensory abnormalities may develop and be easily confused with stroke. HSS was previously termed hyperosmolar non-ketotic coma. This terminology has been changed as coma is a relatively rare feature (<10%) and mild ketosis may be present at diagnosis.

HSS shares many features in common with DKA, the major exception being the absence of significant ketoacidosis. This is likely because of the residual low-level insulin secretion, which suppresses lipolysis sufficiently to avert ketogenesis but not sufficient to prevent hyperglycemia. Additionally, hyperosmolarity itself may decrease lipolysis, limiting the amount of free fatty acids available for ketogenesis. HSS accounts for 10–30% of hyperglycemic emergencies. As the prevalence of T2DM rises inexorably, it is becoming an increasingly common hospital admission. Up to two-thirds of those affected have not previously been diagnosed as having diabetes.

Macrovascular presentations

Acute myocardial infarction

As the risk of ischemic heart disease is linearly related to fasting and postprandial blood glucose concentrations, it is not surprising that both impaired glucose tolerance (IGT) and diabetes are over-represented in populations presenting with acute myocardial infarction (MI) [20]. Consequently, T2DM frequently presents for the first time at hospitalization for MI.

This presentation is complicated by stress hyperglycemia resulting from the catecholamine and cortisol elevations. Although this may cause problems for the purist wishing to evaluate an effect of diabetes per se, from the perspective of the patient with a life-threatening condition exacerbated by dysglycemia, exact definitions of diabetes are not relevant. Stress hyperglycemia and established diabetes have similarly increased mortality from MI. In a New York municipal hospital cohort of patients with MI, 3-year mortality was 52% in those with stress hyperglycemia (defined as admission blood glucose >7.0 mmol/L) compared with 42% in those with diabetes [21]. The 3-year death rate in those with normal glucose levels was 24% in the same study. A meta-analysis has confirmed this effect, with a 3.9-fold increased risk of death associated with stress hyperglycemia compared with a 1.7-fold increased risk of death associated with established diabetes [22]. In this context, one of the most important findings of the Diabetes mellitus, Insulin Glucose infusion in Acute Myocardial Infarction (DIGAMI) study is often overlooked. The effect of reasonable glycemic management (blood glucose <10 mmol/L) for those with no prior insulin therapy and stratified as having low coronary risk factors produced a 52% improvement in mortality [23]. This group would have included those with stress hyperglycemia. In contrast, the DIGAMI study showed no significant benefit of acute blood glucose control for individuals previously treated with insulin.

Estimates of the incidence of stress hyperglycemia at presentation of MI range 10–16% [24, 25]. This compares with

estimates of prevalence of diabetes at presentation of MI of 25–32% [24, 26, 27]. Variation in these figures is likely to reflect the background prevalence of IGT and T2DM in the population, as well as increased awareness and effective screening processes to identify previously undiagnosed T2DM.

Good clinical practice demands measurement of plasma glucose on diagnosis of an acute coronary syndrome. If plasma glucose is raised (7 mmol/L may be quoted, but in the individual, case interpretation depends upon time since last meal), then both fasting plasma glucose and HbA_{1c} should be measured. Raised plasma glucose should indicate a need for particular attention to adequate glucose control during the acute event. Given that the HbA_{1c} result is unlikely to be available immediately, hyperglycemia indicates a need for rapid control in the acute situation when the first few hours are critical. A fasting plasma glucose of >5.6 mmol/L during the acute admission and/or admission plasma glucose of >7.8 mmol/L yielded a sensitivity of almost 90% and a positive predictive value of 44% for detecting diabetes [28].

Where there is diagnostic uncertainty, targeted screening in the post-acute setting with a standard 75 g oral glucose tolerance test (OGTT) is acceptable. But when is the optimal time to perform this test? In a group of people with MI but no previous diagnosis of diabetes, both pre-discharge and 6 weeks post-discharge OGTTs were performed and correlation with pre-discharge OGTT was good [29]. There was 49% concordance between classifications to which each participant was assigned in both OGTTs. The best predictor of abnormal glucose handling (IGT or diabetes) being diagnosed at 3 months was observed to be the 60-minute blood glucose level during the pre-discharge OGTT. However, for all admitted with MI it is essential that HbA_{1c} is measured and that the result is acted upon.

Acute stroke

The prevalence of previously diagnosed diabetes in people with acute stroke is 8–28% but an additional 6–42% have unrecognized pre-existing dysglycemia [30]. Plasma glucose at presentation is a major prognostic factor. One series of 86 people with acute stroke demonstrated that full functional recovery at 4 weeks was restricted to those with presenting blood glucose levels <8 mmol/L [31]. None of the individuals with a raised presenting plasma glucose regained full function by 4 weeks. The extent to which this reflects the metabolic stress response in proportion to the severity of the cerebrovascular insult as opposed to hyperglycemia itself impairing subsequent recovery from ischemic damage cannot be ascertained from these observational data.

The observations on poorer outcome in those who had stress hyperglycemia following MI have been reproduced in respect of acute stroke disease. In a systematic review of observational studies examining the prognostic significance of hyperglycemia in acute stroke, the unadjusted relative risk of in-hospital or 30-day mortality was 3.07 (95% CI: 2.50–3.79) in people without diabetes but with admission plasma glucose level >6–8 mmol/L and 1.30 (95% CI: 0.49–3.43) in those with known diabetes [32]. The relative risk of poor functional outcome in hyperglycemic patients without diabetes was 1.41 (95% CI: 1.16–1.73). It appears that a sudden increase in plasma glucose levels impairs tissue function more in those individuals who have not been habituated to hyperglycemia.

Persistent hyperglycemia (defined as blood glucose >7.0 mmol/L) in the 72 hours after acute stroke was found to be associated with an increase in infarct size, measured using magnetic resonance imaging, and worse stroke outcome [33]. Nonetheless, there are currently no satisfactory outcome studies of control of plasma glucose upon the outcome of stroke [34]. The largest study to date, which included 993 participants, failed to achieve control of plasma glucose at 24 hours [35]. Importantly, no assessment has yet been conducted of plasma glucose control during the first few hours after presentation with acute stroke, and it is likely that it is in this window of time that this particular presentation of hyperglycemia may most beneficially be managed.

Microvascular presentations

Eye presentations

Symptomatic loss of vision may occasionally be the presenting feature of T2DM, where hyperglycemia has been present for an uncertain number of years, silently causing tissue damage and retinopathy. Loss of vision as a diagnostic event is most often a consequence of macula edema but may also be secondary to vitreous hemorrhage. Central or branch retinal vein occlusion is more common in diabetes and may also cause symptomatic presentation of the condition.

Around the time of diagnosis of T2DM, marked retinopathy with cotton wool spots or intraretinal microvascular abnormalities was found to be present in 8% of men and 4% of women in the UK Prospective Diabetes Study (UKPDS) [36]. The critical importance of arranging full retinal examination, preferably by digital retinal imaging, is illustrated in Figure 22.2. Approximately 1% of individuals presenting with symptomatic T2DM have sight-threatening retinopathy at that time. Very early recognition is essential as the initial treatment of the diabetes will decrease blood glucose levels, cause retinal blood flow to return acutely to normal levels and may result in marked worsening of the retinopathy.

In the UKPDS, the severity of retinopathy was found to be related to higher fasting plasma glucose levels. In addition, in men, increased alcohol consumption was related to increased severity of retinopathy, while leaner women had more severe eye lesions. Visual acuity was normal in most patients, but in men there was a trend for those with more severe retinal lesions to have worse visual acuity.

The potential severity of diabetic retinopathy at the time of diagnosis of T2DM is illustrated by the observation that 15% of those with moderate background retinopathy progress to require photocoagulation therapy within 3 years [37]. The specific reason for photocoagulation therapy was maculopathy alone in 72% and proliferative retinopathy in 11% in this group of individuals

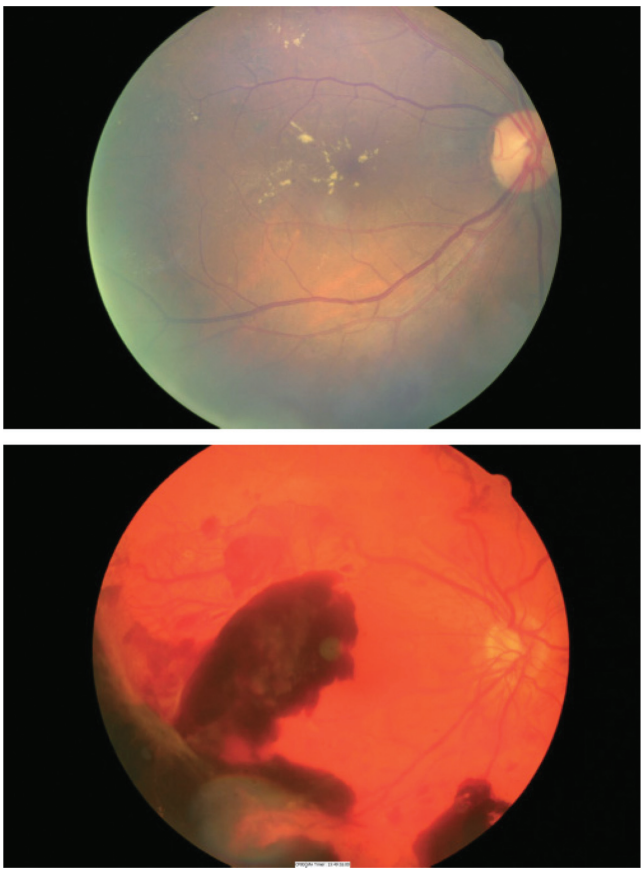

Figure 22.2 Upper panel: immediate laser therapy was required for the macular edema associated with the severe exudative maculopathy present at the time of diagnosis. Lower panel: new vessels are present both arising from the optic disk and from the peripheral retina. Bleeding from the latter caused the prominent pre-retinal hemorrhages which obscure the fovea and in this case caused presentation because of loss of visual acuity.

with T2DM. Although it is likely that the prevalence of retinopathy of all grades of severity is lower if T2DM is diagnosed at routine screening rather than symptomatic presentation, this has yet to be quantified.

Neuropathic syndromes

Although any of the neuropathic syndromes of diabetes may precipitate the initial presentation, symmetrical distal sensory neuropathy, mononeuropathies, and amyotrophy are the most likely candidates. The possibility of diabetes underlying most presentations of neurologic symptoms must be considered.

Diffuse symmetrical sensory neuropathy is the most common neuropathy. A precise estimate of the true prevalence of this neuropathy has been difficult to ascertain, and reports vary from 7 to 60% in people with diabetes, depending on the criteria and methods used to define the neuropathy [38, 39]. The prevalence increases with both age and duration of diabetes. At 12-year follow-up in the UKPDS, 64% of men and 44% of women who were free of neuropathy at baseline developed at least one neuropathic abnormality [40].

Any nerve may be affected by an acute diabetic mononeuropathy, but palsy of cranial nerves III, IV, VI, and VII present most often. It is a rare mode of presentation of T2DM, but not T1DM.

Diabetic amyotrophy may present as weight loss, and unless pain in the thighs is prominent the clinical picture may resemble that of malignant disease. Weakness of quadriceps, with visible wasting and absence of the knee tendon reflex, should allow recognition and lead to the measurement of plasma glucose. Such presentation is likely to be associated with T2DM but again is rare.

A foot lesion can be a presenting sign of diabetes, and it is estimated that the lifetime risk of developing a foot ulcer in people with diabetes may be as high as 25% [41]. Presentation with a black toe is associated with T2DM particularly. Peripheral neuropathy leads to sensory motor and autonomic dysfunction, with loss of the protective pain sensation, dry skin, and callus formation. Loss of pain sensation in the feet is usually unnoticed and subsequent trauma does not come to attention until obvious injury is apparent. In approximately half of those with foot ulcers, concomitant peripheral arterial disease is present [42]. In the EURODIALE study, foot ulcers with presence of peripheral arterial disease were associated with considerably lower healing rates, and higher major amputation and mortality rates [43].

Pregnancy

The time course of presentation of GDM may be predicted from knowledge of its pathogenesis. The key variable is the physiologic insulin resistance that develops during pregnancy. Although several necessarily small studies have quantitated this, it is most clearly illustrated by an observation of the change in exogenous insulin requirements during pregnancy in T1DM. During steady glycemic control and food intake, insulin requirements do not change until around 18 weeks' gestation, whereafter there is a linear increase until around 28 weeks' gestation [44]. The extent of change varies in individual pregnancies from none to over threefold increase, with an average increase in daily insulin dose of 40% [45]. The range is assumed to be a function of the placenta (fetal-derived tissue) as considerable variation is exhibited between successive pregnancies in the same woman.

In the light of this information, it can be understood why the elevated blood glucose levels of GDM are not seen in the first half of pregnancy. Screening for GDM will be most sensitive later in pregnancy but this sensitivity must be balanced with the opportunities to intervene. Current guidelines therefore recommend testing at 24–28 weeks' gestation. Predisposed women cannot mount an adequate β-cell response if the degree of insulin resistance becomes too great. Following one pregnancy complicated by GDM, although increased, the risk of recurrence in a subsequent pregnancy is far from certain, reflecting the variation in

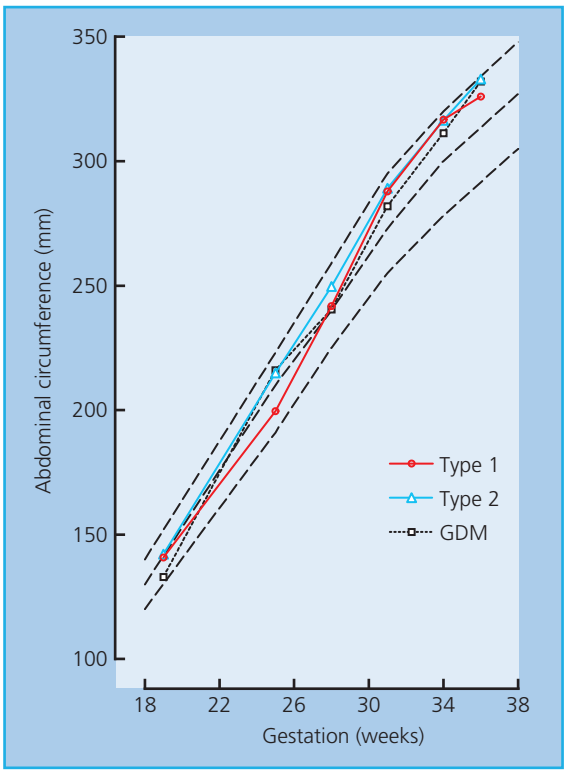

Figure 22.3 Similar rates of increase in fetal abdominal circumference in gestational diabetes (GDM) and pre-gestational diabetes as measured by ultrasound. Source: Lim et al. 2009 [47]. Copyright 2009 SAGE Publications.

insulin resistance in successive pregnancies as the latter is determined by the placenta, tissue which is derived from the individual fetus. Higher rates have been reported in South Asian and Hispanic populations, as would be expected from the higher background prevalence of T2DM (52–69%) [46]. The importance of detection and treatment of GDM is reflected by the data shown in Figure 22.3. The rate of intrauterine growth is as rapid in GDM as it is in T1DM and T2DM [47]. Early diagnosis of GDM carries major advantages for mother and child. The risk of developing subsequent diabetes in those with GDM ranges from 2.6 to 70% over periods from 6 weeks to 28 years [48]. Current NICE guidelines (March 2015) for "Diabetes in pregnancy" recommend that blood glucose should be tested prior to discharge, then fasting plasma glucose should be performed at 6–13 weeks (or HbA_{1c} after 13 weeks) as well as repeated annually for those women with GDM. This will miss a proportion of women with normal fasting plasma glucose and IGT, but it should be noted that the occurrence of GDM should itself be the trigger to advise vigorous lifestyle change and weight loss in particular.

Mild degrees of elevation of plasma glucose may be sufficient to be deleterious to the fetus, and these are far less than those that could produce osmotic symptoms [49]. Screening for GDM is therefore essential. Symptomatic presentation of GDM is unusual in the context of a healthcare system that provides universal screening for GDM. Where osmotic symptoms and superficial fungal infections are part of the clinical presentation, however, it is important to ask whether this is new onset T1DM or T2DM. The former tends to be associated with higher plasma glucose levels and ketonuria. Both are associated with clearly elevated HbA_{1c} levels as the hyperglycemia has been present for several weeks or months. If the presentation is in the first half of pregnancy, it is likely that it will not remit after delivery. If the presentation is in the first half of pregnancy and is associated with raised HbA_{1c}, then a diagnosis of pre-existing diabetes may confidently be made and discussed with the woman [47].

Screening

It has been estimated from the 2002 National Health and Nutrition Examination Survey (NHANES) that one-third of the 13.3 million US adults with diabetes remained undiagnosed [50]. A similar estimate has been made for the UK [51]. Figures based on AHPO diabetes prevalence model (http://bit.ly/aphodiabetes) estimated that 3.2 million people were diagnosed in UK but 634,000 had undiagnosed diabetes in 2013. Universal screening has not been implemented in the UK, however, as criteria for cost-effective and clinically effective screening are not met. The 2012 NICE Guidelines recommend that individuals at high risk due to ethnicity (non-white European), obesity, or family history of diabetes should have fasting plasma glucose or HbA_{1c} tested, and also that a validated risk assessment tool or self-assessment questionnaire should be used in all over the age of 40 years with testing of individuals with a high-risk score [52]. Fasting plasma glucose >7.0 mmol/L (126 mg/dL) or HbA_{1c} >48 mmol/mol (>6.5%) indicates need for a second test to diagnose T2DM. Fasting plasma glucose of 5.5–6.9 mmol/L (99–125 mg/dL) or HbA_{1c} 42–47 mmol/L (6.0–6.4%) is recommended to be managed as pre-diabetes with an intensive lifestyle program.

Fasting glucose, 2-hour post-challenge glucose and HbA_{1c} all equally well predict the future microvascular complications of diabetes and can be considered diagnostic as well as screening tests [53]. The use of the concept of "impaired fasting glucose" with a cutoff of 5.5 mmol/L offers a simple way of excluding or demonstrating dysglycemia [54]. Urinalysis for glycosuria has a high specificity (96–100%) but a low sensitivity (16–43%). Testing random blood glucose is specific but insensitive [55].

The population of individuals with early T2DM who are identified by any screening procedure differs considerably from those who present symptomatically. They are less likely to have established microvascular or macrovascular complications of diabetes. Attitudes to health may differ. The diagnosis will be less welcome as it does not point the way to relief of discomfort and may not be accepted as important for future health. Adherence to therapeutic advice concerning weight, diet, and physical activity may not be as good as following a symptomatic presentation. For these reasons, a more careful approach to discussing the need for future action is required with appropriately sensitive follow-up by the diabetes team.

Other presentations

Ants clustering around urine is a classic description of diabetes, although it is not clear how often this comprises the presenting complaint today. Periodontal disease, especially aggressive periodontitis, is more common in those with diabetes and may occasionally be the presenting complaint [56]. Cataracts typically develop 10 years earlier in people with diabetes [57]. Altered taste or excess production of saliva has been reported as presenting features of diabetes [58].

Conclusions

The mode of presentation of diabetes is enormously varied. Especially as the incidence of diabetes is rising in all age groups, both in the UK and worldwide [59], the onus is upon healthcare professionals to diagnose the condition effectively. Failure to recognize presenting features of diabetes can be costly for the patient.

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23 The Aims of Diabetes Care

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Key points

- People with diabetes are individuals who have a condition that has medical, personal, and social consequences. They are not passive recipients of healthcare and are not defined by their disease state.
- Optimal diabetes management occurs when the multidisciplinary diabetes care team and person with diabetes actively work together as equal partners to achieve diabetes-related goals.
- Life-threatening diabetes emergencies, such as diabetic ketoacidosis, must be effectively managed, and attention paid to their prevention.
- Acute symptoms of hyperglycemia need to be addressed by careful pharmacological management and lifestyle modification support.
- Diabetes management is a balance between supporting short-term optimal glycemic control and quality of life whilst at the same time reducing the risk of long-term complications. This is achieved through effective medical treatment of glycemic control and cardiovascular risk factor management and appropriate psychosocial support and education.
- The time of diagnosis can be traumatic and is a key milestone in the management of diabetes when effective education, support, and treatment are needed.
- Regular lifelong contact between the person with diabetes and their healthcare team is essential in order to support the person with diabetes to cope with the demands of a complex condition that changes throughout a person's life.
- Diabetic complications should be managed effectively if and when they present to reduce the morbidity associated with them.

Introduction

Diabetes is a lifelong condition that for the majority is currently incurable. It is associated with premature mortality and morbidity, from an increased prevalence of cardiovascular disease and microvascular complications affecting the kidney, nerve, and eye [1, 2]. High-quality randomized trials have shown that improving glycemic control is associated with a reduction in microvascular complications [3–5] while a multifaceted approach to cardiovascular risk factors will reduce cardiovascular morbidity and mortality [6]. Addressing the psychosocial challenges faced by people with diabetes has been shown to be effective in terms of reducing psychological distress and improving self-management behaviors [7]. Supporting the person with diabetes in making choices based on the best evidence available, and providing them with autonomy in consultations leads to greater self-care and improved metabolic control [8].

The person living with diabetes will spend the vast majority of their time managing their own diabetes and only an estimated 1% of their time in contact with healthcare professionals. Therefore it is crucial to provide individuals with appropriate medical and psychosocial support to help them optimally self-manage their diabetes. Given the central role of the person with diabetes and the relatively little contact with healthcare professionals, it is important that the purposes of the consultation or other contacts with the diabetes healthcare team are well defined and their aims are made clear. To ensure that the individual derives the maximum benefit from the time spent with their diabetes healthcare team, whether this is in a hospital or primary care setting, the consultation should be collaborative, patient-centered, and goal-focused. As well as the clinic visit, diabetes care may also be provided through phone or email contact or through educational sessions outside a traditional clinic setting.

This chapter provides an overview of the aims and philosophy of diabetes care. Separate aspects of care will be covered in greater detail in subsequent chapters. The aims of diabetes care and management to improve the quality of life of the person with diabetes are fourfold. Life-threatening diabetes emergencies, such as diabetic ketoacidosis or severe hypoglycemia, should be managed effectively including preventative measures. The acute manifestations of hyperglycemia, such as polyuria and polydipsia, need to be addressed. In practice, these occupy only a minority of the work undertaken by diabetes healthcare professionals. Much of the focus of care is therefore directed towards minimizing the long-term complications through screening and working together

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with the person with diabetes to support improved glycemic control and cardiovascular risk factor management. This provides a challenge for the diabetes team because people with type 2 diabetes often have no symptoms at the time of care, yet are asked to make lifestyle changes and take medications that may place a considerable burden upon them. It is also important that clinicians bear in mind the fourth aim of care which is to avoid iatrogenic side effects, such as hypoglycemia. Involvement of the person with diabetes in this care planning is paramount to success.

St. Vincent's Declaration

During the 1980s, there was a transformation in the widely held perceptions of the roles of people with diabetes and philosophy of care. Instead of being viewed as passive recipients of health care, there was an increasing recognition that people with diabetes were individuals with a condition that has medical, personal, and social consequences. During this time there was an increasing awareness and acceptance of the concept that each person with diabetes should accept part of the responsibility for their treatment and act as equal partners with healthcare professionals. In response to this paradigm shift, representatives of Government Health Departments and organizations for people with diabetes from all European countries met with diabetes experts under the auspices of the Regional Offices of the World Health Organization and the International Diabetes Federation in the hillside town of St. Vincent, Italy on October 10–12, 1989. They unanimously agreed upon a series of recommendations for diabetes care and urged that action should be taken in all countries throughout Europe to implement them (Box 23.1) [9]. Since this time this philosophy of partnership working between people with diabetes and healthcare professionals has been adopted within individual nations' strategies to improve the quality of diabetes care.

The diabetes care team

The diabetes care team involves a multidisciplinary group of healthcare professionals who are available to support the person with diabetes (Figure 23.1). A key component of diabetes care is to ensure that the individual with diabetes is at the center of the provision of care. This means that they should be an equal member of the diabetes care team working together with the healthcare professionals. This relationship should provide the information, advice, education, and support of the individual with diabetes to enable them to feel sufficiently empowered to manage their condition themselves whilst ensuring that the care offered is tailored appropriately for the individual and their circumstances.

The large number of health professionals involved in the diabetes care team means that the roles and responsibilities of all must be clearly presented and agreed upon. It is often helpful for the person with diabetes if the key members of the diabetes care team

Box 23.1 St. Vincent's Declaration [7]

- Elaborate, initiate and evaluate comprehensive programs for detection and control of diabetes and of its complications with self-care and community support as major components.
- Raise awareness in the population and among healthcare professionals of the present opportunities and the future needs for prevention of the complications of diabetes and of diabetes itself.
- Organize training and teaching in diabetes management and care for people of all ages with diabetes, for their families, friends, and working associates and for the healthcare team.
- Ensure that care for children with diabetes is provided by individuals and teams specialized both in the management of diabetes and of children, and that families with a child with diabetes get the necessary social, economic, and emotional support.
- Reinforce existing centers of excellence in diabetes care, education, and research.
- Create new centers where the need and potential exist.
- Promote independence, equity and self-sufficiency for all people with diabetes, children, adolescents, those in the working years of life, and the elderly.
- Remove hindrances to the fullest possible integration of people with diabetes into society.
- Implement effective measures for the prevention of costly complications:
  - Reduce new blindness due to diabetes by one third or more.
  - Reduce numbers of people entering end-stage renal failure by at least one third.
  - Reduce by one half the rate of limb amputations.
  - Cut morbidity and mortality from coronary heart disease by vigorous programs of risk factor reduction.
  - Achieve pregnancy outcomes in women with diabetes that approximate that of women without diabetes.
- Establish monitoring and control systems using state-of-the-art information technology for quality assurance of diabetes healthcare provision and for laboratory and technical procedures in diabetes diagnosis, treatment, and self-management.
- Promote European and international collaboration in programs of diabetes research and development through national, regional, and WHO agencies and in active partnership with diabetes person with diabetes organization.
- Take urgent action in the spirit of the WHO program, "Health for All," to establish joint machinery between WHO and IDF European Region, to initiate, accelerate, and facilitate the implementation of these recommendations.

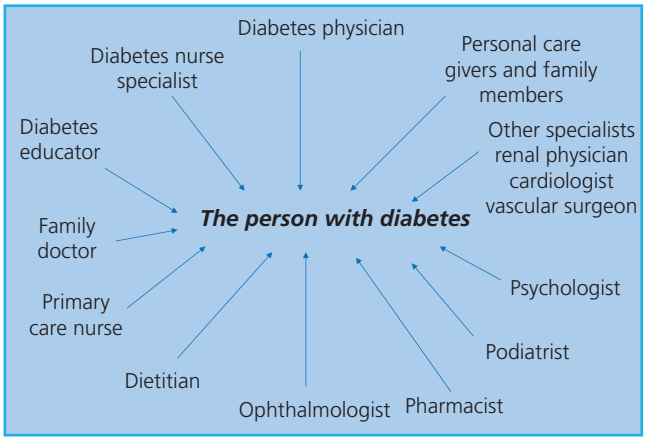

Figure 23.1 The multidisciplinary group of healthcare professionals who are available to support the person with diabetes.

are identified, as they will have more contact with some healthcare staff than others.

The majority of routine diabetes care takes place in a primary care setting but some people with diabetes with complications or complex medical or psychological needs will require management and support in a specialist setting for some or all of their care [10]. The diabetes physician usually takes overall responsibility for the diabetes medical care but other specialists may be involved, for example an ophthalmologist may be needed to examine the eyes carefully and treat diabetic retinopathy, if present. Diabetes care is multidisciplinary involving doctors, nurses, and many allied healthcare professionals whose responsibility is to support the person living with diabetes in the management of their condition. A close collaboration between primary and secondary healthcare professionals and among specialists is needed to ensure that all involved are aware of the issues that are relevant to the individual with diabetes and that care is integrated and coordinated across the wide range of disciplines involved. Placing the person with diabetes at the center of care is likely to facilitate the collaboration.

Given the chronic nature of diabetes, continuity of care is essential. Ideally this should be provided by the same doctors and nurses from visit to visit but where this is not possible, the healthcare team should have access to previous records so that they are fully aware of the medical history and background of the person with diabetes. In some developing countries, this is particularly challenging where medical records are often focused around single episodes of acute care of infectious diseases [11].

With the involvement of the person with diabetes in the diabetes team, that individual assumes a number of responsibilities. The task of implementing the day-to-day management plan of the diabetes lies with the individual; it may sometimes be difficult for healthcare professionals to accept this. It is important to understand that diabetes self-management is challenging and so the diabetes care team should be available to support the person through their experiences with their condition. Adolescence can be a particularly challenging time as this period of the person's life coincides with a time of rapid change, transition to adulthood and increasing independence. Risk-taking, experimentation and increasing responsibility along the path to diabetes self-management by the adolescent are to be expected (Chapter 60).

Improving the outcome of the consultation

The time that a person with diabetes spends with a healthcare professional is limited and should be used as effectively as possible. Clinicians often give conflicting advice, both within the team and from one consultation to the next [8]. Goals are often not followed up, leaving the person with diabetes feeling frustrated. Studies have shown that typically physicians interrupt their patients 18 seconds after the patient starts to describe their problems, approximately half of patients' concerns are not discussed, and in 50% of consultations, the patient and physician disagree on the central problem presented [8]. Such disagreement and inconsistency are associated with poorer outcomes. Greater self-care and metabolic control are achieved through supporting the person with diabetes to make choices based on the best evidence available and providing autonomy in consultations. In the UK, the Department of Health has produced literature entitled "Questions to ask" (Table 23.1) which provides guidance about the questions a person with diabetes might want to ask during a consultation to maximize the benefits from the visit to their healthcare team [12].

The consultation or education program should help the person with diabetes gain a clearer understanding of their condition. This can only be achieved effectively when professionals and people with diabetes are enabled to work together. Taking a holistic approach, such as embodied in the Kaleidoscope model of care [13] (Figure 23.2), can facilitate this collaborative, patient-centered joint goal-setting approach.

The Kaleidoscope model of care presents a novel, holistic, tailored, and individualized approach to healthcare delivery for people with diabetes through an assessment of an individual's current regimen, barriers and motivation, and available support resources. It is flexible and applicable in different health settings, fundamentally promoting the specific needs of the individual with diabetes. These needs are dynamic, taking a different shape at different points in time, whilst recognizing and adapting to the range of care needed.

It is good practice to provide the person with diabetes with copies of any letters written about them [14, 15]. Questions about their treatment should be encouraged and people should be aware of what will happen next, including any requirement for further investigation. Regular review of management plans through joint dialogue, listening, discussion, and decision-making between the individual and the healthcare professional, sometimes known as care planning, is the key to enhancing relationships and partnership working [16]. Contact details should be made available to enable the individual with diabetes to seek help if further questions arise.

Table 23.1 Checklist of questions to ask your doctor at your appointment [10].

Tests, such as blood tests or scans
What are the tests for?
How and when will I get the results?
Who do I contact if I don't get the results?

Before your appointment
Write down your two or three most important questions.
List or bring all your medicines and pills—including vitamins and supplements.
Write down details of your symptoms, including when they started and what makes them better or worse.
Ask your hospital or surgery for an interpreter or communication support if needed.
Ask a friend or family member to come with you, if you like.

During your appointment
Don't be afraid to ask if you don't understand. For example, "Can you say that again? I still don't understand."
If you don't understand any words, ask for them to be written down and explained.
Write things down, or ask a family member or friend to take notes.

Before you leave your appointment
Check that:
You've covered everything on your list
You understand, for example "Can I just check I understood what you said?"
You know what should happen next—and when. Write it down.

Ask:
Who to contact if you have any more problems or questions
About support groups and where to go for reliable information, and
For copies of letters written about you—you are entitled to see these.

After your appointment, don't forget to
Write down what you discussed and what happens next. Keep your notes.
Book any tests that you can and put the dates in your diary.

- **Ask:**
"What's happening if I'm not sent my appointment details," and
"Can I have the results of any tests?" (If you don't get the results when you expect—ask for them.) Ask what the results mean.

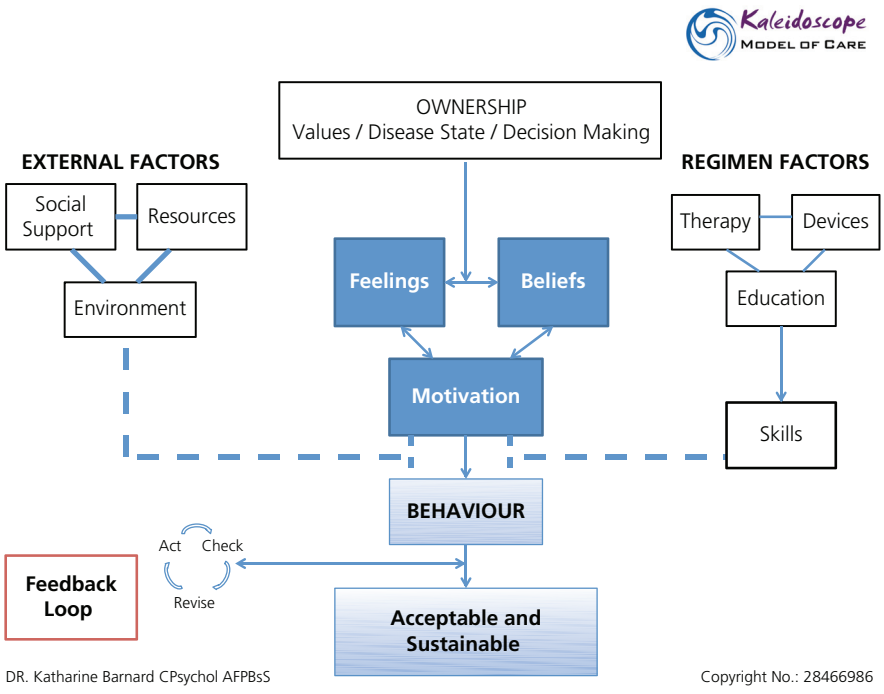

Figure 23.2 The Kaleidoscope model of care [13].

Following diagnosis

The period following the diagnosis of diabetes is crucial for the long-term management of diabetes. A huge amount of information and skills need to be assimilated by the person with diabetes at a time when they may be least able to do so, perhaps because of denial of or anger with the diagnosis [17]. Empathy and considerable skill are therefore needed to support the person with diabetes at this time. The diabetes team should perform a medical examination (usually the physician) and work with the individual to develop a program of care that is individualized and includes treatment-oriented goals.

Issues relating to diagnosis

The diagnosis of diabetes is based on the finding of one or more glucose values above internationally agreed values [18, 19] (Chapter 2). Usually a diagnosis has been made prior to referral to the diabetes clinic but this is not always the case. In the absence of symptoms, individuals require two glucose or glycated hemoglobin values above the diagnostic criteria to fulfil the diagnosis of diabetes.

Advice may be required to determine the type of diabetes as the distinction is not always as clear as may be expected. When a young pre-school child develops weight loss, polyuria, polydipsia, and ketoacidosis over a short period of time, the diagnosis is obviously type 1 diabetes (T1DM). In contrast if an asymptomatic elderly overweight individual is found to be hyperglycemic, the diagnosis is type 2 diabetes (T2DM) (Chapter 22). These presentations lie at two ends of a spectrum, and the diagnosis of the type of diabetes may be less clear when the onset occurs in an overweight adult in their 30s who is found to have islet cell antibodies. Diabetes healthcare professionals should also be alert to the possibility of monogenic causes of diabetes (Chapter 18).

Although a precise diagnosis may not be needed from the outset, an early decision should be made about the necessity for insulin therapy (Chapter 22). While there may be clinical features that suggest the type of diabetes, time is often a useful diagnostic tool to determine whether the person with diabetes requires insulin.

Diabetes education

A key component of the empowerment of the person with diabetes is the provision of diabetes education [20] (Chapter 24). This information should be provided in a patient-centered manner as it is retained more effectively when delivered in this way. Education may be provided individually or in a group setting.

It is essential that the person with diabetes understands their diabetes and develops the skills and competencies required to self-manage the condition as well as possible. People with newly diagnosed diabetes should have the chance to speak with a diabetes specialist nurse (or practice nurse) who can fully explain what diabetes is [21]. This will provide an opportunity to discuss the treatment and goals as well as providing a practical demonstration of any equipment required to support self-management, for example, blood glucose meters or insulin devices. The importance of ketones testing for those with T1DM should be explained. Where self-monitoring has been advocated, it is essential that the individual knows how to interpret the results and how to act appropriately in response to that information.

A qualified dietitian should provide advice about how to manage the relationships between food, activity, and treatment (Chapter 25). Where necessary, they should explain the links between diabetes and diet and the benefits of a healthy diet, exercise, and optimal diabetes control. As an essential member of an effective clinical care team, a diabetes specialist nurse or practice nurse also has a role in providing dietary advice together with relevant literature [21].

The social effects of diabetes should be discussed, as they may relate to employment, insurance or driving (Chapter 58). Some countries require individuals with diabetes to inform the appropriate licensing authorities. Advice about diabetes and foot care should also be given (Chapter 48).

Although education is essential following diagnosis, it is important to appreciate that this is a lifelong process that should take into account recent advances in medical science and changes in circumstances of the person with diabetes [20].

The best measure of successful education is not simply that someone knows more, but rather that they use the new knowledge to enhance diabetes self-management. The simple provision of knowledge by itself is often insufficient to influence behavioral change. High demands are placed on the person with diabetes regardless of the type of diabetes, especially when the benefits are not immediate, may only accrue with time and even then may not be appreciated. The individual with diabetes needs to gain an understanding that improved glycemic control can help in preventing the long-term complications of diabetes, such as a myocardial infarction or proliferative retinopathy, even though they may have never experienced these conditions.

The diagnosis of diabetes may provoke a grief reaction and support is needed from the diabetes team to help the person with diabetes work through this (Box 23.2). Engagement is needed to help the individual adapt to living with diabetes and engage in optimal self-management rather than being left feeling overwhelmed by diabetes or that their healthcare team can take control for them. For some it may take a very long time to accept their diabetes and the demands this places on their life. Therefore emotional and psychological support and techniques need to be available in the long term.

People with newly diagnosed diabetes often want to speak with others who have diabetes who have had similar experiences while developing diabetes. Many countries have diabetes-related charities that can provide this support and it is important that information about what help is available, including local centers or patient support groups, is provided in a timely fashion.

Box 23.2 Case study

Dave is 25 years old and recently diagnosed with type 1 diabetes. The diagnosis was made following an acute admission to hospital with diabetic ketoacidosis and insulin therapy was initiated.

Initially appearing to accept the diagnosis, Dave quickly became very angry about his perceived loss of control over his life and the reduction in his quality of life because of the new demands placed by diabetes and its treatment. Feeling guilty about whether he could have prevented it, and despairing about the lifelong condition, Dave found it increasingly difficult to keep up with the daily tasks of self-management, which in turn contributed to his feelings of despair and loss of control.

The healthcare team helped Dave identify some short-term goals for diabetes self-management and sign-posted social media support online including Twitter, as well as a local support group. Dave and his healthcare team worked together on problem-solving techniques to help make some of the diabetes tasks more achievable in his daily routine.

Ongoing clinic visits

The diabetes team needs to work to together with the person with diabetes to review the program of care including the management goals and targets at each visit [22]. It is important that the individual shares equally in all treatment decisions as this improves the chances of jointly agreed goals being adopted following the consultation. A family member, friend, or carer should be encouraged to attend the clinic to help support the person with diabetes, and to stay abreast of developments in diabetes care [23].

An important goal of management is to prevent the microvascular and macrovascular complications of diabetes without inducing iatrogenic side effects. This involves active management of hyperglycemia together with a multifaceted approach targeting other cardiovascular risk factors.

Glycemic management

It is important to enquire about and discuss hyperglycemic symptoms and problems with medications, including issues relating to injections, hypoglycemia, and self-monitoring of blood glucose.

Hyperglycemic symptoms

Symptoms relating to hyperglycemia usually occur when the blood glucose rises above the renal threshold leading to an osmotic diuresis. Polyuria, particularly at night, polydipsia, and tiredness may ensue. General malaise may also occur and is not always ascribed to the hyperglycemia.

Medications

The diabetes care team is responsible for ensuring that the person with diabetes has access to the medication and equipment necessary for diabetes control. In many, but not all, countries this is available for free or at a reduced rate; many people with diabetes may be unaware of this and timely advice may alleviate some of the anxieties about the cost of diabetes.

Oral glucose-lowering drugs

Each of the oral glucose-lowering drugs has its strengths and profile of side effects (Chapter 31) and these should be discussed. Strategies may be devised to maximize the tolerability of diabetes medications. For example, the timing of metformin in relationship to meals, or the use of long-acting preparations may reduce the risk of gastrointestinal upset. Where treatments are not being tolerated, these should be changed, in order to facilitate improved concordance with the regimen. Another example is the need to discuss the risks of hypoglycemia with sulfonylureas.

Insulin

Insulin therapy is complex: it must be given by self-injection or pump and there is considerable variation in the doses, regimens, and devices available to people with diabetes. It is important that during the clinic visit, the individual has an opportunity to discuss injection technique and any difficulties with injection sites, which should be examined at least annually. Information about the appropriate storage of insulin and safe disposal of sharps (needles) is needed.

The commonest side effects of insulin are hypoglycemia and weight gain (Chapter 29). In addition to these, there are a number of other issues that should be addressed including injection site problems, such as lipohypertrophy, and device and needle problems.

Assessment of glucose control

Supporting the person with diabetes to achieve optimal glycemic control is a vital component of diabetes care. The methods of assessing glucose control essentially involve short-term measures, such as self-monitoring of blood glucose, and long-term measures, such as glycated hemoglobin (HbA_{1c}) (Chapter 27). Not all people with diabetes will need to undertake self-monitoring of blood glucose but where they do, it is incumbent on the healthcare professional to discuss with them the findings and how these will affect future management. The glycated hemoglobin provides a measure of the longer term adequacy of glycemic control and sometimes there may be a discrepancy between this measure and self-monitored blood glucose. It is important to explore the reasons that underlie the differences, which may range from biological issues, such as genetically determined rates of glycation, through inappropriately timed glucose readings to fabricated results. A pristine sheet (with no blood stains from finger-sticks) and with the use of a single pen color may be a clue to the latter. It is important to explore in a non-judgmental way why the individual might engage in such a practice. The

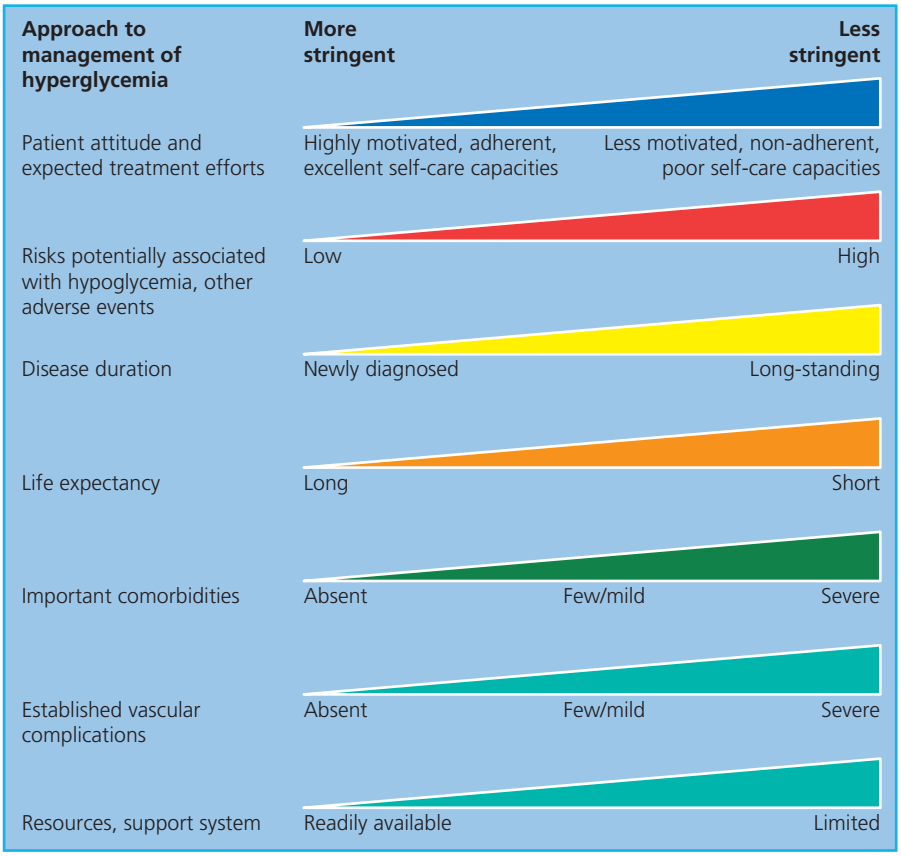

Figure 23.3 EASD/ADA Approach to management of hyperglycemia [24].

use of computers and the ability to download results may help to observe patterns of hyperglycemia although it is important to make sure that the meter has not been shared. Increasingly it is possible to use the Internet to review glucose remotely.

People with diabetes need to be supported in an open and non-judgmental way. Sometimes clinicians can appear to show the opposite, which is unhelpful and counter-productive to joint goal-setting, and collaborative consultation. Feeling reprimanded or misunderstood can be frustrating and upsetting, and it is understandable why someone would not choose to put themselves through the experience if they did not have to. It is better to build a relationship whereby the person with diabetes feels that the healthcare professional is there to support and work together to find solutions and overcome barriers to optimal self-management.

The Diabetes Control and Complications Trial and the United Kingdom Prospective Diabetes Study (UKPDS) have clearly established that lower levels of glycemia are associated with reduced risk of long-term microvascular complications in T1DM and T2DM, respectively [3–5]. For this reason, learned societies such as the American Diabetes Association and European Association for the Study of Diabetes and government bodies such as the National Institute for Health and Care Excellence have set tight glycemic targets to minimize the risk of complications for individuals with diabetes [24–26]. Furthermore in the UK, general practitioners are incentivized financially to achieve tight glycemic control for their patients. However, there has been an increasing awareness of the need to individualize targets for the person with diabetes, depending on factors such as life expectancy, duration of diabetes, comorbidity including cardiovascular disease, resources, and availability of support (Figure 23.3).

The natural history of the development of complications is long and in some situations may be longer than the life expectancy of the person with diabetes. It would be a poor trade to insist on switching a frail complication-free 90-year-old person to insulin if they subsequently fell and broke their hip and died as a result of insulin-induced hypoglycemia. Less melodramatic but still important is the consideration about dietary and lifestyle change in people with low risk of disabling complications: is it really necessary to deny an elderly person with diabetes a piece of birthday cake if this is one of the few food pleasures in their life? A more sensible approach would be to advise a limit to portion size, rather than insist on severe dietary restriction.

Although there is an appropriate clinical emphasis on glycemic targets, the results of The Action to Control Cardiovascular Risk in Diabetes (ACCORD) trial [27], the Action in Diabetes and Vascular disease: Preteraz and diamicron MR controlled evaluation (ADVANCE) trial [28], and the Veterans Affairs Diabetes

Trial (VA-DT) have led to a note of caution [29]. These trials have shown that tight glycemic control in people with a longer duration of diabetes did not prolong life. In the case of the ACCORD trial increased cardiovascular mortality was seen in those receiving intensive glycemic control [27]. Again these findings highlight the need for individualized targets.

Despite clinical guidance and the availability of effective treatments, many people with diabetes are unable to achieve the desired level of glycemic control. It is important for the healthcare professional to explore the reasons why this might be together with the individual. Advice about adjustment of treatment or further education or psychological support may be needed.

A common limiting factor in the ability to achieve optimal control is hypoglycemia which is one of the most unpleasant, socially aversive, inconvenient, and feared side effects of diabetes medication (Chapter 35). The frequency and severity of hypoglycemic episodes should be discussed. An exploration of the underlying causes and advice about prevention is required for the future.

When a person with diabetes is treated with insulin, it is important to ensure that they carry a readily accessible source of fast-acting glucose, such as glucose tablets. Concentrated glucose solution and glucagon should also be made available for use in more severe hypoglycemia. As these treatments may only be used infrequently, it is worth regularly checking whether they are in date. Furthermore as they need to be administered by a third party, it is important to ensure that the friends and relatives of the person with diabetes know how to administer them and are confident in doing so before they are needed.

In some instances, the only way of avoiding disabling hypoglycemia is to accept a lesser degree of glycemic control. This recalibration of glycemic goals should be decided with the individual and a target appropriate for the circumstances should be agreed. As well as the risk of hypoglycemia, other factors should be considered when discussing the target including the overall clinical situation and risk of complications affecting the individual.

Assessment of cardiovascular risk

The commonest cause of death in people with diabetes is cardiovascular disease and much effort has been expended to develop strategies that will reduce its morbidity and mortality [30].

Cardiovascular risk should be assessed at least once a year for people with diabetes. This should include a history of cardiovascular risk factors, such as family history and smoking, an examination to include weight, waist circumference, and blood pressure as well as investigations such as a lipid profile. The results of this assessment can be used to calculate cardiovascular risk using the various risk engines available. Some, such as the UKPDS risk engines for coronary heart disease and stroke, were designed specifically for use in people with diabetes and are readily available on the Internet [31, 32].

Since the risk of myocardial infarction is almost as high in people with diabetes as in those without but with pre-existing cardiovascular disease, the diabetes itself is widely considered to be a major risk factor for cardiovascular disease [33]. This has influenced prescribing guidelines which now recommend that specific pharmacological interventions are required to reduce the incidence of cardiovascular disease in people with diabetes regardless of risk assessment. Large randomized controlled trials have shown the effectiveness of these interventions and are discussed in greater detail in Part 8 [34].

Although physicians may appreciate the close connection between diabetes and cardiovascular disease, many people with diabetes have never been told about this increased risk, and the importance of blood pressure and lipid control. Thus, many individuals are not taking appropriate drugs for cardiovascular prevention, or if they are the doses may be inadequate to achieve recommended targets. When working with someone with diabetes, it is important that strategies to reduce cardiovascular disease and the need for preventative drugs are discussed. In addition, the increased vascular damage promoted by smoking in the setting of diabetes may not be appreciated.

The main classes of drugs used are lipid-lowering drugs, predominantly statins, and antihypertensives, particularly drugs acting on the renin-angiotensin system. Antihypertensives are also important in the prevention of microvascular complications as discussed in the following section.

While each individual intervention for the various risk factors is important in the prevention of macrovascular disease, the Steno 2 study has demonstrated that a coordinated approach to the management of cardiovascular risk can be successful [6]. In this study, the clinic setting and protocol-driven approach to overall cardiovascular risk led to significantly improved mortality compared with routine care.

Microvascular complications

Around 80% of individuals will have developed microvascular complications by the time they have had diabetes for 20 years [35]. Many complications will remain asymptomatic until they have catastrophic consequences. The management of microvascular complications involves measures to prevent, detect, and treat. General measures, such as optimal glycemic and blood pressure control, lead to a reduction in the incidence and progression of microvascular complications but specific preventative measures are also needed and are discussed below [3–5, 36].

Eyes

Diabetic retinopathy remains a common cause of blindness in people of working age (Chapter 38). It is almost invariably asymptomatic until there is a catastrophic sight-threatening hemorrhage. For this reason it is important to screen regularly for retinopathy to allow treatment before hemorrhage and visual loss occur. Traditionally this has been performed by examination of the visual acuity and fundoscopy within the diabetes clinic at least on an annual basis. Alternatively in many countries, dilated ophthalmological examinations are regularly performed by a specialist.

The gold standard for screening now, however, is digital retinal photography, which may be undertaken in several different

settings. When this is performed outside the traditional diabetes clinic, communication between the screener and diabetes team is essential if other aspects of diabetes care are to take account of the development of retinopathy.

Where retinopathy is detected within the clinic, it is the responsibility of the clinic to ensure that the individual is referred for specialist ophthalmological attention in a timely fashion.

Neuropathy

Distal symmetrical polyneuropathy is the commonest form of neuropathy seen in diabetes and is addressed in the following section on the diabetic foot. Autonomic neuropathy may affect the person with diabetes in a number of ways, for example gustatory sweating, postural hypotension, or bloating (Chapter 39). Healthcare professionals should be alert to this possibility if symptoms suggestive of these conditions are raised.

Foot problems

Diabetes is the commonest cause of non-traumatic lower limb amputation in the developed world (Chapter 48). Around 10–15% of people with diabetes develop a foot ulcer as a result of the combination of peripheral neuropathy and vascular insufficiency to the foot.

Prevention of ulceration is an important goal and requires educating the person with diabetes so that they are aware of this possibility. It is important to inform people that they should not delay in obtaining professional help if problems ensue.

An assessment of the risk of foot ulceration is needed at least annually and more frequently when neuropathy or vascular disease is present. The assessment should include a history of previous ulceration, trauma as well as an examination of the skin, vascular supply, and sensation. Opportunistic foot screening should also be performed if an individual with diabetes is admitted to hospital.

In patients with numbness, close attention to discovering unsuspected foot lesions, including examination of the sole of the foot using a small mirror, must be performed by the individual on a regular basis. This can lead to rapid intervention and prevent an early infection from progressing, potentially averting such devastating consequences as osteomyelitis and gangrene.

Prompt referral to the podiatrist and foot clinic should be arranged by the diabetes clinic if needed.

Kidneys

Diabetic nephropathy is characterized by a progressive increase in urinary albumin excretion which is accompanied by increasing blood pressure and decline in glomerular filtration rate ultimately culminating in end-stage renal disease. It is also associated with a marked increase in the rate of cardiovascular disease.

Microalbuminuria, the earliest stage of nephropathy, affects around 50% of people with diabetes after 30 years while frank proteinuria affects a quarter of people with T1DM after 25 years. Diabetic nephropathy is a common reason for the initiation of renal replacement therapy. Although it appears that with modern treatments of diabetes, the percentage of people with diabetes developing end-stage renal disease appears to be falling, the absolute numbers requiring renal replacement therapy is increasing in line with the increased prevalence of diabetes worldwide.

Diabetic nephropathy is asymptomatic and so screening is required annually. This is usually achieved by measurement of urinary albumin excretion. The commonest method is a single urinary albumin to creatinine ratio (ACR) measurement which should be repeated two to three times if abnormal. An estimation of glomerular filtration rate should be obtained annually.

The primary prevention of nephropathy relies on excellent glycemic control as well as tight blood pressure control. Once nephropathy is present, blood pressure management is the mainstay as there is little evidence that glycemic control at this stage slows the rate of progression. The antihypertensive drugs of choice are angiotensin-converting enzyme (ACE) inhibitors or angiotensin-2 receptor antagonists as they have specific effects on renal blood flow [37, 38].

There has been some debate about the value of undertaking urinary ACR measurements in people with T2DM, the argument being that tight blood pressure control (often including an ACE inhibitor or angiotensin-2 receptor antagonist) together with good glycemic control should form part of the general management of cardiovascular risk reduction, regardless of the presence of microalbuminuria.

It is important that the person with diabetes understands the need for screening followed by treatment if nephropathy develops. Timely referral to the nephrology team is needed to ensure that the management of renal disease is managed promptly in those with abnormal renal function.

Diabetes emergencies

Diabetic ketoacidosis and hyperosmolar hyperglycemic syndrome

Diabetic ketoacidosis and hyperosmolar hyperglycemic syndrome are potentially life-threatening emergencies (Chapter 36). The person with diabetes needs to be educated about the risk of these and strategies to prevent them from happening should be discussed. If a person with diabetes has been admitted with diabetic ketoacidosis or hyperosmolar hyperglycemic syndrome, the opportunity should be taken to explore the reasons why this episode occurred and to identify what might be changed to prevent this from happening in future. The commonest causes of hyperglycemic emergencies in those with pre-existing diabetes are infections and insulin omission and errors. It is particularly important that people with diabetes understand the "sick-day" rules where insulin should never be discontinued and indeed doses may need to be increased even when appetite is diminished.

Hypoglycemia

Hypoglycemia is a common diabetic emergency affecting most people with T1DM and ~60% of insulin-treated people with T2DM (Chapter 35). Hypoglycemia may have a major adverse

Table 23.2 Causes of hypoglycemia.

- Excessive insulin administration
  - Person with diabetes, doctor or pharmacist error
  - Deliberate overdose during a suicide or parasuicide attempt
- Excessive sulfonylurea administration
- Unpredictable insulin absorption
  - Insulin is absorbed more rapidly from the abdomen
  - Lipohypertophy
- Altered clearance of insulin
  - Decreased insulin clearance in renal failure
- Decreased insulin requirement
  - Missed, small, or delayed meals
  - Alcohol
    - Inhibits hepatic glucose output
  - Vomiting
    - May occur with gastroparesis, a long-term complication of diabetes
  - Exercise
    - Promotes glucose uptake into muscle
    - Increases rate of insulin absorption
- Recurrent hypoglycemia and unawareness

effect on quality of life and fear of hypoglycemia is the most important limiting factor in the achievement of optimal glycemic control.

It is important that the person with diabetes is educated about the symptoms of hypoglycemia and the actions to be taken to prevent and treat it. As noted earlier, friends and family members should be invited to learn about hypoglycemia and its management in order to intervene when necessary, for example, providing glucagon treatment if the person with diabetes is unconscious. If hypoglycemia becomes disabling or recurrent, it is important to explore underlying causes (Table 23.2).

Lifestyle issues

Diabetes has a number of social, psychological, and medical consequences and an important aspect of diabetes care is to discuss how diabetes may be affecting social issues such as driving, education, and employment (Chapter 58). The healthcare professional may need to act as an advocate for the person experiencing discrimination. Some aspects of lifestyle also affect diabetes care, such as diet, exercise, smoking, and alcohol. These issues should be discussed sensitively in order help the person with diabetes understand how their lifestyle affects their diabetes and general health. Support should be given to help and encourage the individual to make changes to their lifestyle where these are appropriate.

Psychological issues

Both the diagnosis of diabetes and the chronicity of the condition can provoke a number of psychological reactions, such as anger and sadness in the individual which may be akin to a bereavement reaction or a chronic sorrow response (Chapter 56). More serious mental health problems, such as depression, are common in people with diabetes and these can impede the person's ability to achieve optimal glycemic control [39] (Chapter 57).

It is important for those working in diabetes care to explore with the individual whether they are experiencing psychological problems as they may be reluctant to raise this in the consultation. While all members of the diabetes team should be able to recognize and address basic psychological problems, an essential team member is a psychologist who can address more complex needs. Despite the importance of psychological issues, this need is frequently unmet because of a lack of trained healthcare professionals.

The Diabetes Attitudes Wishes and Needs (DAWN™) study, a global survey of people with diabetes and healthcare professionals involved in their care, substantiated the association of diabetes with multiple psychological challenges and the close interrelationship between emotional well-being and diabetes outcome [40]. It also pointed to important deficiencies in the emotional care of and support for people with diabetes, which became the basis for the DAWN Call to Action with the goal of implementing person-centered diabetes care.

In 2012, the second global DAWN™ study (DAWN2™) was conducted to re-evaluate the state of diabetes care, both globally and within each of the 17 participating countries, including the UK. In the global DAWN2 study, nearly half of the surveyed people with diabetes reported diabetes-related distress, 12% rated their overall quality of life "poor" or "very poor," and approximately 14% had likely depression [41]. Notably, family members were also considerably impacted by having a person with diabetes in their household, with 35% experiencing the care for the person with diabetes as a burden [23]. In 45% of family members, diabetes care had its most negative impact on emotional well-being [23].

Sexual health

Sexual dysfunction

Sexual dysfunction is more common in both men and women with diabetes than in the general population. This can affect the person's quality of life considerably. Many people are reluctant to discuss this aspect of their lives because of embarrassment and so it is the responsibility of the healthcare professional to enquire about this. There are now effective treatments for erectile dysfunction and failure to ask about this can deny the person with diabetes the opportunity to receive this treatment.

Pregnancy planning

Starting a family is an important milestone for many and the presence of diabetes can make this decision more difficult for the woman with diabetes (Chapter 61). Women are often worried about the effects that diabetes will have on their pregnancy and vice versa. The implications for the long-term risk of diabetes in the offspring are also of concern.

Planning for a pregnancy by a woman with diabetes can dramatically improve the outcome, reducing the risk of miscarriage, congenital malformations and macrosomia, with its attendant risks of shoulder dystocia, and neonatal hypoglycemia [42]. Most oral medications should not be used in pregnancy and the treatment regimen may need to be altered as part of the planning process.

Despite this, many women enter pregnancy without adequate preparation or pre-conception care. It is therefore incumbent on the healthcare professional to discuss pregnancy with all women of child-bearing age, including adolescents, to ascertain their plans regarding pregnancy. The answers are often not black and white; women may not actively be planning to become pregnant but are sexually active and not using effective contraception. Contraceptive advice is needed and where a pregnancy is being planned, women should be referred to a dedicated pre-conception clinic as these have been shown to improve the outcomes of diabetic pregnancies.

With an increasing number of women with T2DM of child-bearing age, it is important that pre-conception advice is not solely focused on those with T1DM. This is particularly relevant as many women with T2DM are not seen in specialist centers.

Prompt referral to a joint diabetes antenatal clinic is necessary once a woman becomes pregnant.

Men may also have concerns about embarking on a family because of the increased risks of diabetes in their offspring and these anxieties need to be discussed sensitively.

Inpatient diabetes care

It is estimated that around 10–15% of people in hospital have diabetes (Chapter 34). In many instances the diabetes is coincidental to the admission and the individual remains capable of managing their own diabetes, often with greater skill than the healthcare professional around them. Optimal diabetes control remains an important goal as this improves the rate of recovery and may lead to an earlier discharge.

Admission to hospital is a worrying time but much of the fear can be alleviated if a full explanation of the treatment in hospital is given along with an opportunity to discuss any particular concerns. Being given the opportunity to discuss the management of diabetes can be reassuring. Where possible, the person with diabetes should be allowed to continue to self-manage their diabetes. The individual should be encouraged to bring in their own insulin supplies where admissions are planned. There should be access to their regular diabetes healthcare team where possible as the admission may provide an occasion to check techniques and results. Ready access to carbohydrate and appropriate coordination of mealtimes, snacks, and medication should obviate the need for more dramatic treatment of hypoglycemia.

There will be times when the person with diabetes is unable to manage their diabetes themselves. In these instances, the responsibility will fall entirely on the healthcare team, for example, during surgery when the person with diabetes is unconscious and requires intravenous insulin and dextrose.

Following discharge, clear communication with the primary care and hospital diabetes teams is essential so that any changes in management or medication are made known to those involved in the individual's care.

Involving people with diabetes in the planning of healthcare and service development

Involving people with diabetes and their carers in the planning and decision-making of local health services enables these to be built around the needs of those who use the service, rather than the needs of the system [43]. An open dialogue is needed and service users should feel that their views are listened to. This will improve the accountability and legitimacy for any decisions made and is likely to improve clinical and care outcomes. People with diabetes should be encouraged to express their views and concerns about their services as better feedback about service provision should help to improve and shape future provision of care.

Conclusion

The aim of diabetes care is to improve the lives of those with diabetes. This can only be achieved through a partnership between the person with diabetes and a multifunctional healthcare team that should be in place to support the person with diabetes.

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24 Educating the Person with Diabetes

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Key points

- Diabetes education and psychosocial support are critical elements of care for all people with diabetes and their family members.
- Being able to self-manage diabetes requires substantial knowledge, motivation, and behavioral competencies by people with diabetes and their family members.
- Diabetes education needs to be implemented in a sufficiently flexible manner to be incorporated into multiple settings, not just formal and structured diabetes education.
- People with diabetes must be placed at the center at all times in diabetes education. Active involvement in their own healthcare must be prioritized over educator-dominated involvement.
- Diabetes education programs are more effective if they are based on participant- and empowerment-oriented principles and principles of adult learning.
- Group-based diabetes education has a positive effect on clinical, lifestyle and psychosocial outcomes, including glycated hemoglobin (HbA_{1c}), fasting blood glucose concentration, diabetes knowledge, self-management, empowerment, and self-efficacy.
- The provision of appropriate training of diabetes educators, including the management of psychosocial issues, cannot be overestimated.
- Group processes and active participation during diabetes education appear more important for improving coping skills than the didactic content of the program.
- People with diabetes should be supported to work specifically and realistically with setting goals and to think about potential obstacles and facilitators to achieving them.
- Family-based diabetes education interventions seem a potentially important supplement to enhance diabetes management in everyday life
- Evaluation of diabetes education should focus on understanding how, for whom, and under what conditions specific programs will work.
- The main limiting factor of diabetes education is that it almost always does not include ongoing care and education.

Introduction

There is broad consensus in the global diabetes community that diabetes education and psychosocial support are critical elements of care for all people with diabetes and their family members [1]. The aim of providing diabetes education and psychosocial support is to promote behaviors that will lead to the prevention or delay of the complications of diabetes and to enhance good quality of life [1]. The ultimate outcome of diabetes education is effective self-management; hence the preferred term is *diabetes self-management education*.

Diabetes is primarily managed on a daily basis by people with diabetes, who are often supported by the active participation of their family members. As such, self-management requires substantial knowledge, motivation, and behavioral competencies by people with diabetes and their family members [2, 3].

The recent second Diabetes, Attitudes, Wishes and Needs (DAWN2) study, conducted in 17 countries across four continents, revealed that, on average, only 49% of people with diabetes reported having ever participated in a diabetes education program. Of those who participated, 81% found the diabetes education helpful [4] and participation was associated with more positive quality of life and well-being outcomes. For family members, participation in diabetes educational programs was lower (average 23%) but helpfulness was comparable (72%) [5]. These results indicate that diabetes education services are valued but there is insufficient exposure to those who might benefit. Diabetes education services therefore need to be implemented in a sufficiently flexible manner to be incorporated into multiple settings, not just formal and structured diabetes education. Consideration of novel means of providing diabetes self-management education should be strongly encouraged and supported.

Diabetes self-management education is defined in the American Diabetes Association Guidelines as an ongoing process of facilitating the knowledge, skill, and ability necessary for diabetes self-management behaviors. Diabetes self-management

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education is intended to support informed decision-making, self-care behaviors which often involve changing behavior, problem-solving, and active collaboration with the healthcare team to improve clinical outcomes, health status, and quality of life. The process of education must be based on the needs, goals, and life experiences of the person with diabetes and is preferably guided by evidence-based standards. Diabetes self-management support and psychosocial support more broadly include:

> *"Activities that assist the person with diabetes in implementing and sustaining the behaviors needed to manage his or her condition on an ongoing basis beyond or outside of formal self-management training. The type of support provided can be behavioral, educational, psychosocial, or clinical" [1]*

An important recent development, and one that serves as the basis for this chapter, is the combination of self-management education and psychosocial support. Organizing the activities of the educator around the concept of supporting the person with diabetes to engage in the relevant self-management behaviors represents a major shift to being a collaborator as well as an educator.

In this chapter, we will present a framework to guide the diabetes educator. Given that at least one-half of people with diabetes do not participate in formal diabetes education services, this framework needs to be adapted to multiple settings, for example, formal diabetes education services, primary and specialty care services, and public health.

To achieve maximal effectiveness, self-management education and psychosocial support must be integrated. Persons with diabetes must be placed at the center and active involvement in their own healthcare must be prioritized over educator-dominated involvement [3, 6]. This is referred to as patient-centered or person-centered care. Person-centered care can be a challenge for many diabetes educators, who are often more comfortable with providing recommendations and teaching management skills than in addressing the psychosocial context of a person's life as the foundation of supporting self-management [7]. In diabetes education person-centered care composes an essential paradigm shift compared to more traditional didactic diabetes education which communicates disease-specific knowledge [8]. It raises a stressful situation for the educator whereby issues not directly related to diabetes may be overriding priorities for the person with diabetes, thereby limiting the goals and expectations of the educator at any moment in time.

The self-management education process is brought to life through the active involvement of people with diabetes and their family members, using recognized pedagogic processes and educator skills. The educational content follows from an effective partnership between people with diabetes, their family members, and educators, employing a broad concept of health and an individual tailoring in group-based as well as one-to-one education sessions. Thus, diabetes education should be standardized by function, not by content.

This paradigm shift requires a new approach, which presents a substantial challenge when considering the traditional skills of educators providing diabetes education. Educators experience numerous barriers regarding the facilitation of person-centered and participant-involving education [8, 9]. Many agree with the philosophy of this paradigm shift, but its implementation remains a huge challenge [8, 9].

Currently there are many programs available for diabetes education and support with more or less evidence of effect (10–12). However, the focus in this chapter will not be on specific programs or models but rather on the educational and psychosocial principles and methods that guide enhancement of self-management education and support. The rationale for this is that given the varied contexts in which diabetes self-management education is administered and the varying supports available to an educator any chosen method must be fluid and contextual. What works for one person in one context may not work for another.

Theory underlying diabetes education

Person-centered diabetes self-management education has the intention of empowering people with diabetes to engage in the challenging behaviors associated with glycemic, lipid and blood pressure control and complication prevention, for example, foot care. For the healthcare professional, this requires shifting from being an educator to being an educator *and* a collaborator [8, 9, 13, 14]. Adolfsson et al. [9] conclude that educators are entrenched in their roles in traditional didactic patient education, but are challenged to change from an exclusive role as medical expert to include roles as facilitator and catalyst of motivation. A review by Barlow concluded that many educators fail to support patients because of a lack of basic adult educational skills despite the fact that educators may be the main source of support for people with diabetes [15]. The potential of self-management education and support can be realized when guided by two health education principles: dialogue and participation.

Dialogue is to be understood in a broad sense as a way of conducting diabetes education [16, 17]. The traditional one-way didactic model, in which the educator provides information to persons with diabetes in a traditional teacher–student relationship (i.e. monologue, not dialogue), may be successful in conveying information, but is less useful when it comes to encouraging, enabling, and supporting people with diabetes to take responsibility for control and management of their condition [18]. Behavior change theory indicates that educators must instead engage participants in a dialogue to identify challenges, set goals, increase self-efficacy, and address barriers to change [19, 20]. It is useful to take the position that behavior change is hard, and sustained behavior change is even harder. This perspective acknowledges that once behavioral habits become entrenched, much behavior is cued by the environment as well as natural preferences. For example, a 55-year-old man with type 2 diabetes who has never liked exercise and dislikes the idea of medication and illness, and has developed unhealthy eating and drinking habits as part of a stable and supportive friendship circle, is unlikely to change behavior as a result

of listening to lectures on the benefits of healthy eating, medication adherence, and physical activity.

Participation likewise implies a shift in perspective from a disease-centered and paternalistic approach towards care centered on the needs of the person. Effective and meaningful diabetes education requires that people with diabetes are actively involved and that teaching is tailored to the needs and preferences of the individual; in other words, it does not rely exclusively on educator assumptions of needs and preferences [16, 21, 22].

Educator knowledge must take second place to the decisional processes of the person with diabetes. The profile of expert knowledge and teaching is changed in the way the educator engages with those living with diabetes. Consider the same 55-year-old man with diabetes who dislikes exercise, has never been physically active, and has many individual, social and financial barriers to increasing activity. What are the conditions under which this individual will choose to do all of the work necessary to add a disliked behavior to his routine? Overcoming the personal barriers to change is less likely to arise from teaching and telling than it would from effective understanding and supportive negotiation of health behavior choices. In this example, the educator could communicate understanding and respect of the challenges to the recommended behavior, and explicitly acknowledge that the person is in charge of the decision, while seeking permission to discuss ways to overcome barriers, be they informational, motivational, emotional, relational, or practical. This is reflected in the recent promotion by the American Association of Diabetes Educators of the AADE7 Self-Care Behaviors [23]. Within this framework professional services are oriented around the behaviors of healthy eating, being active, glucose monitoring, medication adherence, problem-solving, reducing risk, and healthy coping. However, many educators will need to change their approach in order for self-management support to be effectively implemented. Imagine how an educator might feel and behave if they needed to become comfortable supporting a person with type 1 diabetes who chooses not to take bolus insulin, only basal, out of a fear of weight gain. Several specific aspects of change can be identified as necessary in promoting the educator in the role of self-management support. Specifically, self-management support has significant implications for the diabetes–educator relationship and for the acceptance of complexity as well as for the need for principles to guide method.

Many educators believe that the essence of their professional role is to recommend specific actions based on evidence and to educate persons with diabetes based on their knowledge. It is no surprise that educators often do most of the talking in clinical encounters, that they make frequent recommendations in the form of statements, and that they commonly interrupt people with diabetes if they stray from the agenda of the educator. These relational dynamics place the educator in the dominant position as expert. In some situations this might be acceptable, but unless the person with diabetes is receptive to this type of guidance it could be problematic and result in the person with diabetes feeling judged, or developing learned helplessness [24]. One way of understanding a change-based relationship is to describe the typical approach to intervention as based on the constructs of assessment and diagnosis, treatment and intervention, and finally outcome. From this perspective it follows that competency is based on the skill of the educator. In contrast, a more collaborative, change-based relationship could be described using the constructs of description, prediction, and choice. Here the role of the educator is not to be an expert exclusively but to collaborate in understanding how the current situation has evolved (describe), what the implications of the current situation are (predict), and to explore the potential alternative outcomes if the person with diabetes were to make a different choice (choose) [7].

A second shift that will support effective self-management education is the issue of complexity [25]. Most medical research, and approaches to clinical care, are influenced by reductionism: the intent to find THE solution to problems. This method might have relevance to medications but does not describe behavior. An alternative to the reductionist approach is to consider complexity theory, with the intent of matching the approach to the situation. In situations where complexity is appropriate, interventions are not so much guided by procedure but by principle. Different procedures may be equally appropriate if they impact on the principle in similar ways, for example if self-efficacy is the principle that predicts sustained behavior, then whatever procedure used by an educator that increases self-efficacy is acceptable. Reductionism and complexity, even chaos, can be considered as they relate to two constructs; understanding and agreement [25]. When the degree of understanding about a phenomenon is high and the degree of agreement on how to address the phenomenon is high, this is an indication of a simple system and a situation where reductionist protocols are required. When the degree of understanding and agreement is very low, this is an indication of a chaotic system where there is no precise guidance available. When degree of understanding and agreement are partial, this is a complex system and principles are the approach to take. Consider, for example, a procedure such as regular weighing of those with type 2 diabetes and obesity. Should regular weighing be advised? Although we understand some of the mechanisms that can help control weight, it is not highly under behavioral control. Given the complexity of weight management, it might be better therefore to look for the principle of empowerment or self-efficacy. Thus, if one explores with a patient the impact of weighing on empowerment or self-efficacy, this will guide the healthcare professional to advise either weighing in the case of the person who finds weighing helpful or not weighing in the case of the person who finds it demoralizing.

The third shift associated with self-management support picks up on the distinction between method (what one does) and principle (the guiding rationale for what one does). Given that self-management necessarily places the responsibility on the person with diabetes it becomes necessary to respect the choices made by any given person. If the educator focuses on the principle then they can negotiate the method with the person with diabetes without threatening their personal choice.

Identification and use of theory to guide method

One of the learnings from the behavioral science field is the importance of theory-driven interventions. This is important because many healthcare educators look to the behavioral sciences for tools to implement in their practice. By contrast, the use of tools, without theory, might be misguided. Some understanding of the underlying theory is crucial when an educator decides which tool to choose. Otherwise the implementation might be confusing and limiting. For instance, if one were to use a goal-setting tool based on behavior modification principles with a person who was not ready to change then creating a goal might occur as a way of the patient pleasing the educator. There are a number of theories of behavior available and currently these appear like a shopping list. This makes it difficult for diabetes educators to be guided by these theories. The risk is that different groups will adopt different theories for no reason other than familiarity or fiat. Another choice is to organize these theories in a coherent model that will guide the diabetes educator.

Theoretical models are categorized in reference to the person with diabetes being the decision maker, in reference to drivers of behavior, and in reference to how the educator can influence behavioral choices through counselling methods.

At the center, the person with diabetes can be seen as an individual who will make specific behavioral choices (person as decision maker). The dominant theoretical model describing how people make behavioral choices is the Self-Regulation model, which can be assessed using the Illness Perception Questionnaire [26]. This scale identifies five dimensions of illness beliefs: consequences (e.g. perceived seriousness), personal control, treatment control, timeline, and emotional representation. Understanding these beliefs can be a valuable guide to the diabetes educator and, for instance, when applied to a person newly diagnosed with type 2 diabetes, they can be a helpful guide. Consider the person who perceives the consequences of their diagnosis as minor or someone who does not believe that treatment will reduce complications, perhaps based on a family history of early, devastating complications. Or consider the person who reports overwhelmingly distressing emotions following diagnosis. Understanding these common-sense beliefs will guide the educator to potential solutions.

Also, theoretical models explaining the drivers of behavior can be useful. The Social Cognitive Theory [27], the Theory of Planned Behavior [28], and the Transtheoretical model [29] help to explain what determines a person's behavior and can help the educator identify important motivational constructs that are associated with change. For instance, the constructs of self-efficacy, readiness to change (stages of change) and the influence of the beliefs of important others are explained in these theories.

Perhaps most important are the models that guide the educator on how to counsel a person with diabetes to help them develop the motivation to change. Here the principles of patient centeredness [30], empowerment [31], and motivational interviewing [32] provide specific knowledge and pathways to guide people toward change. Finally, it is also important to consider the person with diabetes as they exist within the immediate social world. The role of the family and the social network is important to incorporate into an understanding of the person and how change can occur. Consider two people; one with positive support from partner and friend and a second who lives without a partner and is socially isolated. Diabetes self-management is likely to be influenced by these factors. Broader social factors, such as the social determinants of health [33], for example, income, socioeconomic status, literacy, and employment, will all play a role, as do cultural factors.

It is not the job of the educator to be an expert in all of these areas; however, it is the job of the educator, from a self-management support perspective, to be aware of these issues in order to incorporate them into any diabetes self-management plan. An educator who is aware that there are many helpful theories that will guide them in effectively collaborating with the person with diabetes can use various theoretical perspectives as general guidance to appropriate methods. An overview of relevant theories is shown in Table 24.1.

Health education methods

Many issues that impair self-management efforts of diabetes educators are grounded in communication challenges [14]. Educators who restrict patient participation through time constraints and pre-planned topics, and use persuasive recommendations that exclude the patients from taking part in the planning of their own care [37] operate counter to strong evidence that goals generated by people with diabetes produce better outcomes than goals produced by healthcare professionals [37]. It only makes sense that a person will be more committed to pursuing goals that are their own than goals that are "given" to them by another person. A Health Technology Assessment of patient education programs concluded that education programs for people with diabetes are more effective if they are based on participant- and empowerment-oriented principles and principles of adult learning [18]. The best outcomes of patient education seem to be produced with an empowerment approach, which is problem-based, individually and culturally tailored to address psychosocial, behavioral, and clinical issues relevant to people's needs and readiness to learn [39]. In reality, educators are responsible for translating abstract concepts and theories to concrete programs tailored to the needs of very different patients [40].

Modalities of education

Most studies of the effects of diabetes education show that group-based diabetes education has a positive effect on clinical, lifestyle and psychosocial outcomes, such as HbA_{1c}, fasting blood glucose, diabetes knowledge, self-management, empowerment, and

Table 24.1 Health education theories.

	Guiding theoretical perspective	Model	Example constructs
Person with diabetes			
Faces the personal responsibility to make behavioral choices	Health beliefs	Self-regulation model [34]	Perceived consequences, personal control, treatment control, timeline, and emotional impact
	Motivation	Social cognitive theory [27] Theory of planned behavior [28] Transtheoretical model [29]	Self-efficacy, perceived social norms, readiness to change/intentions
	Emotion	Diabetes distress scale [35]	Emotional burden, regimen-related distress, physician-related distress, interpersonal distress
Person with diabetes–educator relationship			
The patient–educator relationship can provide a context to consider new behavioral options	Patient centeredness	Patient-centered clinical method [30]	Understand the whole person, explore the person's illness experience, find common ground and cultivate the relationship to overcome barriers
	Motivational communication	Motivational interviewing [36]	Non-judgmental curiosity, effective use of questioning and listening, working with ambivalence and supporting self-efficacy
	Empowerment	Patient empowerment [13]	Appreciating the process of respecting the autonomy of the person with diabetes

self-efficacy [41]. Group-based education can be cost-effective, person-centered and provide interactive learning with a high level of patient satisfaction compatible with individual education [39, 42, 43]. Group-based education is fundamentally based on social learning processes in which people with a chronic illness undergo a process of change via observational learning and modeling [44]. Participants learn to benefit from the possibilities that arise in the meeting with other people with diabetes, as well as educators [45]. Group processes and active participation during diabetes education appear more important for improving coping skills than the didactic content of the program [46].

There are many curricula that utilize evidence-based approaches available for diabetes education. The National Institute for Health and Care Excellence (NICE) in the UK defines structured diabetes patient education as "a planned and graded program that is comprehensive in scope, flexible in content, responsive to an individual's clinical and psychological needs, and adaptable to his or her educational and cultural background" [47]. In its review of the evidence, NICE identifies some principles of good practice including that: "education should be provided by an appropriately trained multidisciplinary team to groups of people with diabetes, unless group work is considered unsuitable for an individual." In more detail NICE underlines the use of established principles of adult education and "a variety of techniques to promote active learning to meet the different needs, personal choices and learning styles of people with diabetes in the formal, regular assessment of individuals' learning needs." The provision of appropriate training of educators is underlined as well as the provision of educational opportunities that are broadly accessible for people with diabetes and taking into account culture, ethnicity, disability, and geographical issues.

Educator skills in group-based diabetes education

Group-based education has become a widespread method of support, yet only a handful of studies have actually sought to show the kind of professional roles and competencies that are needed in participatory, group-based patient education [48, 49]. The educators continually have to manage different roles and the shifting between roles is necessary to provide person-centered education; however, the juggling of roles is challenging. Educators can benefit from understanding each of the roles and be able to perform all of them in order to juggle them successfully. Juggling is thus the ability to master the switching between the different roles to meet the needs of the individuals as well as the group as a whole and to challenge the participants appropriately as regards content and learning styles [17].

Some well-recognized juggler attributes are:

- ***humility*** – the ability to be approachable without projecting one's self and beliefs onto the group;
- ***flexibility*** – openness to try new process approaches, willingness to change, or stretch outside one's boundaries in the facilitator role; and
- ***professionalism*** – being ready to deal professionally with feelings in the group [50].

The roles that are juggled include the embracer, the facilitator, the translator, and the initiator [17, 51].

The **embracing** role is based on empathy [52, 53]. Empathy plays a major role in the treatment of people with diabetes as it encompasses both the desire and the ability to understand them on their own terms [52]. Morse et al. [54] propose a descriptive model of clinical empathy with affective, moral, cognitive and behavioral dimensions. Norfolk et al. [52] propose a new model about the empathic journey towards therapeutic rapport in consultations focusing on the doctor's behavior, motivation, and required skills. The factors mentioned in the Morse and Norfolk studies are important competencies for educators' ability to act in the embracer role in group-based diabetes education; however, it might be more complicated in groups than in one-to-one encounters, since educators need to spread their focus among multiple persons with different needs.

The **facilitator** role is rarely described in the literature. Notable exceptions are guidelines for facilitating patient empowerment programs [55] and a study about speech practices facilitating patient participation in health counselling, in which concrete facilitation skills are suggested [37]. However, other professional fields, such as business and organization, provide more extensive literature on facilitation [56]. The facilitation literature divides facilitator competencies into higher and lower levels of competence, where higher competencies are about developing a participatory environment and lower order competencies relate to specific skills, such as listening and questioning [50].

The **translator** role, in which the educator translates medical concepts into relevant and understandable information, implies a change of the typical health educator roles. In traditional medical and disease-specific patient education, educators give information and advice, handle acute situations and perform problem-solving [53]. In the 1980s, however, following patient demands for a more active role in healthcare, the Ottawa Charter emphasized the need of the individual to be seen as a "whole person" [57]. This implies that educators have to move away from unidirectional teaching to an approach in which they become translators: they are experts in medical knowledge and patients are experts on their lives. Patient experiences must be central to education and professionals have to "unlearn" being in control of the process [58].

The **initiator** role closely links to principles of motivational interviewing [36] and empowerment interventions [59]. The initiator faces the challenge of avoiding confrontation or authority traps such as "knowing best." In general, facilitation and participatory methods are rarely part of the curriculum or the educational experiences of health professional educators [53], which may explain the challenges they experience when delivering participatory, group-based diabetes education.

Dialogue and participation in diabetes education—practical examples

The principles of dialogue and participation have recently been translated into the development of flexible tools to be used in group-based or individual diabetes education. Figures 24.1, 24.2, and 24.3 show how the tools make use of pictures, quotes, and statements to engage and give voice to people with diabetes. The tools and their participatory and person-centered approach thus support the call for flexible and dynamic approaches to diabetes education [60, 61].

Using cultural probes is a new and promising method in diabetes education. It is a research method deriving from the design world [62] and also used as an explorative method in ethnographic studies [63, 64]. Methods include the use of postcards with questions concerning participants' attitudes to their lives, maps where participants can highlight areas of importance to their lives, and cameras with instructions asking participants to take photos of important objects. Visual methods similar to cultural probes such as photos, videos, and drawings are often used as a method for data collection [65, 66]. Cultural probes can be seen as a medium through which participants express themselves, and the method is characterized by a high level of interaction and involvement of participants. Cultural probes have demonstrated positive properties with regard to gaining profound insights into a person's life and strengthening active involvement among participants. Recently the use of cultural probes in diabetes education has been shown as a promising method of translating the theoretical concepts of person-centeredness and of putting active involvement into practice to support both educators and people with diabetes. One example of the use of probes is the Conversation Map tool which successfully facilitates interactive dialogue among people with diabetes through relationship building, trust, and confidence as well as the sharing of personal stories and experiences [67]. Further examples are the DESMOND program [10], and the NEED and EMMA programs [68, 69] shown in Figures 24.1 to 24.3.

"Who am I?" consists of 50 picture cards. The aim of the exercise is to give participants the opportunity to introduce themselves to each other by selecting picture cards that give different associations. The exercise can enable participants to talk about themselves and give the diabetes educator insight into their lives more than their disease.

"Balance Cards" consists of 27 cards with pictures and quotes. The aim of the exercise is to assist participants in talking about the imbalances, challenges, and possibilities they experience in their daily lives with diabetes. The exercise can make it easier for participants to express difficult topics and facilitates dialogue among participants.

The aim of the "My Day" exercise is to establish close contact between the person with diabetes and the educator to gain shared insight into daily life and identify relevant details and challenges related to diabetes behaviors to form the strategy for subsequent actions.

The aim of the exercise "Postcard" is to get people with diabetes to reflect on their own concerns.

The aim of the exercise "Goal and plan" is to assist people with diabetes in working specifically and realistically in setting goals and thinking about potential obstacles and facilitators to achieving them.

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Figure 24.1 Examples of picture cards from the exercise "Who am I"? [68, 70, 71].

Psychosocial support in diabetes education

One of the most challenging aspects of diabetes education is that diabetes is both a biomedical disease and a behavioral challenge [19, 73]. In order for positive diabetes outcomes to be realized the person with diabetes must engage in intentional, effortful, and sustained behaviors. However, the importance of outcomes to the educator (e.g. $HbA_{1c} < 7.0\%$ (53 mmol/mol)) cannot supersede the importance of outcomes for the person with diabetes (e.g. living life as normally as possible) and things go well only when the two are in synchrony.

There is an association between psychosocial problems and poor diabetes outcomes such as risk of hypoglycemia and frequent omission of prescribed medicine [74, 75]. At the same time, poor diabetes outcomes can cause psychosocial problems, such as fear of hypoglycemia, diabetes distress, and functional or occupational interference. Depressive phenomena have been shown to be common in those with diabetes, particularly diabetes distress. Diabetes distress has been found to be distinct from and more prevalent than depression among adults with diabetes [76, 77]. Further, compared to depression, diabetes distress is independently and more strongly associated with poor diabetes self-management and poor glycemic control [77]. It has been suggested that people with diabetes distress may be incorrectly diagnosed as having depression and thus experience an ineffective approach to treatment [78]. A recently published paper by Fisher et al. emphasizes that emotional distress is best considered as a "continuous psychological characteristic," rather than a distinct "comorbid clinical condition" [79]. In this way, diabetes distress is distinct from mental health disorders and thus is a characteristic to be aware of in diabetes education.

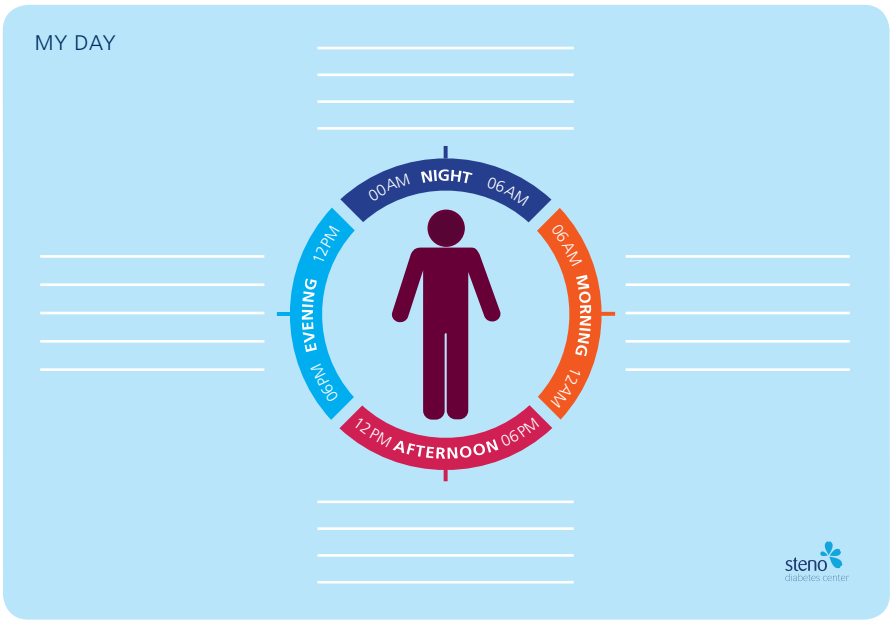
Figure 24.4 illustrates that quality of life is a combination of sources of distress as well as sources of well-being. That is, not only is it important to understand how unhappy a person with diabetes is, it is also important to understand issues of resilience, happiness, meaning, and positive engagement in life [80]. If an educator is able to identify a person with diabetes who reports distress this can be followed by an understanding of the drivers of this distress. Understanding the contribution of living with diabetes, the contribution of non-diabetes-related problems of living, and signs of psychopathology as drivers of this distress can be very helpful. One way this can be of help is to guide the diabetes educator about how to address the uncovered distress. In the

"Balance Cards" consists of 27 cards with pictures and quotes. The aim of the exercise is to assist participants in talking about the imbalances, challenges, and possibilities they experience in their daily lives with diabetes. The exercise can make it easier for participants to express difficult topics and facilitates dialogue among participants.

Figure 24.2 Examples of picture cards from the exercise "Balance Cards" [68, 70].

situation where there is significant diabetes-specific distress it is likely that the diabetes service is the best place for these issues to be addressed. This puts the responsibility of care on the diabetes educator, perhaps with the assistance of a mental health provider. In the situation where there is significant distress associated with problems of living, sensitive advice and support from the diabetes educator would be helpful. In the situation where there is suspicion of psychopathology interfacing the diabetes, referral to mental health services would be recommended. This perspective is in keeping with the work by Fisher on the distinction between diabetes distress and depression [35, 79].

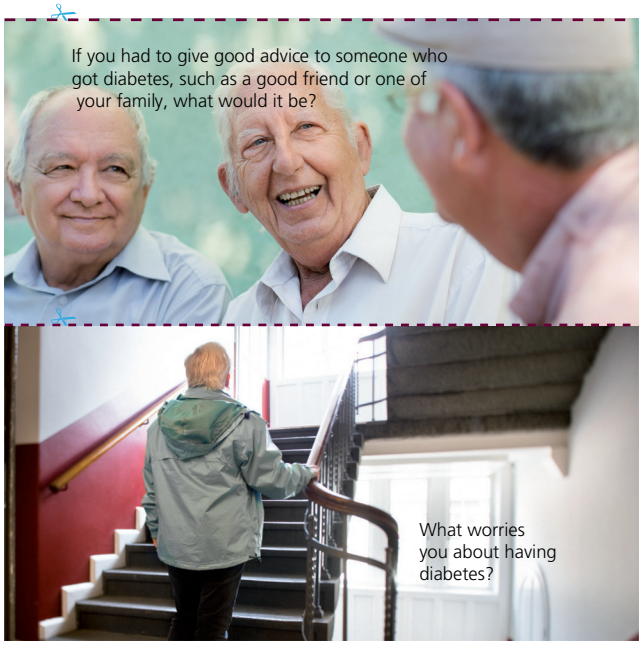
While it can be stressful for diabetes educators without a background in psychology to address psychosocial issues within their scope of practice, it can be helpful to know that often the



(a) The aim of the "My Day" exercise is to establish close contact between the person with diabetes and the educator to gain shared insight into daily life and identify relevant details and challenges related to diabetes behaviors to form the strategy for subsequent actions

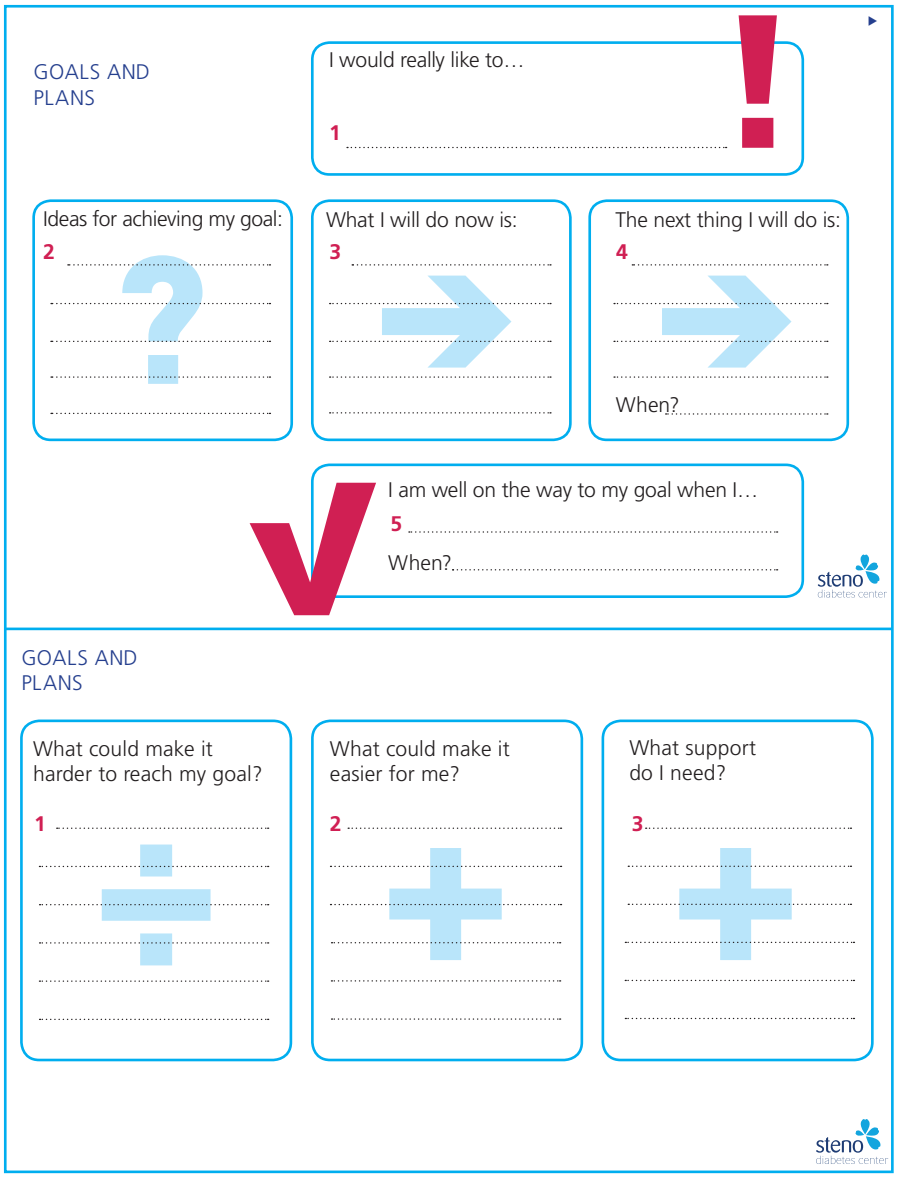
POSTCARD

There is a question on each of the two postcards. The idea of the questions is that you should think about them a little before next time. On the back of the cards, you can jot down your thoughts and answers, either as a short story or as bullet points. If you do not wish to write anything, you can tell me about your thoughts on your next visit.



(b) The aim of the exercise "Postcard" is to get people with diabetes to reflect on their own concerns.

Figure 24.3 (a–c) Examples of exercises from the patient education program EMMA (Empowerment, Motivation and Medical Adherence) [69, 72].



(c) The aim of the exercise "Goal and plan" is to assist people with diabetes in working specifically and realistically in setting goals and thinking about potential obstacles and facilitators to achieving them.

Figure 24.3 (*Continued*)

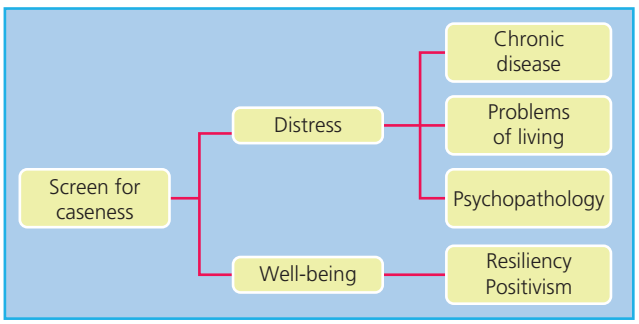


Figure 24.4 Determinants of quality of life.

ability to communicate one's distress (i.e. to be heard) is often experienced as very beneficial. If the educator takes the position that they are not the expert and that it is not their responsibility to "fix" the potential problems, then supportive communication can be easier. For instance, it would not be inappropriate for a provider to declare "I'd be interested in hearing about what you are going through and possibly make any recommendations that I think might be helpful." Research indicates a positive association between the presence of physician empathy and better diabetes outcomes [81].

The Diabetes Distress Scale is a useful guide for the diabetes educator as it involves four very understandable dimensions of

distress: emotional burden, regimen-related distress, physician-related distress, and interpersonal distress. Table 24.2 adapts these self-report scales into easy to use questions that would support the educator in addressing these dimensions. For instance, if the person with diabetes indicates feeling judged by healthcare providers the educator could address this in a direct and supportive manner.

It is also useful for the diabetes educator to be mindful of how diabetes fits into the social world of an individual. The idea of diabetes-specific as well as general social support is important here [82, 83]. Individuals with diabetes can experience benefit from having sensitive discussions with their diabetes educator about the presence or absence of support from others regarding diabetes self-management. The potential of engaging peers in supporting diabetes outcomes should also be noted [84].

Family perspectives in diabetes education

The second Diabetes, Attitudes, Wishes and Needs (DAWN2) study included a survey of 2057 adult family members of adults with diabetes. According to this study, supporting a relative with diabetes was perceived as a considerable burden by 35% of family members. The study also revealed that 40% of family members experienced high levels of distress related to concerns about their relative with diabetes, and 61% stated they were very worried about hypoglycemia in their family member with diabetes [5, 85].

Persons with diabetes generally engage in self-management of their diabetes within a family setting. Family members play a role in the everyday tasks such as meal preparation and time management and often provide moral, emotional, and practical support. Thus, struggles with self-management and blood glucose control, poor well-being, and psychological distress are relevant not only to the individual adult with diabetes. To the contrary, these problems affect—and are affected by—the entire family. Unfortunately, the majority of education programs exclusively target individuals with diabetes [86–89]. Furthermore, research targeting the interface between adults with chronic disease and their families is relatively scarce and family factors have until recently been virtually ignored in relation to adults with diabetes. Shields et al. [90] reviewed chronic health interventions involving couples and families and were unable to identify any studies pertaining to adults with diabetes.

Family-based diabetes education interventions seem a potentially important supplement to enhance diabetes management in everyday life. However, considering the emerging state of research in this area it is unclear how to educate and support family members of people with diabetes most effectively [88, 91]. The inclusion of family members in information and education processes may be useful. However, there is an urgent need for educational interventions for family members to enable translation of knowledge about diabetes into positive and constructive support of the person with diabetes. The family is an under-utilized resource with potential for benefitting diabetes management.

Evaluation of diabetes education

Given the literature on the potential positive role that diabetes education can have on persons living with diabetes and their family, perhaps the most important indicator in the evaluation of diabetes education is the availability of and access to diabetes education. Biological outcome measures have for a long time dominated the evaluation of diabetes education, which is unsurprising as they make up essential outcomes in diabetes. In reviews and meta-analyses of diabetes education the most commonly used outcome measures can be divided into four categories: biological, behavioral, knowledge, and psychosocial outcomes. Most attention has been paid to biological outcomes, particularly, HbA_{1c}, and knowledge-based outcomes. Less attention has been placed on behavioral outcomes and least on psychosocial outcomes [92].

An interesting and useful perspective, which is consistent with the complexity of diabetes education, is to examine the mechanisms by which an education program works [91, 93]. If an education program is found to have effect, how do we know what to replicate and what to change when we implement the program somewhere else? Why do some programs work in one place for one group of participants, and not for another? How do we identify what it is about the context that makes a difference? Focusing on mechanisms of effects is complicated as the education process typically involves multiple interacting components. It is thus difficult to identify the precise mechanisms leading to effects of the various components [15, 94]. Further, outcomes depend on the competencies of educators and the preconditions and motivation of participants as well as organizational conditions, all of which may be difficult to capture in a randomized controlled trial [94]. In response to this, theory-driven forms of evaluation have gained attention as they can generate knowledge about the effectiveness of an education program as well as knowledge about the underlying mechanisms of effects [95]. Simultaneously important information is generated about elements of importance for the replication and improvement of an education program [96, 97].

Theory-driven evaluation consists of "an explicit theory or model of how the program causes the intended or observed outcomes and an evaluation that is at least partly guided by this model" [96]. Thus, a core element of theory-driven forms of evaluation is the development and use of theory in the evaluation process. The theory, often referred to as program theory, specifies relationships between intervention actions and intended outcomes [95].

An education program is an incarnated theory of change; a theory about how to change problematic conditions or behavior. However, this theory is often unrecognized or poorly articulated perhaps due to the fact that a program is an active open system which:

- is apt to change over time as the program unfolds;
- works through the ideas and intentions of those implicated in them;
- works differently among different subgroups.

Table 24.2 Exploring diabetes distress in diabetes education and support.*

Components of diabetes distress	Diabetes distress scale	Suggested probes (questions)
	Scale items	
Emotional burden	- feeling that diabetes is taking too much mental and physical energy; - feeling angry, scared, or depressed when I think about living with diabetes; - feeling that diabetes controls my life; - feeling that I will end up with long-term complications no matter what I do; - feeling overwhelmed by the demands of diabetes.	If diabetes were a weight that you carried in a knapsack on your back, how heavy would it be? (Not at all… A little… Moderately… Very… Overwhelming) To what extent does living with diabetes upset you? (Not at all… A little… Moderately… Very… Overwhelming) Problematic emotional reactions to living with diabetes occur for some people. Would you say yes to any of the following emotions as being problematic for you because of your diabetes?: - sad/down - anxious/worried - frustrated/angry
Regimen-related distress	- feeling that I am not testing my blood sugars frequently enough; - feeling that I am failing with my diabetes regimen; - not feeling confident in my day-to-day ability to manage diabetes; - feeling that I am not sticking closely enough to a good meal plan; - not feeling motivated to keep up with diabetes self-management.	To what extent do you feel burdened by the activities required to manage your diabetes? (Not at all… A little… Moderately… Very… Overwhelming) Are there aspects of managing your blood sugars that you find particularly stressful? Do you ever think that you are not doing a good job following the guidelines for diabetes? To what extent do you find the tasks of diabetes upsetting (frustrating, overwhelming, worrying)?
Interpersonal distress	- feeling that friends or family are not supportive of my self-care efforts; - feeling that family or friends don't appreciate how difficult diabetes can be; - feeling that friends or family don't give me the emotional support I would like.	To what extent do you find it stressful dealing with other people because of your diabetes? (Not at all… A little… Moderately… Very… Overwhelming) To what extent do family, friends or other people make it harder for you to live with diabetes? (Not at all… A little… Moderately… Very… Overwhelming) Do you find that there are people in your life who make your experience of diabetes stressful to you? When you think about people in your life who are either supportive or not supportive of your diabetes would you say that there are more unsupportive people than supportive? Which of the following social situations do you find stressful regarding diabetes?: - family - friends - work
Educator-related distress* *This concept is adapted to include all healthcare educators	- feeling that my doctor doesn't know enough about diabetes; - feeling that my doctor doesn't give me clear enough directions; - feeling that my doctor doesn't take my concerns seriously enough; - feeling that I don't have a doctor who I can see regularly about diabetes.	To what extent do you find it stressful dealing with your healthcare educators? (Not at all… A little… Moderately… Very… Overwhelming) When you think of healthcare educators who you find either unhelpful or helpful regarding your diabetes would you say that there are more unsupportive healthcare educators than supportive? Do you find any of the following healthcare educators that are stressful to deal with?: - family doctor - diabetes specialist - diabetes educator

*Scale questions developed with the permission of Drs. Lawrence Fischer and William Polonsky (January 2015) [35].

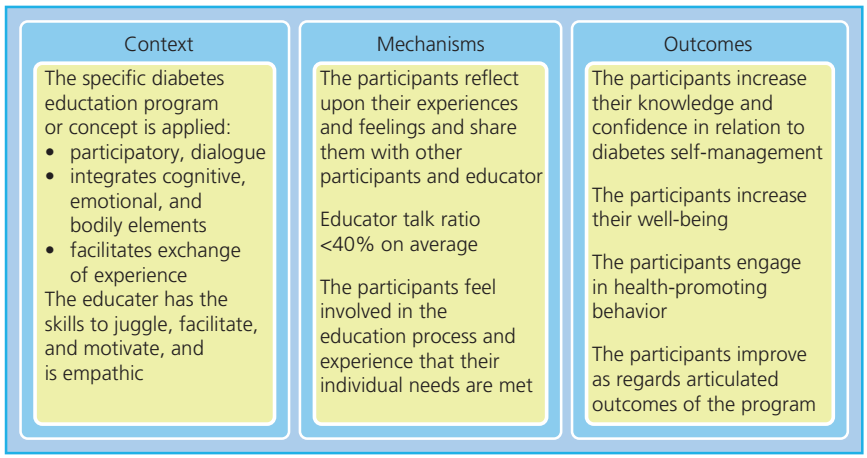


Figure 24.5 Program theory [97].

Pawson and Tilley [98] described "realistic evaluation," which focuses on three key concepts for understanding how, for whom, and under what conditions programs will work: *outcomes* that are likely to be the most effective, *mechanisms* through which outcomes occur, and *contexts* where the outcomes potentially will be replicable. Mechanisms refer to the process of how people interpret and act upon the intervention to produce outcomes. Mechanisms are not assumed to be fixed, but contingent on particular contexts. Thus the program theory can be expressed as context-mechanism-outcome (C-M-O) configurations. The evaluation implies the development of a theory about how outcomes, mechanisms and contexts operate and use of this theory to direct empirical work. The evaluation focuses on exploring whether the theory can explain the observational data [98]. In a recent review regarding use of "realistic evaluation" the use of C-M-O configurations were found to provide clarity in complex evaluation environments and rich information about what type of interventions work for whom in what context [99].

Figure 24.5 shows a program theory: If a person with diabetes is recruited to the program and completes it, and if the program takes a specific educational approach, then the person will attain improved knowledge and skills related to the management of diabetes and increased autonomy and quality of life. Working with program theory, ideally a second level of data collection and analysis is needed in order to evaluate whether (a) the theory is right but not properly implemented; (b) the theory should be refined; or (c) the theory is wrong. (See also Box 24.1.)

Box 24.1 Key points in program theory

- Realist evaluation is about theory testing and refinement
- Realist evaluation develops and tests C-M-O configurations (hypotheses) empirically
- Realist evaluation applies any approaches, tools, and methods that are appropriate to test a program theory
- Realist evaluation is potentially time-consuming as there are no independent criteria for closure

Conclusion

The main limiting factor of diabetes education is that it almost always does not include ongoing care and education. Once people with diabetes complete the program in its entirety, they do not have a component of ongoing support to allow tailoring of the education to their continued diabetes care needs. The provided education becomes education for life and therefore conclusive, without any opportunity for an information refresher or support mechanism needed to adjust to changes in perceived needs and preferences of people with diabetes. The lifelong process of diabetes self management requires continued adjustments in knowledge, skills, motivation, and support. Education and support should be a lifelong process, starting at the point of diagnosis and remaining as an essential component of diabetes care.

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25 Lifestyle Issues: Diet

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Key points

- Weight loss is primary mediator of diabetes risk reduction and management of type 2 diabetes in those overweight or obese.
- Calorie content of and adherence to the diet is more important than macronutrient content for successful weight loss maintenance.
- The type and quality of dietary fat and carbohydrate, respectively, are more important than amounts of these macronutrients for prevention and management of diabetes and its complications.
- A number of dietary patterns are effective for weight loss, and diabetes and cardiovascular risk, and should take into account individual preferences.
- Matching carbohydrate to insulin dose, either as part of multiple daily insulin or continuous subcutaneous insulin injections, is the most effective approach for the management of glycemia in type 1 diabetes.
- Women with diabetes planning to become pregnant should take 5 mg of folic acid per day to prevent neural tube defects.
- Calorie restriction to lose weight should not be recommended during pregnancy, but limiting weight gain can improve pregnancy outcomes.
- Low glycemic index foods may help control blood glucose concentrations during pregnancy.

Introduction

Diet plays an important role in the effective management of type 1 diabetes (T1DM) and type 2 diabetes (T2DM) and is fundamental to the prevention of T2DM.

The aim of nutritional management of diabetes is to optimize glycemic control and blood pressure, correct any lipid abnormalities, and, in doing so, reduce the risk of long-term complications [1–3]. Dietary advice must be evidence-based and individualized, taking into account personal and cultural preferences, and ensuring the diet is appropriate and compatible with the person's lifestyle, existing treatment regimen, other comorbidities, and willingness to change [1–3].

Individuals with diabetes are up to four times more likely to develop cardiovascular disease (CVD) [4, 5], with an elevated risk also seen in impaired glucose tolerance [5] compared to individuals with normoglycemia. Therefore, evidence-based nutritional recommendations for individuals with diabetes are based on the glucose management of the diabetes, reducing the risk of developing CVD and the complications of diabetes and CVD [1, 2, 6]. The strength of evidence for the different nutritional recommendations for both management of diabetes and prevention of CVD is graded according to the type and quality of published studies as well as by statements from expert committees [1]. The gold standard for evidence-based guidelines are meta-analyses of large well-controlled trials with long follow-up periods that include fatal or non-fatal clinical endpoints. However, this information is often not available and instead surrogate endpoints, such as glycemia, body composition, lipoprotein profile, blood pressure, insulin sensitivity, and renal function are used to determine the potential of dietary modification to influence glycemic control and risk of acute and chronic complications of diabetes [1, 2].

While nutritional science illuminates the underlying mechanisms of diet on disease risk, in practice, nutrients are consumed as foods and as part of dietary patterns. Therefore, throughout this chapter, while reference will be made to the impact of individual macro- and micronutrients on clinical outcomes, the reader is referred to how these nutrients form part of an overall healthful dietary pattern for diabetes prevention and management. Tables 25.1 and 25.2 summarize such dietary approaches.

Energy balance and body weight

Weight management is now understood to be the primary strategy for prevention of diabetes and glycemic control in people with T2DM who are overweight or obese [1, 2]. Weight gain is associated with increased diabetes incidence [7] and insulin

Textbook of Diabetes, Fifth Edition. Edited by R. Holt, C. Cockram, A. Flyvbjerg and B. Goldstein.

Table 25.1 Table showing the association of particular dietary components on risk or management of type 2 diabetes, and their inclusion or exclusion in established dietary patterns or guidelines. Orange indicates components with a protective association; blue indicates components with a deleterious association.

Dietary components	Mediterranean	DASH	Diabetes UK	NICE	Effect on diabetes management/risk
Fruit	*	*	*	*	Dietary fiber associated with reduction of risk.
Vegetables	*	*	*	*	Dietary fiber associated with reduction of risk.
Nuts/seeds	*	*	*	*	↑ PUFA/MUFA:SFA ratio associated with reduction in FPG, HbA_{1c} and insulin resistance. Insoluble fibers associated with reduction in risk of diabetes. Magnesium associated with reduction of risk of diabetes.
Pulses	*	*	*	*	Soluble fibers reduce postprandial glucose in randomized control trials.Low GI associated with reduction of risk, and reduces HbA_{1c} by 0.5%.
Fish and seafood	*		*	*	No known effects of omega-3 on diabetes management or risk
Increased white:red meat ratio			*	*	↑ PUFA/MUFA:SFA ratio associated with reduction in FPG, HbA_{1c} and insulin resistance.
Wholegrains/cereal fiber	*	*	*	*	Insoluble fibers associated with reduction in risk of diabetes. Magnesium associated with reduction of risk of diabetes.
Low glycemic index			*	*	Associated with reduction of risk, and reduces HbA_{1c} by 0.5%.
Olive oil	*				↑ PUFA/MUFA:SFA ratio associated with reduction in FPG, HbA_{1c} and insulin resistance.
Vegetable oil (sunflower, rapeseed oil)			To replace butter and SFA spreads	To replace butter and SFA spreads	↑ PUFA/MUFA:SFA ratio associated with reduction in FPG, HbA_{1c} and insulin resistance.
Low-fat dairy		*	*	*	Dairy intake associated with reduction of risk; milk proteins may leads to reduced glucose concentrations and increased insulin secretion. Vitamin D and calcium associated with reduction of risk.
Alcohol	Moderate	↑			Moderate intake associated with reduction of risk.
Decreased red or processed meat					Diets high in red, especially processed meat associated with increased risk of diabetes.
Butter	Limited		Replaced with non-SFA spreads	Replaced with non-SFA spreads	↓PUFA/MUFA:SFA associated with increased risk of diabetes, FPG, HbA_{1c} and insulin resistance.
Sweetened beverages		*	Limit	Limit	Sugar-sweetened beverages associated with increased BMI, leading to increased risk of diabetes.
Sodium					No known effects of omega-3 on diabetes management or risk

* = included in dietary pattern.
BMI, body mass index; DASH, Dietary Approaches to Stop Hypertension; FPG, fasting plasma glucose; GI, glycemic index; HbA_{1c}, glycated hemoglobin; MUFA, monounsaturated fat; NICE, National Institute for Health and Care Excellence; PUFA, polyunsaturated fat; SFA, saturated fat.

resistance [8], while weight loss reduces insulin resistance and glucose handling in people with and without diabetes [9]. A series of large-scale lifestyle-based randomized control trials [10, 11] have conclusively shown that a 5–7% weight loss in people at risk of diabetes reduces risk by up to 66% (Figure 25.1) [10]. While these programs also included other components such as increasing fiber, decreasing total and saturated fat and increasing physical activity, weight loss was the primary driver of the reduction in risk [12]. Interestingly, there also appears to be a legacy effect of weight loss on diabetes prevention, such that even 3 years after the intervention stopped, there was still a 48% risk reduction in the intervention group [13].

Weight loss also reduces important risk factors for CVD including circulating triglycerides and blood pressure [1]. A systematic review of studies with at least 2 years' follow-up showed that intentional weight loss in people with T2DM can reduce their mortality risk by 25%, with a higher risk reduction with greater weight loss [14]. The recent LookAHEAD study found that an intensive lifestyle for primary prevention of CVD did not significantly reduce CVD-related morbidity or mortality after nearly 10 years of follow-up [15]. However, this may reflect the limitations of dietary improvements in long-term mortality in people treated aggressively with antihypertensive and dyslipidemic medications [16], and does not discount the role for weight

Table 25.2 Table showing the association of particular dietary components on risk of cardiovascular disease, and their inclusion or exclusion in established dietary patterns or guidelines. Orange indicates components with a protective association; blue indicates components with a deleterious association.

Dietary components	Mediterranean	DASH	Diabetes UK	NICE	Effect on CVD risk
Fruit	*	*	*	*	Dietary fiber associated with reduction of risk.
Vegetables	*	*	*	*	Dietary fiber associated with reduction of risk.
Nuts/seeds	*	*	*	*	↑ PUFA/MUFA:SFA ratio associated with reduction in LDL, neutral effect or ↑HDL, reduction in CVD risk. Dietary fiber associated with reduction in risk of CVD.
Pulses	*	*	*	*	Dietary fiber associated with reduction in risk of CVD. Low glycemic index associated with reduction in risk.
Fish and seafood	*		*	*	No known effects of omega-3 on diabetes management or risk
Increased white:red meat ratio			*	*	↑ PUFA/MUFA:SFA ratio associated with reduction in LDL, neutral effect or ↑HDL, reduction in CVD risk.
Wholegrains/cereal fiber	*	*	*	*	Dietary fibers associated with reduction in risk of CVD.
Low glycemic index			*	*	Associated with reduction of risk.
Olive oil	*				↑ PUFA/MUFA:SFA ratio associated with reduction in LDL, neutral effect or ↑HDL, reduction in CVD risk.
Vegetable oil (sunflower, rapeseed oil)			To replace butter and SFA spreads	To replace butter and SFA spreads	↑ PUFA/MUFA:SFA ratio associated with reduction in LDL, neutral effect or ↑HDL, reduction in CVD risk.
Low-fat dairy		*	*	*	No consensus on effect of dairy on CVD risk.
Alcohol	Moderate	↑			Moderate intake associated with reduction of risk.
Decreased red or processed meat					Diets high in red, especially processed meat associated with increased risk of diabetes.
Butter	Limited		Replaced with non-SFA spreads	Replaced with non-SFA spreads	↓PUFA/MUFA:SFA associated with increased LDL concentrations and CVD risk.
Sweetened beverages		*	Limit	Limit	Sugar sweetened beverages associated with increased BMI, leading to increased risk of CVD.
Sodium					Sodium restriction reduces blood pressure and CVD risk.

* = included in dietary pattern.
BMI, body mass index; CVD, cardiovascular disease; DASH, Dietary Approaches to Stop Hypertension; HDL, high-density lipoprotein; LDL, low-density lipoprotein; MUFA, monounsaturated fat; NICE, National Institute for Health and Care Excellence; PUFA, polyunsaturated fat; SFA, saturated fat.

loss and dietary change in improving quality of life [16], reducing intensification of medical treatment of diabetes and CVD, and greater physical functioning [15, 16]. Reductions of 5–10% are effective at reducing CVD risk factors and are achievable and feasible, although larger weight loss may reduce risk further [17].

Weight management has also been considered for people with T1DM as the prevalence of overweight and obesity is increasing in T1DM [18], and the co-presentation of insulin resistance is associated with poorer glycemic control [19]. However, there is little evidence that body weight or weight loss influences glycemic control in people with T1DM [18]. Furthermore, in both T1 and T2DM, caution should be applied to intentional versus unintentional weight loss as unintended weight loss in people with diabetes may also be an indication of a suboptimal medical management or poor concordance with medications leading to poor glycemic control [20].

Therefore national [2, 21] and international [5] guidelines recommend initial weight loss of 5–10% in overweight or obese people for the purposes of T2DM management and prevention of T2DM and CVD.

Currently there is no consensus on the optimal diet to achieve and maintain the recommended weight loss [1]; however, the overall energy content of the diet is more important than macronutrient composition [1, 22–26]. Effective strategies for which there is evidence in people with diabetes include low-carbohydrate [27], low-glycemic index [28], low-fat [10, 11], very-low-calorie-diet [29], and meal replacement [30]. There has been particular interest in low-carbohydrate diets [31] which appear to be most effective at promoting weight loss over the short term, and may also have beneficial effects on glycemia independent of body weight [32–34]. While there is little evidence for their added benefit over the long term [35–37], practitioners should be open to this approach and individual preference. The primary factor in achieving and maintaining weight loss remains adherence, and the best approach is therefore one that fits with a person's lifestyle, habits, and goals [1, 2, 35].

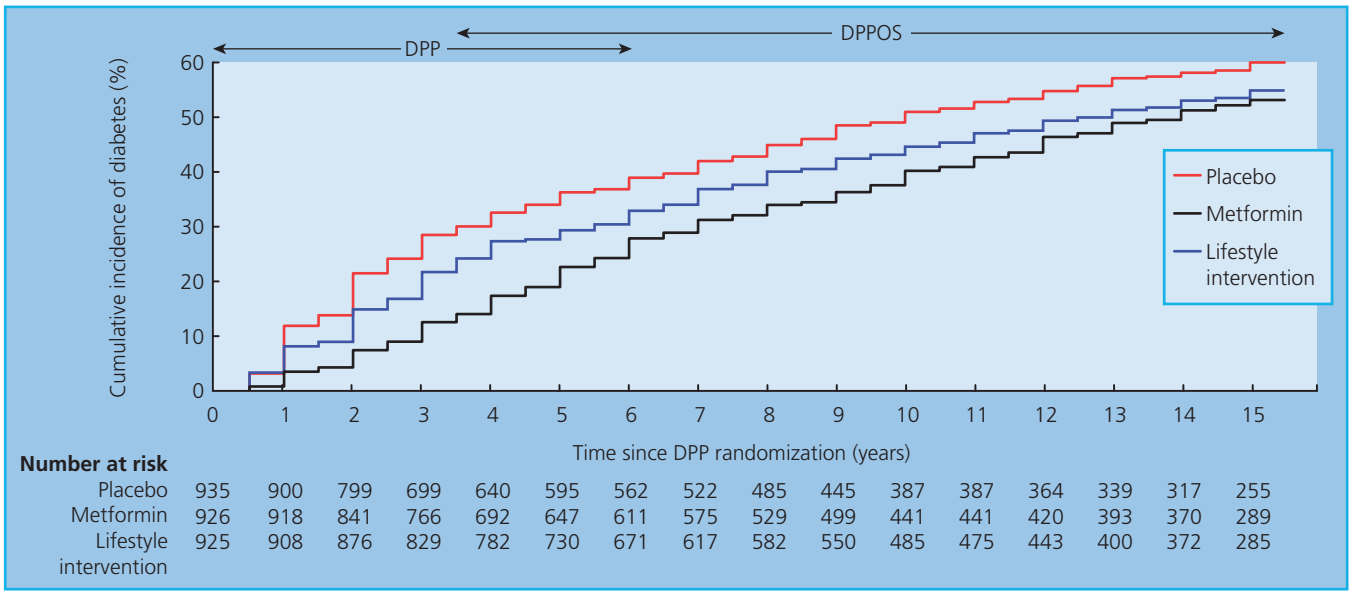

Figure 25.1 Reduction in the incidence of diabetes in the US Diabetes Prevention Program (DPP). This figure shows the data from the DPP itself and data from the follow-on Diabetes Prevention Program Outcomes Study (DPPOS) which followed the same individuals up to 15 years. Source: Diabetes Prevention Program Research Group. Long-term effects of lifestyle intervention or metformin on diabetes development and microvascular complications over 15-year follow-up: The Diabetes Prevention Program Outcomes Study. *Lancet Diabetes Endocrinol* 2015; **3**(11):866–875. Copyright 2015 Elsevier.

Carbohydrate and diabetes

The carbohydrate content of diets for the prevention and management of T2DM is of secondary importance to the overall energy content of the diet but remains the primary determinant of glycemic control in people with T1DM [1].

Quantity

There is no evidence for a specific quantity of carbohydrate in the diet for the management of T2DM [1], although as little as 20% of calories from carbohydrate has been used in T2DM over 2 years and appears safe [37]. Currently there are no randomized control trials investigating eucaloric carbohydrate restriction on risk of diabetes, but epidemiological data suggest there is no relationship between total carbohydrate intake and risk of diabetes [1, 38–41). In both prevention and management of diabetes, quality and source of carbohydrate are more important than total amount (see carbohydrate quality).

In contrast, carbohydrate counting forms the basis of management of T1DM, where recommended carbohydrate intake should take into account energy requirements, blood glucose concentrations and insulin dosing [1,42–45]. Carbohydrate counting is a meal planning approach which involves matching 10 g or 15 g carbohydrate portions to a particular bolus insulin dose [43, 44], and is based on the premise that carbohydrate is the primary driver of postprandial glucose concentrations [45]. As a concept, carbohydrate counting has been around since the 1920s [46], but has been widely employed since its use in the Diabetes Control and Complications Trial [47]. It is now the dietary strategy of choice in T1DM. Approaches to carbohydrate counting can vary immensely between country, region, institution, and individual practitioner but may include:

- carbohydrate awareness;
- basic carbohydrate counting and label reading;
- development of the patient's skills in monitoring and recording blood glucose levels in relation to food intake, medications, and physical activity;
- sophisticated matching of carbohydrate to insulin dose
  - this may include the use of wizard bolus meters or apps to aid in the estimation of carbohydrate intake and insulin requirement.

These techniques should enable the person with T1DM to add or subtract short- or rapid-acting insulin at meals and snacks to control and correct blood glucose levels [43, 44, 48, 49]. The heterogeneity in these approaches must be taken into account when interpreting the evidence for carbohydrate counting [48].

Adjustment of insulin to carbohydrate intake

In people with T1DM treated with multiple daily insulin or continuous subcutaneous insulin infusion (CSII), carbohydrate counting with insulin dose adjustment is an effective approach to lower HbA_{1c}, reduce the occurrence of hypoglycemic episodes, and improve quality of life and other clinical markers such as body mass index (BMI) and waist circumference [3, 50–55]. However, there is a need for good quality education, and appropriate clinical support is necessary to ensure accurate and consistent insulin dose adjustments [3, 48]. Inaccuracy in carbohydrate counting or dose adjustment is common, and is associated with poorer clinical outcomes [48, 56–58]. Care must be taken to ensure that carbohydrate

counting and dietary advice is not detrimental to an individual's weight management goal. Additional snacks are not automatically required and should be tailored to the individual's needs. Referral to a structured education program of proven benefit, such as the DAFNE (dose-adjustment for normal eating) program, ideally 6–12 months after diagnosis, is recommended [3]. In individuals with fixed or biphasic insulin regimens, consistency in carbohydrate intake is recommended and is associated with reductions in HbA_{1c} [1, 59, 60].

A small number of recent studies have suggested that the fat and protein content of the meal should also be taken into account when planning an insulin regimen [61, 62]. However, any potential physiological benefits of these approaches need to be balanced with the complexity and burden for the person with diabetes.

Carbohydrate in the treatment of mild to moderate hypoglycemia

Mild or moderate hypoglycemia is a common occurrence with insulin treatment in both T1DM and T2DM. Glucose is the most effective treatment and should be given immediately [3]. National and international guidelines recommend 15–20 g should be given immediately (Box 25.1), followed by another 15 g if blood glucose does not rise by 4 mmol after 15 minutes [44]. A follow-up carbohydrate snack (15–20 g) may be necessary to reduce the risk of further hypoglycemia, particularly in circumstances where blood glucose is likely to continue to decrease, such as following alcohol consumption or physical activity [44].

Carbohydrate quality

Dietary carbohydrates represent a heterogeneous group of compounds which include glucose, cellulose, fructose, lactose, starch, resistant starch, sucrose, oligosaccharides, and lignin. The diverse effects of these different structures on diabetes and metabolic risk factors [63] are too numerous to expand on in this chapter, but these factors emphasize the limitations of such terms as a high or low carbohydrate diet. Nevertheless, the "quality" of these different carbohydrates can be imperfectly but usefully captured by use of the glycemic index.

The glycemic index (GI) is an indication of the glucose-raising potential of the carbohydrate, and is defined by the incremental area under the blood glucose curve (iAUC) as a percentage of each person's average iAUC for a standard food, usually 50 g glucose or white bread [64, 65]. The glycemic load, which is the product of the dietary glycemic index and total dietary carbohydrate, may also be used to express the overall quality of carbohydrate in the diet [65].

Box 25.1 Foods containing 15–20 g of fast-acting carbohydrate

- Small glass of sugary (non-diet) drink
- At least three glucose tablets
- Five sweets, e.g. jelly babies
- Small carton of pure fruit juice
- Glucose gel

In people with T2DM, a Cochrane review of randomized controlled trials suggests adoption of a low GI diet can lead to HbA_{1c} reductions of 0.5% [65]. While data from epidemiological studies suggest low GI diets are associated with a lower BMI [66, 67], the data from randomized control trials have demonstrated a reduction in HbA_{1c} independent of changes in body weight [68, 69]. Low GI diets are associated with a lower risk of T2DM [70], but there are currently no controlled trials examining the effect of the glycemic index on T2DM incidence as a primary outcome.

The evidence of effectiveness of low-GI diets in management of glycemia of T1DM is unclear [1] and the latest National Institute for Health and Care Excellence (NICE) guidelines do not recommend their use in people with T1DM [3].

Glycemic index may also reduce CVD risk by lowering triglyceride and low-density lipoprotein (LDL) cholesterol levels and increasing high-density lipoprotein (HDL) cholesterol [71]. However, current guidelines do not make specific recommendations regarding glycemic index and CVD risk.

Dietary fiber

The indigestible nature of dietary fibers renders them low or non-glycemic [72, 73]. However, dietary fibers themselves and foods high in fiber appear to influence glucose homeostasis beyond their glycemic index [74–76]. Increasing dietary fiber by approximately 18 g/day up to total intake of 50 g/day leads to a reduction in fasting plasma glucose of 0.7–0.9 mmol/L [75, 76] and of HbA_{1c} of 0.3% [75]. According to the American Diabetes Association, there is currently insufficient evidence to recommend people with diabetes consume fiber in amounts exceeding the current recommended daily allowances (RDA) [77]. Furthermore, the majority of people in Western populations do not meet the minimum recommendations, and targeting this should be a dietary priority.

Dietary fiber is inversely associated with diabetes risk in cohort studies [78]. In the Finnish Diabetes Prevention Study, participants were advised to consume 15 g/1000 kcal of fiber [79], which appeared to reduce diabetes risk, an effect partly independent of its effects on body weight [80]. Current guidelines for diabetes prevention recommend increasing fiber intake to reduce diabetes risk [1, 77].

Epidemiological data support a protective role of dietary fiber against CVD, with the data most consistent for wholegrains [81–83]. There are currently insufficient data from randomized control trials, and current guidelines do not make specific recommendations for the role of fiber on CVD risk.

Dietary mono- and disaccharides

Sucrose

Despite controversy about the role of sugar in diabetes management, moderate intake of sucrose (10–15% total energy) or other

added sugars can be included in the diet of people with diabetes without worsening glycemic control or insulin sensitivity [1, 60, 84–87]; however, care must be taken not to exceed energy requirements [1, 2, 77, 88]. In a randomized controlled trial, there was no difference in insulin resistance after 6 weeks' of 25% versus 10% of energy from sucrose in healthy people [86]. In contrast, 1 liter per day of a sucrose-containing beverage increases hepatic lipid deposition compared to isocaloric quantities of milk, water, or aspartame-sweetened beverages [89]. The effect of sucrose on glucose excursions is no different from other sources of sugars or starch, provided the total amount of carbohydrate is equal [1, 60, 84–87]. There is no definitive evidence that sucrose per se influences CVD risk. Therefore recommendations for sucrose intake for people with or at risk of diabetes are based on those for the general population, namely limiting the consumption of energy-dense, nutrient-depleted sucrose.

Fructose

Fructose is a low-glycemic monosaccharide and isocaloric exchange of fructose for other carbohydrate improves glycemic control in people with T2DM over the short term, even when consumed up to 160 g/day [90]. However, the metabolism of fructose leads to processes detrimental to human metabolism including increased *de novo* lipogenesis, ectopic lipid accumulation, elevated triglycerides and uric acid, leading to non-alcoholic fatty liver disease and increased cardiovascular risk [91]. While there is a need to identify the optimal quantity of fructose which improves glycemia without deleterious cardiometabolic effects [92], a variety of fruits and vegetables are to be encouraged as part of an overall dietary pattern [1, 2, 86] (Tables 25.1 and 25.2).

Non-nutritive sweeteners

The non-nutritive sweeteners approved for use in the UK and Europe include aspartame, saccharin, asulfame potassium, cyclamate, and sucralose [93]. The increased sweetness of these compounds means they are consumed in miniscule amounts in the diet, and recommendations for people at risk of or with diabetes are the same as the general population [94]. These sweeteners do not contribute to energy intake or influence glucose levels [94]. Other sweeteners commonly used are sugar alcohols. While moderately glycemic, sugar alcohols are consumed in such minor amounts that their consumption does not require alterations in insulin adjustment [1].

Dietary fat

The role of dietary fat in diabetes management has been of interest for decades following observations that dietary fat can modify insulin signaling in the 1950s [95] and the association between saturated fat and CVD [1, 96]. However, there appears to be little association between total fat in the diet and risk of diabetes [95]. Although diabetes prevention programs have limited total fat [10, 11], weight reduction per se and not macronutrient composition of the diet was the primary driver of risk reduction [12]. Similarly, there is no consensus on percent calories from fat in relation to diabetes management [1, 77, 95]. Instead, the types and sources of fat consumed and total quality of the diet appear to be more important.

Saturated fat

Replacement of saturated fat (SFA) with polyunsaturated fat (PUFA) is associated with a reduction in diabetes risk in multiple cohort studies [95, 97]. The evidence is currently stronger for replacement with PUFAs than monounsaturated fatty acids (MUFAs) but this may reflect the close association of MUFAs with SFAs in Western diets and the availability of biomarkers for PUFA intake in prospective studies [95]. Data from randomized controlled trials do not consistently demonstrate a detrimental effect of saturated fat on insulin sensitivity [98–100], but methodological differences in these studies, such as sample size, duration, and the macronutrient which replaces saturated fat may explain these inconsistencies [95, 98–100].

The proposed relationship between saturated fat and CVD largely arose based on early population studies [101]. However, several updated meta-analyses have questioned the conclusion that simply reducing SFA intake will necessarily reduce CVD prevalence [102, 103]. Instead, replacing macronutrient appears to be important: replacement of saturated fat with refined, but not high-quality carbohydrate or unsaturated fat has been linked to worsening of atherosclerotic risk factors including elevated triglycerides, reduced HDL cholesterol, and increased concentrations of small, dense LDL particles [102–106], emphasizing the need to consider the quality of the diet as a whole.

Similarly, recent studies have also drawn attention to the heterogenic nature of dietary fat classes, with short-chain, long-chain, and odd-chain saturated fats associated with diabetes risk reduction, and medium-chain saturated fats associated with increased risk [107, 108]. Odd-chain fatty acids are predominantly found in dairy products, but whether or not these fatty acids have beneficial effects per se or whether these associations reflect other nutrient components found in dairy is currently unclear.

Similarly, saturated fats come from a variety of food sources, including red and processed meats, dairy products, nuts and oils, and a prudent approach is therefore to promote foods associated with healthful dietary patterns such as nuts, seeds, oils, low-fat dairy, fish, and fruit and vegetables, and to limit red (particularly processed) meat and butter (Tables 25.1 and 25.2).

In summary, current guidelines recommend limiting saturated fat to 7% of energy intake, but careful consideration should be given to the replacing macronutrient and overall dietary pattern (Tables 25.1 and 25.2).

Polyunsaturated fat

The most abundant PUFA in the diet is linoleic acid, which is inversely associated with diabetes incidence and CVD in prospective cohort studies [95, 97]. The use of long-chain PUFAs as

biomarkers for intake strengthens the subjective nature of cohort studies, which typically rely on self-reported dietary intake [95, 109]. Clinical trials evaluating the effect of PUFA on insulin sensitivity or surrogate markers for diabetes risk have not been consistent [110, 111]. The short duration of some of these studies may be important as PUFAs are believed to act partly via altering membrane fluidity, which may take up to 3 months [95].

As stated above, replacement of saturated fat with PUFAs reduces CVD risk, and surrogate risk markers [105–107, 112, 113], and sources of PUFAs such as nuts, seeds, and vegetables oils should be encouraged as part of a healthy diet (Tables 25.1 and 25.2).

Omega-3 fatty acids

There is little evidence from observational and experimental studies that omega-3 fats improve glycemia in healthy individuals and people with T2DM [95, 114–117] or reduce risk of developing diabetes [116]. Of concern, high doses of fish oil have been shown to impair glucose homeostasis [115].

In contrast, the cardioprotective effects of omega-3 fats such as reducing serum triglycerides, and modifying platelet aggregation and thrombogenicity [117] have led to recommendations to include oily fish twice a week to reduce CVD [1–3, 21, 118]. Importantly, "more" is not better, and previous support for omega-3 supplementation for prevention of CVD in people with diabetes was withdrawn by NICE [21].

Monounsaturated fat

Recent evidence from the PREDIMED and earlier KANWU trials suggests MUFAs may improve insulin sensitivity and reduce diabetes risk independent of energy restriction, particularly where MUFAs replace SFAs [99, 119]. There is also good evidence from randomized controlled trials that diets high in monounsaturated fat can reduce glucose concentrations in people with T2DM [120–122], and can be used to replace carbohydrate without detrimental effects [1, 123]. There are few studies that have specifically examined the effect of MUFAs on glycemic control in individuals with T1DM, and there is insufficient evidence to make firm recommendations.

Replacing saturated fat with monounsaturated fat can reduce risk of CVD [124, 125], and controlled trials demonstrate high-MUFA diets can increase HDL cholesterol, lower blood pressure, and other surrogate markers of CVD risk [105–107, 111, 113, 126–128].

Monounsaturated fat is a significant component of a Mediterranean diet [129], and it is important to consider the confounding effects of other aspects of this dietary pattern including fish, fruits and vegetables, and moderate alcohol on clinical risk factors. For example, in the PREDIMED trial, extra virgin olive oil had a greater effect on CVD risk reduction than olive oil, despite identical proportions of monounsaturated fat, indicating nutritive and non-nutritive components are also important [130]. Therefore, while monounsaturated fats appear to have independent effects on glucose homeostasis and CVD risk, greater risk reduction is likely achieved by following a diet rich in wholegrains, fruit, vegetables, fish, and limited saturated fat [1, 129, 130].

Trans fats

Trans fats occur naturally in foods such as milk or other dairy products as a bi-product of rumination or are produced industrially (partially hydrogenated vegetable oils). There is little evidence that total trans fat in the diet influences glucose homeostasis [131]; however, prospective studies using the dairy fat trans-palmitoleic acid as a biomarker have shown this naturally occurring trans fat is inversely related to diabetes risk [132]. However, it is unclear whether the fat per se has beneficial effects on glucose homeostasis, or whether the erstwhile nutrients of dairy mediate this risk reduction. Naturally occurring trans fats are found in minute amounts in dairy foods, whereas industrially produced trans fat can contribute up to 4 g a day in US diets [133].

There is compelling evidence from clinical and epidemiological studies that industrially produced trans fats have a deleterious effect on CVD risk [133–135], and national and international guidelines have recommended their reduction or complete elimination in the diet [1, 20, 133, 136].

In practice, these observations support and inform recommendations for a healthy dietary pattern (Table 25.2), with dairy products forming a part of approaches, such as the well-researched Dietary Approaches to Stop Hypertension (DASH) diet, and minimizing foods high in hydrogenated vegetable oil, which typically include biscuits, cakes and other sweet, high-fat goods.

Dietary cholesterol

There is little evidence that dietary cholesterol increases diabetes risk [137]. Instead, recommendations to limit cholesterol intake come from some clinical studies, which have demonstrated that dietary cholesterol can raise LDL cholesterol [138]. This contention has been a subject of considerable debate for many years. A recent meta-analysis of prospective studies examining whether dietary cholesterol ultimately influences risk of CVD were inconclusive [139] and the American Heart Association/American College of Cardiology have raised concerns about the heterogeneity of the data available [140].

However, given the potential impact of dietary cholesterol on LDL cholesterol, the possible increased absorption of dietary cholesterol in people with diabetes [141], and the elevated risk of CVD in people with diabetes, any changes to current guidelines to limit dietary cholesterol to 200–300 mg per day are premature [142].

Protein

Given the primary role of weight loss in prevention and management of T2DM and prevention of CVD, numerous studies have evaluated the effect of higher protein intakes on satiety and weight management in amounts of up to 40% energy from protein [23, 143–145]. However, the concomitant changes in the amount

and quality of carbohydrate and fat in these studies make it difficult to draw any firm conclusions, and the long-term effects of consuming more than 20% of calories from protein on diabetes management and complications are unknown [77]. Guidelines therefore reiterate that the most effective weight-loss diet is one that takes into account an individual's preferences, beliefs, cultural values, and practical considerations [1, 2, 22, 77].

Protein is also a macronutrient of interest due to its capacity to increase insulin secretion acutely [146]. However, whether high dietary proteins impair, improve or have a neutral effect on glycemia is not clear [46, 146–149] while long-term studies up to 12 weeks' length do not show any chronic effects of high-protein diets on insulin secretion [148, 149].

There is therefore insufficient evidence to suggest current guidelines for the general population, which recommend 15–20% of calories should come from protein, should be modified for individuals with T1DM or T2DM who have normal renal function [1, 78]. Suggestions that dietary protein may be modestly linked to increased risk of diabetes [150] may reflect sources of protein such as red or processed meats; dietary patterns that provide vegetable sources of protein alongside low-fat meat represent a prudent approach (Table 25.1).

Micronutrients

A number of micronutrients have been specifically linked to diabetes risk in cohort studies; however, very few randomized controlled trials have confirmed these associations. Such micronutrients include magnesium [151], vitamin D [152–154], calcium [153, 154], and chromium [155]. Similarly, epidemiological trials and *in vitro* data have suggested that antioxidant vitamins and folate (Vitamins A, C, E, and beta-carotene) could play a role in modifying CVD risk. However, well-designed randomized control trials to confirm these associations are lacking [156], and NICE do not recommend such supplementation [157].

Therefore current guidelines recommend regular consumption of a variety of vegetables, fresh fruit, legumes, dairy products, vegetable oils, nuts, wholegrain breads, and oily fish to ensure that recommended vitamin and mineral requirements are met [1] (Tables 25.1 and 25.2). This message should be reinforced alongside clarification that there is no proven benefit of vitamin or mineral supplements for management of diabetes.

Salt or sodium

Reduced sodium intake can lower blood pressure, and sodium intake should be limited across the population including individuals at higher risk of CVD [158, 159]. A reduction in mean salt intake of 3 g per day for adults (to achieve a target of 6 g per day) would lead to around 14–20,000 fewer deaths/year from CVD [21]. Dietary patterns, such as the DASH diet, which are low in sodium and high in potassium, magnesium, and calcium form an effective approach to control hypertension and are appropriate in people with diabetes (Table 25.2).

Sterols and stanols

Plant sterols and stanols have no known effect on glucose homeostasis but have been shown to reduce LDL and total cholesterol in people with and without diabetes [160]. Dietary guidelines have recommended 2–3 g per day of fortified foods to lower LDL and total cholesterol irrespective of whether the individual is taking statins [1], but they are not included in the updated NICE guidelines for lipid modification in the prevention of CVD in people with diabetes [21].

Alcohol

In cross-sectional and prospective studies, a modest alcohol intake is associated with a reduced risk of diabetes and CVD, while excessive (>30–60 g/day) and chronic intake appears to raise blood pressure, plasma triglycerides, and increase the risk of CVD [161–163].

In people with diet-treated diabetes, alcohol consumed with carbohydrate may raise glucose levels, but does not appear to affect glucose or insulin concentrations when consumed alone [78]. However, in people treated with insulin or insulin secretagogues, alcohol increases the risk of hypoglycemia [1, 77]. The risk increases with the quantity of alcohol consumed and may remain elevated the following day [164]. Therefore, in these people, alcohol should be consumed with food [77].

Finally, alcohol is a source of energy and associated with increases in BMI and greater waist : hip ratio [165]. Therefore, recommendations for prevention and management of diabetes are the same as those for the general population: 2–3 units per day in women; 3–4 units per day in men [1, 2]. One alcohol unit is measured as 10 mL or 8 g of pure alcohol. This equals one 25 mL single measure of whisky (ABV 40%), or a third of a pint of beer (ABV 5–6%) or half a standard (175 mL) glass of red wine (ABV 12%). The new UK Department of Health guidelines currently out for consultation recommended only 14 units per week for both men and women [166].

Diet in special circumstances

Diet in pregnancy

Diabetes increases the risk of adverse pregnancy outcomes, and the risk increases with the duration of diabetes (see Chapter 61) [167, 168]. Maintenance of HbA_{1c} level towards the target of 48 mmol/mol (6.5%) is likely to reduce the risk of congenital malformations [168], but may be associated with increased episodes of hypoglycemia [168]. Excess weight gain is associated with poorer glycemic control [77]. Therefore, women with a BMI

of 27 kg/m^2 should be provided with advice and support to attain a healthy weight prior to pregnancy [169]; however, weight reduction should not be attempted during pregnancy [169]. In the UK there are no specific guidelines on weight gain during pregnancy, though NICE emphasizes that energy needs do not change in the first 6 months of pregnancy and increase by a modest degree (approximately 200 kcal/day) in the last 3 months [169]. The Institute of Medicine has more defined guidelines for weight gain over each trimester, which range from 11–20 lbs (5–9 kg) for mothers who are obese at conception to 28–40 lbs (13–18 kg) for underweight mothers [170]. There is little evidence to support particular dietary approaches during pregnancy. However, a low glycemic index diet may modestly improve glycemia [1].

Folic acid requirements increase to 5 mg/day for women with diabetes, as risk of neural tube defects is increased [168]. Folic acid should be taken up to 12 weeks' gestation to prevent neural tube defects. However, in practice, 50% of pregnancies in the UK are unplanned, in which case, folic acid supplementation should be commenced immediately [168].

Diet in children with diabetes

Management of T1DM and T2DM does not differ substantively from adults [77, 171, 172]. Children and their families (or carer) should receive education, which covers insulin therapy and dosage adjustment; blood glucose monitoring; detecting and managing hypoglycemia, hyperglycemia, and ketosis; and the effects of diet, physical activity, and intercurrent illness on blood glucose control [171]. Additionally, age and maturity, emotional well-being and life goals should be considered in an individualized approach. As energy requirements change with age, growth rates have to be monitored and the evaluation of a meal plan should be rechecked at least once a year [171].

As in all healthy children, energy and nutrient intakes should be adequate to ensure optimal growth and development. Good nutrition may also contribute to maintaining normal serum lipid values and meeting blood pressure goals. Meal plans must be individualized to accommodate food preferences and the eating pattern of the family [171, 172].

Exercise and insulin-treated diabetes

Physical activity and exercise have numerous benefits for people with diabetes, including improved glucose control, blood pressure, reduced requirements for medications, and lower CVD risk (see Chapter 26) [1–3]. However, risk of hypoglycemia increases with exercise intensity and duration in insulin-treated diabetes, and careful management of glucose levels is critical [1, 3]. There is not sufficient space to expand on optimal management of different modalities, duration and intensity of exercise here, and referral to a specialist diabetes dietitian is recommended [3]. However, general recommendations for insulin-treated diabetes are to adjust insulin dosing for planned exercise, and provide additional dietary carbohydrate for unplanned exercise [1, 42]. In practice, for the majority of people who engage in moderate physical activity, additional carbohydrate requirements increase only modestly, and an additional 10–15 g per hour should be sufficient to maintain blood glucose levels [42].

For more serious exercisers and athletes, the amount of carbohydrate required will be based on the individual, with sufficient carbohydrate prior to exercise in order to maintain glucose levels during the exercise, and replenishment of glycogen stores in the post-exercise period to enhance performance and prevent hypoglycemia during the next exercise bout, particularly for those who exercise daily [173–175].

Many exercisers, particularly young men engaged in weight training, have specific questions about protein intake. There is little evidence that excessive protein intake increases muscle growth or mass in most casual exercisers; but for weight lifters or endurance athletes, the American College of Sports Medicine recommends 1.4–1.7 g/kg/day [175, 176]. In general, most athletes or weight-training males will meet this protein requirement through diet alone. For individuals who do not consume sufficient protein, protein shakes supplemented with proteins such as whey can be consumed. However, careful monitoring of blood glucose is advised as whey has been shown to lower glucose levels in people without diabetes [177]. Although no studies have been carried out in people with T1DM, whey could theoretically increase the risk of post-exercise hypoglycemia. In practice, most shakes of this type will contain additional carbohydrate which may counteract any glucose-lowering effect.

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26 Lifestyle Issues: Exercise

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Key points

- In people with type 1 diabetes exercise improves fitness and strength, reduces cardiovascular risk factors, and improves well-being.
- While regular exercise has not conclusively been found to improve glycemic control in type 1 diabetes, it is associated with decreased long-term morbidity and mortality in this population
- Managing type 1 diabetes in the context of exercise can be complicated by both hypoglycemia and hyperglycemia during and after exercise.
- It is recommended that individuals with type 1 diabetes adjust their insulin dose and carbohydrate consumption prior to, during and/or after exercise to accommodate the type, intensity, and duration of exercise performed.
- Structured, supervised diet and exercise interventions can reduce the risk of developing type 2 diabetes by about 60% in individuals with impaired glucose tolerance.
- Regular exercise improves fitness and strength, reduces cardiovascular risk factors and improves HbA_{1c} and is associated with decreased long-term morbidity and mortality in people with type 2 diabetes.
- In people with type 2 diabetes to maximize the effect of exercise on glucose control combined aerobic and resistance exercises should be undertaken for ≥150 minutes per week.
- While regular exercise has not conclusively been found to prevent gestational diabetes there is emerging evidence that it can improve glycemic control in women with gestational diabetes.

Defining exercise, type of exercise and intensity

Physical activity, exercise, and physical fitness are terms that describe different concepts. However, they are often confused with one another, and the terms are sometimes used interchangeably. Physical activity refers to bodily movements that involve muscle contraction to produce energy expenditures above the basal level, whereas exercise is a form of physical activity, which is planned, structured, and repetitive with the objective of improving or maintaining one's physical fitness [1].

Physical activity is measured in metabolic equivalent (MET) units that estimate the oxygen consumption of an activity. One MET is equivalent to 3.5 mL O_2/kg/min of oxygen consumption in a resting seated adult. Moderate exercise is equivalent to 3–6 METs, which include leisure cycling, swimming, walking, and general house cleaning. Vigorous exercise is activity equivalent to >6 METs such as running, rope jumping, and sit-ups.

Physical fitness refers to the circulatory and respiratory systems' ability to supply oxygen during sustained exercise. The intensity of an exercise is typically measured as percentage of maximal oxygen consumption (VO_{2max}). Moderate activity is when the body utilizes 40–60% of VO_{2max}, whereas high-intensity activity reaches 80–90% VO_{2max}. The volume of exercise is usually measured by the duration of the activity.

Exercise can be categorized into aerobic, anaerobic, and resistance training. There are few data to support that one type of exercise is superior to another in terms of general health benefits [2]. However, an exercise that is enjoyable and suitable to the individual is likely to be performed regularly and maintained for a longer period.

Aerobic exercise engages large muscle groups with repetitive and continuous movements for ≥10 minutes to produce improved oxygen utilization with the aim of enhancing cardiovascular and respiratory fitness. Examples include walking, cycling, and jogging.

Anaerobic exercise comprises short, but high-intensity, bursts of physical activity that rely on rapid release of energy produced via glycolysis, rather than being dependent on oxygen consumption. This exercise builds lean muscles, improves muscle and bone strength, and enhances sports performance.

Textbook of Diabetes, Fifth Edition. Edited by R. Holt, C. Cockram, A. Flyvbjerg and B. Goldstein.

Resistance training enhances muscle strength by working muscles against a resistance load or weight. By altering the combination of weight load and frequency of repetition, this exercise improves muscle endurance and strength as well as increasing the lean muscle mass and metabolic rate.

Aerobic, anaerobic, and resistance training exercises can be used alone or in combination to achieve the desired effect of improving cardiorespiratory fitness, muscle strength and endurance, weight loss and its maintenance. The type, intensity and volume of exercise should be tailored to individual needs to allow maximal adherence and long-term health benefits. Although the benefits greatly outweigh the risks, there are restrictions to exercise for people with certain medical conditions in terms of the type and intensity of physical activity. Gradual increases in exercise intensity and volume are generally advisable, but especially in those who are ordinarily sedentary at the start of an exercise program.

Type 1 diabetes and exercise

Prevention of type 1 diabetes

Most people view type 1 diabetes (T1DM) as affecting young, fit individuals. This together with its autoimmune pathogenesis means that regular exercise is not typically thought to prevent T1DM. Evidence is now emerging that exercise may be one of the modifiable agents that interact with genetic predisposition to determine if and when T1DM develops [3].

Figure 26.1 shows the possible mechanism by which exercise could improve or maintain β-cell mass. Physical exercise induces elevations in circulating levels of growth hormone (GH), IGF-1, glucagon-like peptide 1 (GLP-1), IL-6, and IL-1 receptor agonist (IL-1ra), all of which increase proliferation of β cells [4–8]. By reducing fat and visceral fat mass, exercise reduces pro-inflammatory adipokines, such as leptin and TNF-α, and increases anti-inflammatory adipokines, such as adiponectin, which may help to reduce β-cell death [9]. Exercise may reduce the destructive immune response to the β cell by reducing the Toll-like receptors on monocytes and macrophage immune cells [10]. Finally exercise improves insulin sensitivity which in turn helps to normalize plasma glucose [11] and serum lipids [12], which when chronically elevated cause β-cell death.

In animal models of diabetes, exercise protects the β cell from oxidative stress [13]. In healthy individuals [14], individuals at risk of type 2 diabetes (T2DM) [15] and people with T2DM, regular exercise improves β-cell function [16]. No studies to date have reported on the effect of exercise on β-cell function or incidence of diabetes in people with T1DM. However, the fact that insulin resistance, which is improved by exercise, predicts progression to T1DM [17] and that in a cross-sectional study increased physical activity was associated with better diabetes control, lower insulin needs, and higher C-peptide levels at T1DM onset [18], suggests that more human research is needed in this area.

Treatment of type 1 diabetes

Although the evidence for benefit is not as great as that seen in T2DM, there is sufficient evidence to suggest that exercise should be encouraged in people with T1DM. Figure 26.2 summarizes the benefits that people with T1DM can expect to see with exercise.

Physical fitness, CVD, and mortality

Although there are only a few small studies of fitness in people with T1DM, young adults (17–44 years old) with T1DM are less

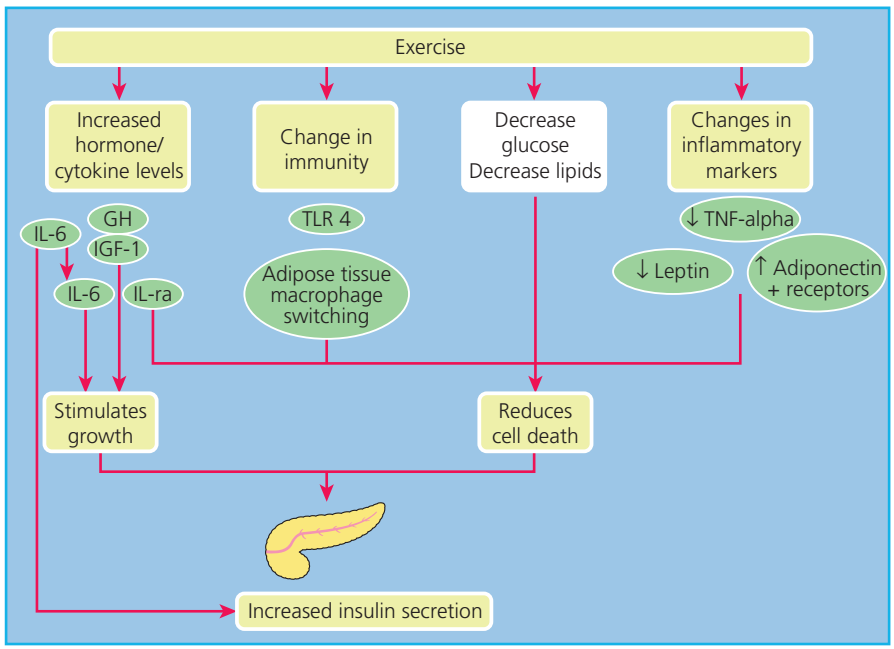

Figure 26.1 Potential mechanisms through which exercise could improve β-cell mass and/or function. Source: Narendran et al. 2015 [3]. Reproduced with kind permission from Springer Science+Business Media.

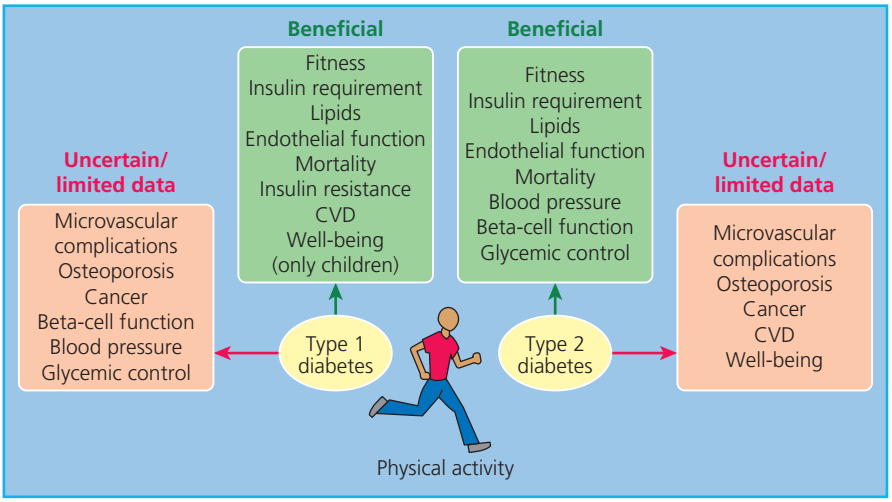

Figure 26.2 Health benefits of physical activity in type 1 and type 2 diabetes. Source: Chimen et al. 2011 [19]. Reproduced with permission from Springer.

fit than matched individuals without diabetes, despite similar levels of physical activity [20–23]. Abnormalities in cardiac muscle and autonomic nerve function [24], as well as an altered cardiac metabolism that favors non-esterified fatty acids (NEFA) over glucose as a fuel source [25], may contribute to this. Supervised physical activity programs do, however, improve fitness in people with T1DM [26–28] with increases in VO_{2max} of up to 27% reported [22, 28–32].

No large RCT or prospective studies have examined whether regular physical activity reduces CVD disease or mortality in T1DM. A large retrospective study, the Pittsburgh IDDM Morbidity and Mortality study, suggests that regular physical activity may be of benefit. This study demonstrated that in men who had had T1DM for 25 years, those who had participated in team sports during high school were three times less likely to report macrovascular disease and had mortality rates three times lower than those who did not [33]. This pattern was not seen in women, but their participation in team sports was lower (24% reported participation vs. 39% in men). The level of physical activity in adulthood (measured using a validated questionnaire) also predicted mortality at 6 years [20]. Sedentary men were three times more likely to die than active men, and a similar (but, again, non-significant) effect was seen in women.

Glycemic control and insulin requirements

The effect of physical activity on glycemic control in people with T1DM is unclear with some studies showing benefit but the majority showing no benefit. Table 26.1 lists the intervention studies where the controls have T1DM and Table 26.2 lists other studies.

The intervention studies have tended to use supervised exercise programs of short duration (1–3 months), have involved small numbers of participants (all but one had fewer than 60), and predominantly involved adolescents or young adults. Three recent meta-analyses of the effect of exercise on HbA_{1c} in T1DM have reported. Kennedy et al. included only studies in which there was a non-intervention group of participants with T1DM [64]. They found no glycemic benefit of exercise in people with T1DM. However, subanalyses suggested that exercise may confer glycemic benefit in the young, and when undertaken for longer periods. They also stated that exercise can be carried out by people with T1DM without significant risk of hypoglycemia. This is important because some studies have reported that hypoglycemia is a barrier to exercise in T1DM [65, 66].

Tonoli et al. [67] used less stringent criteria including trials with no control groups, but excluded some of the studies used in the Kennedy analysis. Exercise overall resulted in a small but statistically significant reduction of 0.3%. When exercise was analyzed by type, aerobic exercise reduced HbA_{1c} by 0.2%, strength training did not lower HbA_{1c}, and combined aerobic exercise and strength training showed a statistically significant reduction in HbA_{1c} of 1.6%.

In the meta-analysis by Yardley et al. [68], studies were only included if they were prospective, randomized and controlled with a non-exercising T1DM control group and the exercise intervention comprised supervised or unsupervised aerobic, resistance or combined physical activity offered at least twice weekly for ≥8 weeks. Only four studies were identified that met their criteria and had HbA_{1c} before and after the intervention. Although there was a 0.8% fall in HbA_{1c} in the exercise group compared to the control group, the authors concluded that there were insufficient well-designed studies to ascertain the true effect of exercise training on HbA_{1c} in T1DM.

Studies in people with T1DM that have examined the effect of exercise on plasma glucose concentrations have also failed to show a consistent benefit on fasting glucose [28, 33, 69, 70]. However, these studies have shown, as seen with healthy individuals [41], that blood glucose decreases (without hypoglycemia) around the time of exercise [37, 71]. The lack of glycemic benefit as assessed by HbA_{1c} may result from rebound hyperglycemia immediately following exercise, and better control of this may show a benefit.

Two main factors may account for the poor effect of exercise on HbA_{1c}. Many individuals with T1DM consume energy when physically active, either as a fuel source or to manage hypoglycemia, and this may counteract any glucose-lowering effect

Table 26.1 Intervention studies evaluating the effect of physical activity on HbA_{1c} in people with type 1 diabetes (T1DM). All studies quoted have included people with T1DM in both the intervention and control groups. The studies are listed in chronological order according to whether or not physical activity improved HbA_{1c}. Source: Chimen et al. 2011 [19]. Reproduced with permission of Springer.

						T1DM control group		T1DM intervention group	
Study	***n* (Control/T1DM)**	**Mean age ± SD /age range (years)**	**RCT?**	**Duration**	**Type of physical activity**	**HbA_{1c} before (%) (mmol/mol)**	**HbA_{1c} after (%) (mmol/mol)**	**HbA_{1c} before (%) (mmol/mol)**	**HbA_{1c} after (%) (mmol/mol)**
No HbA_{1c} effect									
Yki-Jarvinen et al. [28]	6/7	NA	no	6 weeks	Supervised aerobic physical activity	8.6 ± 0.4 (70 ± 5)	8.6 ± 0.4 (70 ± 5)	8.6 ± 0.4 (70 ± 5)	8.6 ± 0.4 (70 ± 5)
Landt et al. [30]	6/9	14 to 16	no	12 weeks	Supervised aerobic physical activity	12 ± 1 (108 ± 11)	12 ± 1 (108 ± 11)	12 ± 1 (108 ± 11)	12 ± 1 (108 ± 11)
Wallberg-Henriksson et al. [32]	7/6	25–45	no	5 months	Non-supervised aerobic physical activity	10.6 ± 0.6 (92 ± 7)	10.4 ± 0.6 (90 ± 7)	10.4 ± 0.6 (90 ± 7)	10.5 ± 0.6 (91 ± 7)
Huttunen et al. [34]	16/16	8.2 to 16.9	no	3 months	Supervised aerobic physical activity	9.4 ± 2.1 (79 ± 23)	9.7 ± 2.2 (83 ± 24)	9.8 ± 2.3 (84 ± 25)	10.5 ± 2.5 (91 ± 28)
Laaksonen et al. [26]	28/28	32.5 ± 5.7	yes	12–16 weeks	Supervised aerobic physical activity	8.2 ± 1.1 (66 ± 12)	8.2 ± 1.0 (66 ± 11)	8.3 ± 1.3 (67 ± 14)	8.5 ± 1.6 (69 ± 18)
Fuchsjager-Mayrl et al. [29]	8/18	42 ± 10	no	4 months	Supervised aerobic physical activity	7.4 ± 0.4 (57 ± 6)	7.2 ± 0.2 (55 ± 2)	7.3 ± 0.2 (56 ± 2)	7.5 ± 0.3 (58 ± 4)
HbA_{1c} improvement									
Dahl-Jorgensen et al. [35]	8/14	5 to 11	no	5 months	Supervised aerobic physical activity	13.4 ± 1.9 (123 ± 21)	12.9 ± 1.6 (117 ± 18)	15.1 ± 2.2 (142 ± 49)	13.8 ± 1.9 (127 ± 21)
Campaigne et al. [36]	9/10	9 ± 0.47	yes	12 weeks	Supervised vigorous physical activity	13.9 ± 0.61 (128 ± 8)	13.3 ± 0.54 (122 ± 6)	12.5 ± 0.65 (113 ± 7)	11.3 ± 0.5 (100 ± 5)
Durak et al. [37]	8/8(cross over)	31 ± 3.5	yes	10 weeks	Supervised heavy resistance training	6.9 ± 1.4 (52 ± 15)	6.9 ± 1.4 (52 ± 15)	6.9 ± 1.4 (52 ± 15)	5.8 ± 0.9 (40 ± 10)
Perry et al. [38]	30/31	20–69	yes	6 months	Non-supervised aerobic physical activity	8.7 ± 2.0 (72 ± 21)	8.8 ± 2.3 (73 ± 25)	8.9 ± 2.6 (74 ± 28)	8.6 ± 2.1 (70 ± 23)
Salem et al. [39]	48/Moderate 75/Intensive 73	14.5 ± 2.4	yes	6 months	Supervised aerobic and resistance physical activity	8.3 ± 2.1 (67 ± 23)	8.9 ± 1.4 (74 ± 15)	Moderate: 8.9 ± 1.4 (74 ± 15) Intensive 8.9 ± 1.6 (74 ± 17)	Moderate: 8.1 ± 1.1 (65 ± 12) Intensive 7.8 ± 1.0 (62±11)

Table 26.2 Interventional and observational studies evaluating the effect of physical activity on HbA_{1c} in people with type 1 diabetes (T1DM). All studies quoted have included people with T1DM in the intervention group, but the control group has either not been present or has included people without diabetes. The studies are listed in chronological order according to physical activity effect on HbA_{1c}. Source: Chimen et al. 2011 [19]. Reproduced with permission of Springer.

Study	*n* (T1DM)	Mean age (years)	Design	Duration	Type of exercise	VO_2 max	HbA_{1c} before (%)	HbA_{1c} after (%)
No HbA_{1c} effect								
Wallberg-Henriksson et al. [27]	9	NA	Case series	16 wk, 1 h, 2–3 times/wk	Aerobic exercise: jogging, running, ball games, and gymnastics	↗ 8%	10.4 ± 0.7	11.3 ± 0.5
Wallberg-Henriksson et al. [40]	10	NA	Control trial	8 wk, 45 min, 3 times/wk	Aerobic exercise: running	↗ 13%	NA	NA
Zinman et al. [41]	13	30 ± 1.8	Control trial	12 wk, 45 min, 3 times/wk	Aerobic exercise: cycling	↗ 8%	10.7 ± 0.3	10.3 ± 0.8
Baevre et al. [42]	6	14–17	Case series	6 m	Aerobic exercise	NA		
Selam et al. [43]	50	NA	Cross-sectional study	Weekly energy expenditure	Total physical activity index (questionnaire)	NA	NA	NA
Lehmann et al. [44]	20	NA	Case series	3 m, ≥135 min/wk	Endurance training	↗	7.6	NA
Ligtenberg et al. [45]	221	31.7	Cross-sectional study	Measurement of physical activity for past year	Total physical activity index (questionnaire)	NA	No correlation between total physical activity and HbA_{1c}	NA
Rigla et al. [31]	14	25.5 ± 6	Case series	3 m, 1 h min, 3 times/wk	Aerobic activity at 60–75% VO2 max: treadmill, bicycle	↗ 5%	6.5 ± 0.8	6.7 ± 1
Rigla et al. [46]	14	25.5 ± 6	Control trial	3 m, 1 h, 3 times/wk	Aerobic exercise: running, cycling	↗	6.5 ± 0.8	6.7 ± 1
Roberts et al. [47]	24	Adolescent	Case series	24 wk	Supervised training	↗ 17% in aerobic capacity	NA	NA
Sarnblad et al. [48]	26	15.7 ± 2.1	Cohort study	7 days	Measurement of physical activity	NA	No association between time spent exercising and HbA_{1c}: 7.6 ± 1.4	NA

(*continued*)

Table 26.2 (*Continued*)

Study	*n* (T1DM)	Mean age (years)	Design	Duration	Type of exercise	VO_2 max	HbA_{1c} before (%)	HbA_{1c} after (%)
Mittermayer et al. [49]	11	44 ± 3	Control trial	4 m, 50 min, 2–3 times/wk	Supervised aerobic exercise: cycling	NA	7.2 ± 0.2	7.6 ± 0.3
Haider et al. [50]	18	42 ± 10	Control trial	4 m, 1 h, 2–3 times/wk	Supervised aerobic exercise	NA	7.3 ± 0.9	7.5 ± 1
Ramalho et al. [51]	13	13–30	Case series	12 wk, 40 min, 3 times/wk	Aerobic vs. resistance	NA	Aerobic: 8.7 ± 1.6 Resistance: 8.2 ± 2.9	Aerobic: 9.8 ± 1.8 Resistance: 7.6 ± 1.6
Harmer et al. [52]	8	25 ± 4	Control trial	7 wk, 3 times/wk	Supervised aerobic exercise: intense cycling	NA	8.6 ± 0.8	8.1 ± 0.6
Aman et al. [53]	NA	11–18	Cross-sectional study	NA	Measurement of leisure time activity	NA	No association of physical activity	NA
Edmunds et al. [54]	46	12.8 ± 2.1	Cross-sectional study	Measurement of physical activity for 2 weeks	Moderate and vigorous activity (Questionnaire)	NA	No association between time spent exercising and HbA_{1c}	NA
HbA_{1c} deterioration								
Woo et al. [55]	10	11.21 ± 0.97	Control trial	12 wk, 3 times/wk	Aerobic exercise: treadmill	→	8.09 ± 0.5	8.33 ± 0.8
HbA_{1c} improvement								
Marrero et al. [56]	10	12–14	Case series	12 wk, 45 min, 3 times/wk	Aerobic fitness program	↗	11.41 ± 4.47	10.01 ± 3.21
Bak et al. [57]	7	27.9 ± 7.1	Control trial	6 wk	Physical training	↗	7.9 ± 1.4	7.7 ± 1.5
Mosher et al. [22]	10	17.2 ± 2.9	Control trial	12 wk, 45 min, 3 times/wk	Aerobic exercise: circuit training	↗ 4%	7.72 ± 1.26	6.76 ± 1.07
Zoppini et al. [58]	53	NA	Cross-sectional study	Measurement of physical activity	30 regular exercise, 23 sedentary exercise	NA	7 ± 1 in regular exerciser group	7.8 ± 1.2 in sedentary group
Salvatoni et al. [59]	69	8.98 ± 3.9	Cross-sectional study	Measurement of physical activity for 1 wk	3 ± 2.9 h/wk	NA	6.3 ± 0.3 in group ≥7 h exercise/wk	7.7 ± 0 in group 2–4 h exercise/wk
Sideraviciute et al. [60]	19	14–19	Control trial	14 wk, 45 min, twice/wk	Aerobic exercise: swimming	↗	8.5 ± 0.4	7.8 ± 0.3
Herbst et al. [61]	19143	12.9–14	Cross-sectional study	0, or 1–2 or ≥3 times/wk	Measurement of regular physical activity	NA	8.4 ± 1.9 in 0 time/wk group	8.0 ± 1.6 in 1–2 and ≥3 times/wk)
Herbst et al. [62]	23251	12.7 ± 4.3 to 13.9 ± 3.1	Cross-sectional study	0, or 1–2 or ≥3 times/wk	Measurement of regular physical activity	NA	8.1 ± 1.9 in 0 time/wk group	7.8 ± 1.6 in 1–2 and ≥3 times/wk)
Ruzic et al. [63]	20	12.81 ± 2.14	Case series	2 wk, intense exercise program, 5 days of at least 1 h of exercise	Aerobic exercise: swimming, cycling, running …	NA	8.28 ± 1.3	7.92 ± 1.42 (but increase 2 m after camp)

of physical activity [41]. Similarly people with T1DM who exercise regularly reduce their daily insulin dosages by 6–15% [28, 29, 51]. Whilst this may be required to manage hypoglycemia, these reductions may mask improvements in HbA_{1c}.

Vascular risk factors other than glucose

People with T1DM commonly have hypertension and dyslipidemia that are associated with increased risk of vascular disease [70]. Most studies suggest that physical activity in people with T1DM improves lipid profile [22, 26, 28, 29, 31, 44]. These studies were of short duration (generally ≤4 months) and showed similar benefits to those seen in individuals without diabetes. HDL cholesterol increased by 8–30%, while LDL cholesterol and triglycerides decreased by 8–14% and 13–15%, respectively. Exercise also reduces apolipoprotein B, which is pro-atherogenic and is associated with premature mortality in T1DM [71], and increases the anti-atherogenic apolipoprotein A-I [26]. These benefits are independent of changes in glycemic control and weight and most pronounced in those with an adverse lipid profile.

Only four studies have examined the effect of physical activity on blood pressure in T1DM. All four studied young adults and used similar supervised exercise programs. Two showed no benefits in systolic or diastolic blood pressure [29, 31] and two showed a 2–3% reduction in blood pressure [39, 44]. Three studies were small, 26, 14, and 20 participants, respectively [29, 31, 44]. The remaining study was larger and included 196 participants and was one of the studies to show a benefit [39].

People with T1DM have clear evidence of endothelial dysfunction and this is worse if microalbuminuria is present [21]. Regular exercise can reverse endothelial dysfunction [72] and improve vascular function but this improvement is not as great as that seen in individuals without diabetes [29, 73]. Improved vascular function is also seen in vascular beds not supplying exercising muscles suggesting that this is a global rather than local benefit of exercise. Benefits only persist whilst people are exercising regularly and cease soon after regular activity is stopped.

Although less insulin resistant than those with T2DM, people with T1DM are more insulin resistant than matched individuals without diabetes [21, 28]. This insulin resistance can be improved by up to 23% through both resistance and endurance exercises [27–29, 51].

The beneficial effects of physical activity on insulin resistance, as well as on lipid levels and endothelial function, suggest that physical activity should reduce vascular complications in T1DM.

Microvascular complications

Increased physical activity is associated with fewer diabetes-related complications in individuals with T1DM [74]. In the Pittsburgh IDDM Morbidity and Mortality Study [75], in men but not women, activity levels were inversely associated with the risk of nephropathy and neuropathy but not retinopathy. However, a retrospective analysis of baseline physical activity in the Diabetes Control and Complications Trial (DCCT) found the rates of development or progression of diabetic retinopathy, nephropathy, and neuropathy were unaltered by physical activity after a mean follow-up of 6.5 years [76].

Other studies have shown an inverse association between physical activity and the severity of several complications in T1DM [74, 77]. A follow-up study involving 1945 individuals with T1DM reported that those involved in either little leisure time physical activity or low-intensity activity were more likely to have impaired renal function and more proteinuria as well as greater rates of retinopathy and cardiovascular disease when compared to their more frequently and more vigorously active counterparts [74]. Balducci and colleagues randomized 78 people (21 T1DM and 57 T2DM) without signs and symptoms of peripheral diabetic neuropathy to either supervised exercise or a control group [77]. The percentage of people with diabetes who developed motor and sensory neuropathy during the 4 years of the study was significantly higher in the control than the exercise group, 17.0% versus 0.0%, and 29.8% versus 6.4%, respectively. Thus long-term aerobic exercise training seems to prevent the onset of diabetic neuropathy or modify its natural history [77].

More recently, a cross-sectional multi-center study of 18,028 people with T1DM reported [78] that the frequencies of retinopathy and microalbuminuria were lower in active compared with inactive people. However, due to the cross-sectional design no causality can be inferred. It remains unclear whether the presence of comorbidities affected people's ability to exercise or whether being physically active decreased the risk of developing these complications.

Beta-cell function

T1DM is a chronic inflammatory autoimmune disease characterized by destruction of insulin-producing β cells and subsequent insulin deficiency [79]. This loss of β cells is gradual and at the time of diagnosis of T1DM significant β-cell function remains [80]. While it is generally assumed that the remaining β cells are completely destroyed soon after diagnosis, studies now indicate that these cells can persist for many years [81].

The preservation of these remaining β cells has important clinical benefits. A meal-stimulated C-peptide value of >200 pmol/L is associated with improved glucose control for the first 4 years after diagnosis, reduced risk of developing retinopathy and nephropathy, and a >50% reduction in hypoglycemia rates [82]. Thus interventions that have the potential to preserve β-cell function are worth striving for.

In diabetes animal models [13], healthy individuals [14], and people with T2DM physical activity preserves β-cell function [15]. The possible mechanisms by which exercise could preserve β-cell function are shown in Figure 26.1. This benefit of physical activity has not been examined in T1DM although a pilot study is currently underway to examine this [83].

Bone density

People with T1DM have reduced bone mineral density (BMD), osteoporosis and increased risk of fracture [84] but no studies have

examined whether physical activity increases BMD or reduces fracture risk in people with T1DM.

Cancer

Whether people with T1DM are at increased risk of cancer is unknown [85]. Physical activity appears to protect the general population from cancer and improve outcomes in those who do develop cancer (surgical outcome, side effects of chemotherapy, subsequent prevention of recurrence). Again, this has not been examined in T1DM.

Well-being

People with T1DM are 2–3 times more likely to suffer with depression than the general population [86]. In young adults, physical activity is associated with significantly greater satisfaction with life and well-being [58] but these associations were not found in the one study that examined this in children [65].

Exercise and type 2 diabetes

Prevention of type 2 diabetes

Prospective observational studies

The earliest evidence that indicated that exercise might play a role in prevention of diabetes came from large prospective cohort studies. In these studies higher levels of physical activity and/or cardiorespiratory fitness were consistently associated with reduced risk of developing T2DM [87, 88, 90–99]. After adjustment for confounding variables, the most active participants had a 25–60% lower risk of subsequent diabetes compared to those who were most sedentary. This reduction was seen regardless of the presence or absence of additional diabetes risk factors such as hypertension, parental history of diabetes, and obesity. In addition, similar magnitudes of risk reduction were seen with walking compared to more vigorous activity, when total energy expenditures were similar [95].

Non-randomized studies

The first large study to assess the effectiveness of lifestyle modification in preventing and treating diabetes was the Malmö Study [100]. In this non-randomized study, 41 participants with T2DM and 181 with impaired glucose tolerance (IGT) accepted enrolment into a 6–12-month intervention in which they were given advice to reduce energy intake and increase physical activity. The control group comprised 114 healthy individuals and 79 with IGT who declined the intervention.

At 6 years follow-up, 10.6% of those with IGT in the intervention group had progressed to T2DM, compared with 28.6% in the control group, a risk reduction of 63% [16]. Over 12 years, mortality among the controls was 14.0 per 1000 person-years, but only 6.5 per 1000 person-years in the intervention group [101]. Since this seminal study, many randomized controlled trials (RCT) have assessed the effect of lifestyle programs in preventing T2DM.

Randomized studies

A summary of the RCTs that have assessed whether lifestyle can prevent T2DM are shown in Table 26.3. The China Da Qing Diabetes Prevention Study included 577 participants with IGT who were randomized by center into four arms: diet only, exercise only, diet and exercise, or control, and were followed for 6 years [102]. The cumulative incidence of T2DM was 68% in controls, but only 44%, 41%, and 46% in the diet, exercise, and diet and exercise groups, respectively. Even more encouraging is the long-term follow-up which indicates that the benefits from these lifestyle interventions continue for many years after completing "active treatment"; the so-called "legacy effect." After 20 years follow-up, 14 years after leaving the study, those in the interventional groups had 43% lower incidence and spent on average 3.6 fewer years with diabetes compared to the control group [103].

In the Finnish Diabetes Prevention Study 522 people with IGT were randomized to an exercise and diet intervention or control [104]. The intervention was intense and included individualized exercise plans, thrice-weekly supervised facility-based aerobic and resistance exercise, and seven 1-hour meetings with a dietitian focusing on weight reduction, reduced fat intake, and reduced total caloric intake. Participants in the control group had one meeting per year. At 4 years, 22% of the control group and only 10% of the intervention group had developed diabetes, a 58% risk reduction. Again a legacy effect was seen with participants in the intervention arm having a 43% lower risk of developing diabetes 3 years after leaving the study [105].

In the American Diabetes Prevention Program [106], 3234 American men and women with IGT were randomly assigned to placebo, metformin, or a lifestyle-modification program. Again the lifestyle intervention was intense with the participants provided with 16 lessons in the first 24 weeks. These lessons were delivered individually and covered diet, exercise, and behavior modification. A minimum of two supervised exercise sessions per week, and at least monthly contact with the study personnel were maintained thereafter. Cumulative incidences of T2DM were 11.0/100 person-years in the placebo group, 7.8 per 100 person-years in the metformin group, and only 4.8 per 100 person-years in the intensive lifestyle group. The risk of T2DM was 58% lower in the lifestyle group than in the placebo group, and 39% lower than in the metformin group [107].

The Indian Diabetes study randomized 421 men and 110 women with IGT (mean age 45.9 ± 5.7 years, BMI 25.8 ± 3.5 kg/m^2) into four groups [108]. Group 1 was the control, Group 2 was given advice on lifestyle modification (LSM), Group 3 was treated with metformin (MET), and Group 4 was given LSM plus MET. The lifestyle advice was less intense than that given in the American and Finnish prevention studies. Participants in the LSM group were asked to increase their activity to 30 minutes per day; if they were already achieving this they were asked to maintain this activity. Exercise was not supervised.

Table 26.3 Controlled studies that have looked at preventing diabetes. C, control; D, diet; E, exercise; LSM, lifestyle modification; MET, metformin.

Name	Number of participants	Design of study	Study participants	Detail of intervention	Duration	Outcome
Malmö Study [100, 101]	222	Non-RCT	C: 114 healthy and 79 participants with IGT; LSM: 41 participants with T2DM and 181 participants with IGT	Participants were given advice to reduce energy intake and increase physical activity. Intervention lasted for 0.5–1 year.	6 years	Progression to T2DM: 10.6% vs. 28.6% for LSM vs. C group. A 63% risk reduction for the development of T2DM. Over 12 years, mortality was 14 vs. 6.5 per 1000 person-years in the C and LSM groups, respectively.
The China Da Qing Diabetes Prevention Study [102, 103]	577	RCT	Participants with IGT randomized into 4 arms: D, E, D+E, or C	D: received prescribed diet, advice on healthy eating and calorific reduction; E: taught exercise with increased exercise intensity; D+E: include both diet and exercise instructions as the D and E groups. All intervention groups received regular counselling sessions.	6 year, and follow-up at 20 years	Cumulative incidence of T2DM was 44%, 41%, 46%, 68% in D, E, D&E, C groups, respectively. Legacy effect: D, E and D&E groups had 43% lower incidence and spent average 3.6 fewer years with T2DM compared to C group.
Finnish Diabetes Prevention Study [104, 105]	522	RCT	Participants with IGT randomized into 2 arms: LSM and C	LSM; Individualized exercise plans, thrice-weekly supervised facility-based aerobic and resistance exercise, and seven 1-h meetings with a dietitian focusing on weight reduction, reduced fat intake and reduced total caloric intake.	4 years and follow-up at 7 years	Development of DM 10% in LSM compared to 22% in C group. Risk reduction 58%. Legacy effect: 43% lower risk in the interventional arm.
American Diabetes Prevention Program [106, 107]	3234	RCT	Participants with IGT randomized into 3 arms: placebo, MET, or a LSM program	LSM included intense 16 lessons in the first 24 weeks, delivered 1 to 1 and covering diet, exercise and behavior modification. A minimum of two supervised exercise sessions per week, and at least monthly contact with the study personnel were maintained thereafter.	Average 2.8 years	Cumulative incidences of T2DM were 11, 7.8, and 4.8 per 100 person-years in the placebo, metformin, and lifestyle groups, respectively.
Indian Diabetes study randomized [108]	531	RCT	Participants with IGT, randomized into 4 arms: C, LSM, MET, and LSM + MET	LSM: asked to increase or maintain their activity to 30 minutes per day. Non-supervised exercise. Diet modification included reduction in total calories, refined carbohydrates and fats, avoidance of sugar, and inclusion of fiber-rich foods. LSM participants were contacted monthly by telephone and seen 6-monthly during the study.	2.5 years	3-year cumulative incidences of diabetes were 55.0%, 39.3%, 40.5%, and 39.5% in control, LSM, MET, and LSM + MET, respectively. The relative risk reduction was 28.5% with LSM, 26.4% with MET, and 28.2% with LSM + MET as compared with the control group.

Diet modification was advised for each participant and included reduction in total calories, refined carbohydrates and fats, avoidance of sugar, and inclusion of fiber-rich foods. To aid adherence to the LSM, people were contacted monthly by telephone and seen 6 monthly during the study. The median follow-up period was 30 months, and the 3-year cumulative incidences of diabetes were 55.0%, 39.3%, 40.5%, and 39.5% in Groups 1–4, respectively. The relative risk reduction was 28.5% with LSM, 26.4% with MET, and 28.2% with LSM + MET as compared with the control group.

In these prevention studies, weight loss seems to be the main factor in the reduced diabetes incidence. In the US Diabetes Prevention Program, among those in the intervention arm, for every kilogram in weight loss a 16% reduction in diabetes was seen, when adjustment for changes in diet and lifestyle were made [109]. Results from a meta-analysis also suggest that the effectiveness of these lifestyles programs may be greater in more overweight individuals.

Weight loss, however, does not explain all the intervention effects. In the Indian Diabetes Prevention Program a 28.5% reduction in diabetes incidence was achieved without weight loss or reduction in waist circumference [108]. In the exercise intervention arm of the Da Qing IGT and Diabetes Study a 46% reduction in diabetes incidence was achieved without weight loss [102]. These factors suggest that some aspects of diet as well as physical activity, not necessarily related to weight loss, may be involved in mediating the beneficial effect of lifestyle modification in the prevention of T2DM.

Little data exist on the benefits of diet alone or exercise alone interventions for the prevention of diabetes in high-risk populations.

Treatment of type 2 diabetes

There is very clear evidence that exercise alone has profound benefits in people with established T2DM. Figure 26.2 summarizes the benefits that people with T2DM can expect to see with exercise.

Physical fitness, CVD, and mortality

People with T2DM diabetes have a significantly lower VO_{2max} than healthy age, BMI, and activity-matched people without diabetes [110]. Meta-analysis of 9 RCTs ($n = 266$), comparing exercise and control people with T2DM shows that regular exercise, at an intensity of at least 50% of VO_{2Max}, improved overall VO_{2Max} by 11.8% in the exercise group versus a reduction of 1% in the control group. Additionally, higher intensity exercise produces even larger improvements in cardiorespiratory fitness [111].

Observational studies have shown that increased physical activity improves cardiorespiratory fitness and lowers mortality rate in participants without diabetes [112, 113] while prospective studies in people with diabetes report that even walking for 2 hours a week is associated with less cardiovascular mortality; however, the effect is greater with 3–4 hours of walking a week [114]. No RCT has assessed the effect of improved physical fitness on mortality in T2DM.

Glycemic control

Supervised exercise training

Structured exercise training is normally defined as an intervention in which people engage in a planned, individualized, and supervised exercise program. The most recent meta-analysis that examined the effect of structured exercise training on HbA_{1c} in T2DM reported in 2011 [115] (Figure 26.3). This included 23 RCTs with 1533 participants. Studies had to be RCTs of ≥12 weeks' duration and have a control group of people with T2DM. Overall structured exercise reduced HbA_{1c} by 0.7% when compared to control participants. When dividing the studies into exercise type, 18 studies (848 people) demonstrated that structured aerobic exercise training reduced HbA_{1c} by 0.7%, four studies (261 people) showed that structured resistance exercise training reduced HbA_{1c} by 0.6%, and seven studies (404 people) demonstrated that the combined aerobic and resistance exercise reduced HbA_{1c} by 0.5%. This meta-analysis also showed that structured exercise duration of ≥150 minutes per week was associated with greater benefit than structure exercise duration of ≤150 minutes, 0.9% reduction versus 0.4% reduction, respectively.

Using a meta-regression analysis, Umpierre et al. assessed the association between intensity and volume of supervised exercise training (aerobic, resistance or combined) and HbA_{1c} changes in T2DM [138]. Higher baseline HbA_{1c} was associated with greater HbA_{1c} reduction with training. For supervised aerobic training and combined aerobic/resistance training, higher volume of exercise was associated with greater HbA_{1c} reduction. For example, for each set of aerobic exercise added within the exercise week, it produced a 0.4% HbA_{1c} reduction. No exercise variables were found to be possible candidates to explain the effects of supervised resistance training.

A meta-analysis of RCTs that compared supervised resistance exercise with aerobic exercise in people with T2DM sought to clarify whether there was an optimum type of exercise for treating T2DM [139]. The 12 included studies of 626 participants were RCTs of duration of ≥8 weeks that compared supervised resistance exercise with supervised aerobic exercise. Although there was a greater reduction of HbA_{1c} with supervised aerobic exercise compared to supervised resistance exercise, the difference was only 0.2% and not clinically significant.

Two RCTs have compared the three commonly used types of supervised exercise for treating T2DM, namely aerobic, resistance training or a combination [124, 132] (Figure 26.4). In the Diabetes Aerobic and Resistance Exercise (DARE) trial [124], 251 previously sedentary individuals with T2DM were randomized into four arms: aerobic exercise training, resistance exercise training, combined aerobic and resistance exercise training, or a non-exercising control group. Compared to the control groups, HbA_{1c} values decreased significantly in the aerobic group by 0.5% and the resistance group by 0.4%. In the combined exercise group, HbA_{1c} values fell by an additional 0.5% compared with the aerobic group and 0.6% compared with the resistance group.

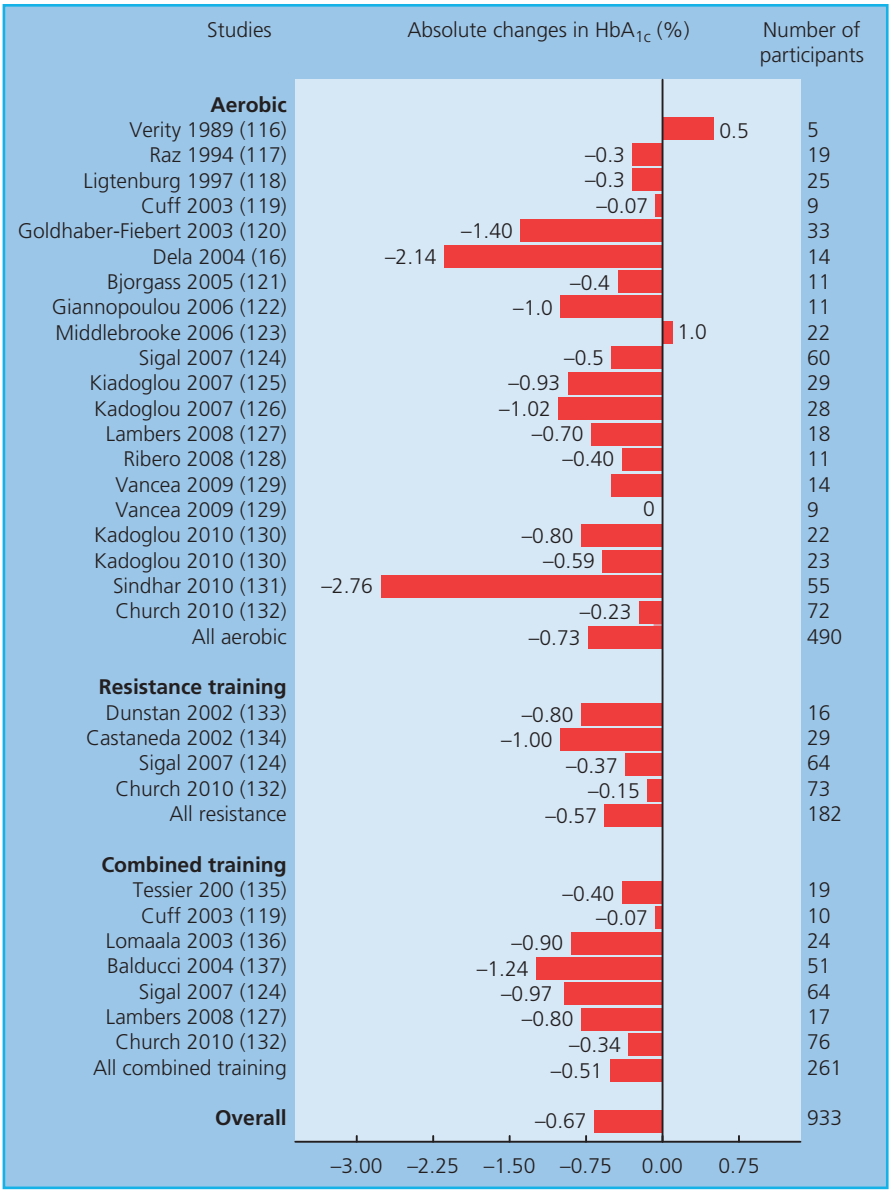

Figure 26.3 Absolute changes in HbA_{1c} of individual studies of structured exercise training versus no intervention. Numbers of participants in each exercise regimen is shown in the far-right column. Source: Adapted from Umpierre et al. 2011 [115].

In people with $HbA_{1c} \leq 7.5\%$, HbA_{1c} only decreased significantly in the combined exercise training group.

Church et al. [132] randomized 262 sedentary people with T2DM to four groups: aerobic exercise training, resistance exercise training, combined aerobic and resistance exercise training, or a non-exercising control group. Compared with the control group, neither the resistance nor aerobic training produced a significant change in HbA_{1c}. For the combination training exercise group, a fall in HbA_{1c} of 0.3% was seen compared to the control group.

High-intensity interval training (HIT) is the newest form of exercise to be tried in the management of T2DM as it takes less time to perform and can produce similar physiological effects to longer duration of standard exercises [140]. Recently a meta-analysis of four small studies which aimed to quantify the effects of HIT on markers of glucose regulation with control conditions or continuous training has reported [141]. Compared with control conditions, in people with T2DM, HIT decreased HbA_{1c} by 0.2%. HIT was not superior to continuous training at lowering HbA_{1c}.

Physical activity advice

Although structured exercise training may be available to a subset of people with T2DM, physical activity advice is more feasible. Physical activity advice is normally defined as formal instructions to exercise regularly with or without an individualized exercise prescription. The most recent meta-analysis that assessed the effect of physical advice on HbA_{1c} in people with T2DM reported in 2011 [115] (Figure 26.5). This included 24 studies with 7025 participants. Overall physical activity advice produced a 0.4% decrease in HbA_{1c} compared to control. When the studies were broken down to those that also gave dietary advice and those

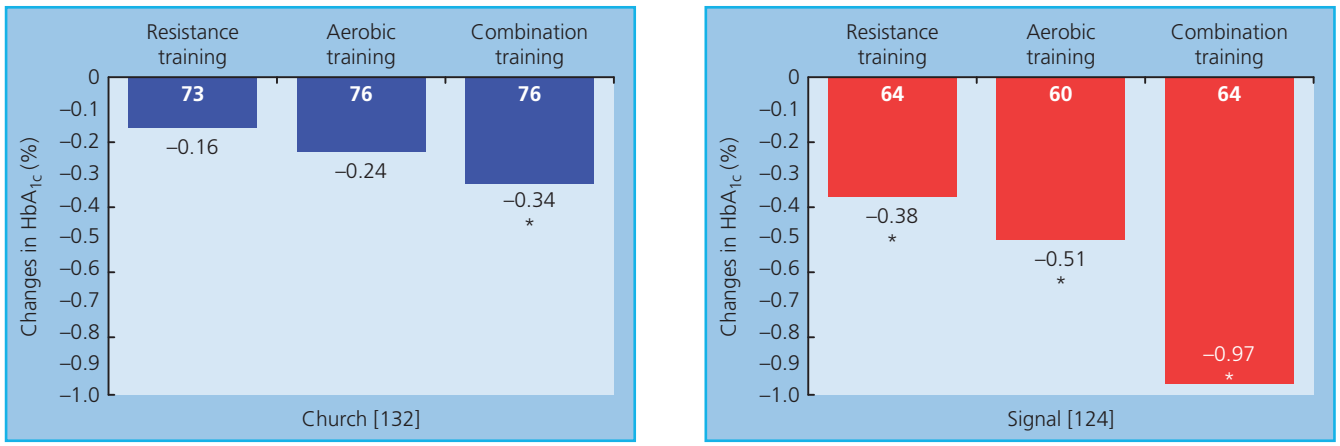

Figure 26.4 Reduction in HbA_{1c} (%) seen with different exercise regimens compared to control group in two studies, Church et al. [132] and Sigal et al. [124]. Numbers of participants in each exercise regimen is shown in the boxes in white. A star denotes significant improvement compared to control group. Source: Adapted from Sigal et al. 2007 [124] and Church et al. 2010 [132].

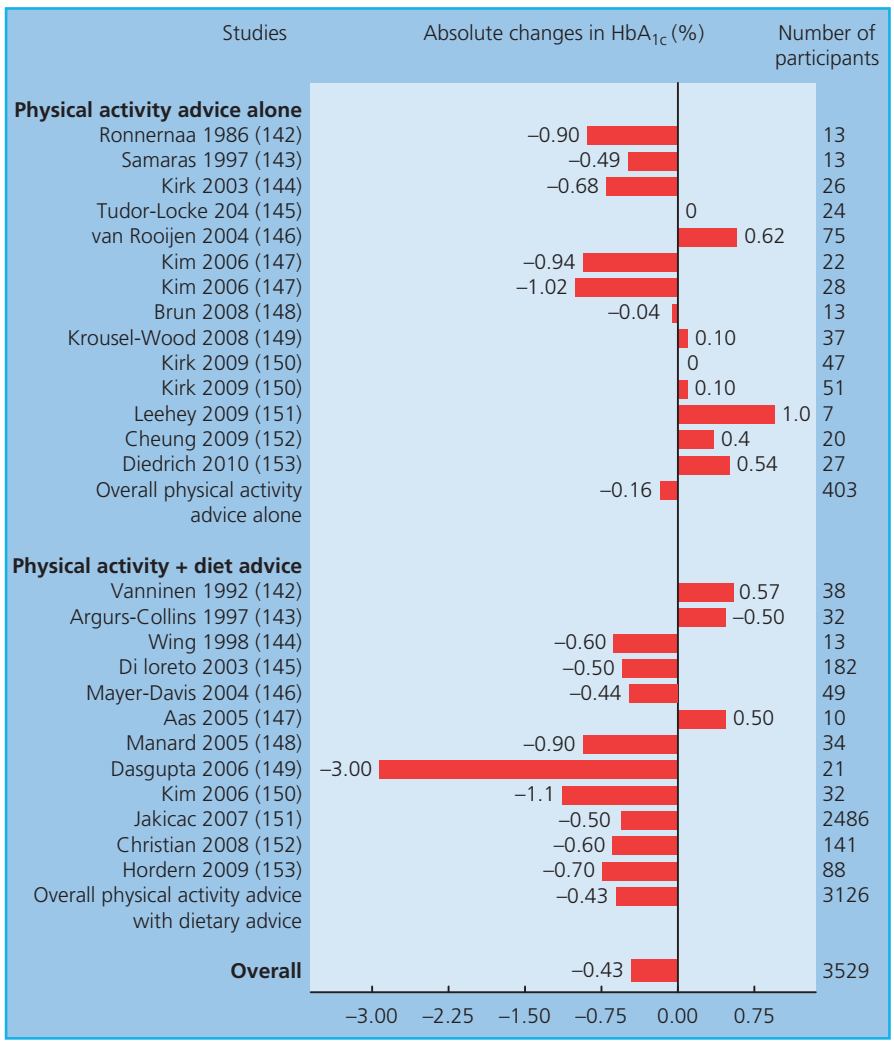

Figure 26.5 Absolute changes in HbA_{1c} of individual studies of physical activity advice versus no intervention. Numbers of participants in each exercise regimen is shown in the far-right column. Source: Adapted from Umpierre et al. 2011 [115].

that did not, some interesting findings were seen. Physical activity advice given with dietary advice (12 studies, 6313 people) was associated with a 0.6% HbA_{1c} reduction as compared with control but physical activity advice alone (14 studies, 712 people) was not associated with HbA_{1c} changes.

Structured exercise training versus physical activity advice

Only one RCT has compared structured exercise training to physical activity advice. In the Italian Diabetes and Exercise Study [166], 606 individuals with T2DM were randomized to a full year of either physical activity advice alone or supervised facility-based combined aerobic and resistance exercise training twice weekly plus physical activity advice. HbA_{1c} fell by 0.1% in the advice group and 0.4% in the supervised exercise group, with this difference being significant. This study suggests that supervised exercise programs are more effective than physical activity advice.

Vascular risk factors other than glucose

In healthy people, aerobic and resistance training lower both systolic (SBP) and diastolic blood pressure (DBP), whereas combined training only lowers DBP [167]. In 2014, Figueira and colleagues conducted a meta-analysis to assess the effect of physical activity advice alone or structured exercise training on blood pressure in T2DM [168]. Thirty RCTs (2217 participants) of structured exercise training and 21 (7323 participants) physical activity advice alone RCTs were identified. Overall structured exercise reduced SBP by 4 mmHg and DBP by 2 mmHg when compared to controls. Greater reductions in blood pressure were seen when exercise duration was ≥150 minutes and when intensity of the exercise was higher. When exercise training was broken down into exercise type, compared to control, aerobic exercise training reduced SDP by 5 mmHg and DBP by 2 mmHg, and resistance exercise training reduced SDP by 4 mmHg and DBP by 3 mmHg. Combined exercise training was not associated with a reduction in blood pressure. Physical activity advice alone produced a 3 mmHg reduction in SBP and a 1 mmHg reduction in DBP.

Several studies have examined the effect of aerobic and combined aerobic and resistance supervised exercise on lipids in T2DM. In a meta-analysis both reduced triglycerides by 0.3 mmol/L but had no effect on HDL cholesterol and LDL cholesterol [169]. Only one study has assessed the effect of resistance training and found no effect on total cholesterol, HDL cholesterol, LDL cholesterol, or triglycerides [124].

People with T2DM have impaired endothelial function [170, 171], which is a powerful and independent predictor of long-term cardiovascular events [172, 173]. Only a few small studies have assessed the effect of exercise on endothelium function in T2DM but a meta-analysis of five studies including 217 participants reported supervised exercise improved endothelium function [173].

Insulin resistance is one of the hallmarks of T2DM and is involved in the pathogenesis of hypertension and CVD. Both aerobic and resistance training improve insulin resistance in T2DM [119]. Although in healthy controls, resistance exercise has a greater effect on insulin sensitivity than aerobic exercise there is insufficient evidence to confirm whether this is the case in T2DM [174].

Microvascular complications

As exercise improves HbA_{1c} and blood pressure, the two key risk factors in the development of diabetic microvascular complications, regular exercise should protect against microvascular complications. Few studies have examined whether this is the case. Impaired exercise capacity is associated with diabetic nephropathy and retinopathy [175]. In retrospective and prospective cohort studies regular physical activity was associated with reduced progression and development of diabetic kidney disease [176, 177]. In the Look AHEAD study people randomized to the intervention arm (diet, exercise, and weight loss) were less likely to develop retinopathy or neuropathy [178]. In contrast in the Japan Diabetes Complications Study in which 2033 participants were randomized to a lifestyle intervention (diet and exercise) or usual care, there was no difference in incident retinopathy or nephropathy between groups at 8 years follow-up [179]. No RCTs have examined the effect of exercise alone on microvascular risk in people with T2DM.

Beta-cell function

In the UK Prospective Diabetes Study, progressive decline of β-cell function was associated with worsening of glycemic control in people with T2DM, irrespective of treatment strategy [180]. Thus maintenance of β-cell function is important if we wish to maintain good control in people with T2DM. Several studies have shown that aerobic exercise of varying intensity improves insulin secretion in T2DM [181–184].

Bone mineral density

People with T2DM are at increased risk of fractures despite normal, or even increased, bone mineral density (BMD) [185]. This increase in fracture risk may be due to altered bone architecture or an increased risk of falling due to neuropathy. No studies have assessed the effect of physical activity on BMD or fracture risk in T2DM.

Cancer

T2DM is associated with an increased risk of developing cancer [186]. In the general population regular physical activity reduces cancer risk and improves outcomes in those who develop it. Again no studies have examined whether this holds true for people with T2DM.

Well-being

People with T2DM have a higher chance of developing depression [187, 188]. They also have a poorer quality of life [189] and a higher prevalence of general anxiety disorder (14%) than the general population [190]. The effects of exercise training on quality of life, symptoms of depression, symptoms of anxiety and emotional well-being in T2DM have been recently reviewed [191]

Table 26.4 Effect of exercise on well-being.

		Number of studies	Length of interventions	Number of participants	Results
Quality of life	Aerobic	Five [127, 194, 196–198]	8, 16, 16 and 52, 12, and 12 weeks	18, 50, 44, 29, 38	Four found no effect [30, 34, 35, 38] and one found effect on physical health and sleep subscales but not on other subscales [33].
	Resistance	Four [164, 201, 204, 205]	16, 16, 12 and 26, and 16 weeks	58, 48, 110, 37	One found no difference [43], one found a significant effect [3], and two found effects on mental component [7] and general health subscale [31] but no effect on other subscales.
	Combined	Ten [127, 135, 161, 193, 195, 197, 199, 203, 205, 207]	24, 52, 16 and 52, 12 and 26, 8, 12, 26, 12, 16, and 16 weeks	84, 606, 64, 109, 36, 77, 43, 28, 38, 29	Six found no effect [34, 36–38, 44, 46]. Three found improvement across all measures of quality of life [32, 42, 47]. The remaining one found improvement in emotional role, mental health, and vitality but not for other subscales [29]
Well-being	Aerobic	Three [192, 202, 206]	6, 8, and 8 weeks	58, 40, 20	Two showed improvement [2, 5] and one no improvement [6]
	Resistance	Two [192, 205]	8, 12, and 26 weeks	20, 110	One showed improvement [7] the other did not [6]
	Combined	One [205]	12 and 26 weeks	109	No effect
Depression	Aerobic	Two [200, 202]	6 and 8 weeks	78, 58	Both showed no effect
	Resistance	One [201]	16 weeks	58	Improved
	Combined	One [193]	8 weeks	36	No effect
Anxiety	Aerobic	One [200]	6 weeks	58	Reduced anxiety
	Resistance	None			
	Combined	None			

(Table 26.4). No form of exercise improved quality of life and emotional well-being while depressive symptoms were only improved by resistance training and anxiety symptoms only improved by aerobic training.

Gestational diabetes and exercise

Prevention of gestational diabetes

Gestational diabetes (GDM) is a condition in which women without a previously diagnosis of diabetes develop glucose intolerance during pregnancy (Chapter 61) [192]. The prevalence of GDM ranges from 1% to 14% depending on the diagnostic criteria used and the population being studied [193]. It is associated with adverse maternal and fetal outcomes; women with GDM have an increased risk of developing GDM in subsequent pregnancies and of developing T2DM. Offspring of mothers with GDM are at high risk of macrosomia [194] and as adults are more likely to become obese [195] and develop T2DM [196]. Preventing GDM is therefore a clinical priority.

A number of prospective studies have shown that low physical activity is associated with the development of GDM. In the largest of these studies (21,765 women) Zhang et al. found that when comparing the highest with the lowest quintiles of vigorous activity there was a relative risk of 0.77 (197). Among women who did not engage in vigorous activities, women who briskly walked ≥30 minutes or climbed ≥15 flights of stairs daily also had lower risk of GDM [197].

A 2012 Cochrane database systematic review including five trials and 1115 pregnant women assessed the effects of physical exercise for preventing glucose intolerance or GDM [198]. GDM incidence did not differ between women receiving additional exercise interventions or routine antenatal care. A more recent Cochrane database systematic review also found no difference in GDM incidence between women receiving routine antenatal care or additional diet and exercise interventions [199]. Both reviews felt that larger better quality studies were needed to confirm or refute these findings. A number of large high-quality studies are underway which will report in the next few years.

Treatment of gestational diabetes

Regular exercise during pregnancy is associated with many benefits, including improved cardiorespiratory fitness, less low back pain, reduced urinary incontinence, reduced depressive symptoms [200], and less weight gain in pregnancy [201]. Although diet and exercise are recommended as the first step in managing GDM, there is debate about whether there is clear evidence

about the effectiveness of exercise. A 2006 Cochrane review concluded that "there is insufficient evidence to recommend, or advise against, diabetic pregnant women to enrol in exercise programs. Further trials, with larger sample size, involving women with gestational diabetes, and possibly type 1 and 2 diabetes, are needed to evaluate this intervention" [202]. A more recent systematic review identified seven studies that had examined the effect of exercise in managing GDM [203]. Five studies found improvements in glycemic control and/or a limitation in insulin use [204–208] but two reported no effect [209, 210].

Exercise advice in type 1 and type 2 diabetes

Exercise guidelines

The American Diabetes Association has published recommendations and guidelines for exercise in individuals with diabetes [211]. These and other guidelines are summarized in Table 26.5.

Where possible advice should be tailored to the individual, taking into account their interests, level of fitness, possible contraindications, and personal goals. There are many examples of people with diabetes competing at the highest level, and so diabetes should not interfere with an individual's sporting goal and treatment should be adjusted according to the demands of the activity. For activities and competitions considered to be high risk for individuals with diabetes (car racing, flying, diving, etc.) individual governing bodies should be consulted regarding restrictions in competition. It is also important to note that insulin is considered a banned substance by the World Anti-Doping Agency, and that elite level athletes with diabetes will be require a Therapeutic Use Exemption (TUE) certificate prior to competition.

Table 26.5 Exercise guidelines for adults and children with type 1 and type 2 diabetes and pregnant women with diabetes. Source: Based on recommendations in [200] and [211].

Categories	Physical activity recommendations
Adults with T1DM and T2DM	At least 150 min/week of moderate-intensity or 75 min/week of vigorous-intensity aerobic physical activity, or equivalent combination of the two. This should be spread over 3 days with no more than 2 consecutive days without exercise. Additionally, muscle-strengthening activities that involve all major muscle groups should be performed on 2 or more days of the week. Reduction in sedentary time is also recommended [1]
Children and adolescents with T1DM and T2DM	At least 60 min of physical activity daily, this should include vigorous-intensity aerobic activity, muscle-strengthening activities and bone-strengthening activities at least 3 days of the week [1]
Pregnant women with DM	At least 30 min or more of moderate exercise daily if there are no medical or obstetric complications [2]

Most guidelines recommend ≥150 minutes of moderate aerobic activity, and/or ≥90 minutes of vigorous aerobic exercise every week, and that this activity be spread over at least three days [211]. A day's activity need not occur in a single session, but may be accumulated in bouts of 10 or more minutes at a time, performed throughout the day. Performing ≥150 minutes of moderate activity is associated with greater benefit, so if a person with diabetes has reached the target of 150 minutes they should be encouraged to do more if possible.

In addition to aerobic exercise, many guidelines also suggest that resistance training should be carried out at least twice per week, as combining aerobic exercise with resistance training has the greatest effect on HbA_{1c}. Ideally at least three sets of resistance exercise should be done at each session as the resistance exercise studies that have used three or more sets have shown the greatest reduction in HbA_{1c} [37, 133, 212]. Weight lifting is safe in people with cardiac disease [213] and is not associated with increased proliferative retinopathy risk [214].

Newer guidelines also recommend that people with diabetes should also try and reduce their sedentary time [211]. This is because higher sedentary time is associated with a poorer metabolic profile in T2DM and reduced sedentary time improves metabolic profile [215].

Minimizing risk of exercise-related adverse events

Assessment

There is often concern about the safety of exercise for people with diabetes, although for most people, the benefits of exercise will outweigh the risks. Prior to starting exercise for the first time or when beginning a program of vigorous physical activity, people with diabetes should be assessed for conditions that might increase the risks associated with certain types of exercise or predispose them to injury. Table 26.6 provides guidance on what pre-exercise assessment should be undertaken.

Specific considerations for people with type 1 diabetes who exercise

In normal healthy individuals changes in insulin and counter-regulatory hormone secretion during exercise are dependent on the type of exercise being performed [216]. These changes facilitate an increase in liver glucose production to match skeletal muscle glucose uptake [156]. A change in the secretion of these hormones is also seen post exercise to facilitate recovery and adaption to exercise. As a result of these changes, blood glucose levels remain relatively stable before, during, and after exercise.

In T1DM, because insulin lies in subcutaneous depots and is not under regulation, insulin levels do not change in a physiological manner during exercise, thus they cannot fall in response to exercise and there may be impaired secretion or action of counter-regulatory hormones. This impairs normal fuel regulation [217].

Table 26.6 Pre-exercise assessment and advice for people with diabetes complications.

Complication	Advice
Cardiovascular disease	Symptoms of cardiovascular disease should be asked about and where there is concern patients should be referred to a cardiologist for further assessment. There is no evidence for screening of asymptomatic individuals. Cardiovascular assessment is recommended for people with autonomic neuropathy.
Peripheral neuropathy	It is vital to ensure that appropriate footwear is worn and feet are examined regularly particularly if peripheral neuropathy is present. Weight-bearing exercise should be avoided in those with active foot disease. Walking does not increase the risk of ulceration in people with peripheral neuropathy There is evidence that exercise delays the progress of neuropathy and so exercise should be encouraged.
Retinopathy	When proliferative or severe non-proliferative retinopathy is present it may be sensible to avoid vigorous activity (both aerobic and resistance) because of the possible increased risk of vitreous hemorrhage or retinal detachment.
Nephropathy	No evidence for restriction of any type of exercise in people with diabetic renal disease. In fact there is evidence that exercise can reduce progression and so exercise should be encouraged.

The inability of the pancreas to modulate insulin and counter-regulatory hormones (in particular glucagon) following exercise can also hamper recovery and adaption to exercise. This increases the risk of hypoglycemia both during and following exercise. Furthermore, hyperglycemia prior to and following some types of exercise can be problematic [218]. Consequently, people with T1DM have three main problems when exercising, which are:

1 problems controlling their blood glucose during and immediately following exercise;

2 unexplained severe hypoglycemia particularly at night;

3 reduced performance through excessive fatigue and reduced muscle strength.

To help overcome these problems people need to understand how different exercises affect glucose, know when it is safe to exercise, and have strategies to manage glucose during and after exercise.

How different exercise effects blood glucose

Both intensity and exercise type will determine what happens to blood glucose concentrations (Figure 26.6). The most rapid drop in blood glucose occurs during aerobic or endurance exercise, when circulating insulin suppresses metabolic fuel production and increases muscle glucose uptake [219]. With intermittent high-intensity exercise, there is a mixture of both aerobic and anaerobic exercise, which is characteristic of team sports and children's play; blood glucose is either stable or falls slowly [220]. High-intensity or anaerobic exercise tends to raise blood glucose, as a result of increased catecholamines that are normally seen with these exercises [221].

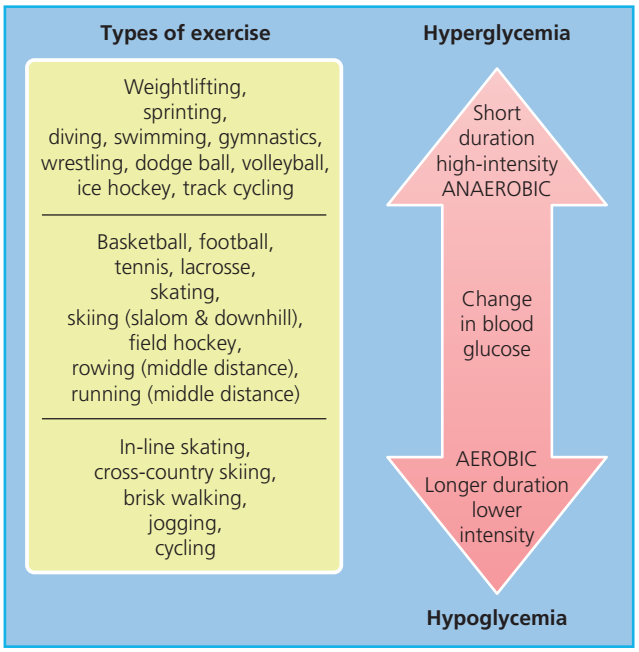

Figure 26.6 Effects of differing sports on blood glucose concentrations.

When it is safe to exercise

Hypoglycemia in the 24 hours preceding exercise blunts the counter-regulatory hormone response to exercise-induced hypoglycemia placing an individual at greater risk of exercise-induced hypoglycemia. This risk is proportional to the severity of the preceding hypoglycemia, with the effect starting at 3.9 mmol/L [222]. There is currently no evidence to guide individuals as to when it is safe to exercise following a hypoglycemic episode. However, we would suggest the following:

- Do not exercise within 24 hours of severe hypoglycemia requiring third-party assistance.
- Do not exercise within 1 hour of self-treated hypoglycemia. If an individual insists on doing so, they should treat the hypoglycemia and wait 45–60 mins once the glucose is stable before commencing activity.
- Take extra precautions when there has been an episode of self-treated hypoglycemia within the previous 24 hours. This would include more frequent glucose testing, exercising with an informed partner, and, if possible, including an anaerobic component to their training because this will tend to raise their blood glucose.

If there is hypoglycemia during exercise, exercise should be discontinued and the hypoglycemia treated. The individual should wait at least 45 mins before recommencing activity (or until blood

Table 26.7 Insulin dose adjustment table for exercise. MHR, maximum heart rate. Borg scale is based on the Borg rating of perceived exertion scale [232].

		Intensity		
	Duration	**Low (<50 MHR % or Borg scale 10)**	**Medium (50–75% MHR or Borg scale 10–15)**	**High (>75% MHR or Borg scale >15)**
% Dose reduction	<30 min	10–20%	20–45%	40–60%
	30–60 min	20–30%	30–55%	50–75%
	>60 min	30–50%	45–70%	100%

glucose is stable). If an episode of severe hypoglycemia occurs during exercise, then the activity should be stopped altogether because of the high risk of further hypoglycemia.

When the blood glucose level is ≥14 mmol/L before exercise, the presence of ketones (capillary or urine) should be assessed [223]. If ketones are present, exercise is contraindicated and supplemental insulin should be considered (1 unit for 2–3 mmol/L glucose reduction). Exercise should only be commenced when ketone-free and blood glucose is ≤14 mmol/L [224]. Where the blood glucose level is ≥14 mmol/L and ketones are not present, advice depends on timing of the last meal (and, therefore, last quick-acting insulin dose). If a meal has been eaten in the last 1–2 hours, commence exercise but monitor blood glucose closely. If the last meal was eaten ≥2 hours ago, then 30% of their usual correction dose should be given.

Strategies to manage glucose during exercise

An initial strategy for managing blood glucose during exercise is to replace the carbohydrate (CHO) that will be used during exercise orally. In its simplest form, this is a fixed CHO replacement regimen. In adults, we initially recommend 15 g of CHO for every 30 min of exercise [225]. Although activities vary widely in terms of fuel requirements, this range represents a safe starting point for most people beginning moderate-intensity exercise. Estimates of CHO requirement based on body mass can be used in preference to fixed dose CHO replacement. Therefore for moderate and intensive activity 0.5 g/kg/h and 1 g/kg/h, respectively may be used [226].

An alternative approach that adjusts for the variable fuel requirements of different exercises is using standardized tables. These have been devised to help athletes of different body

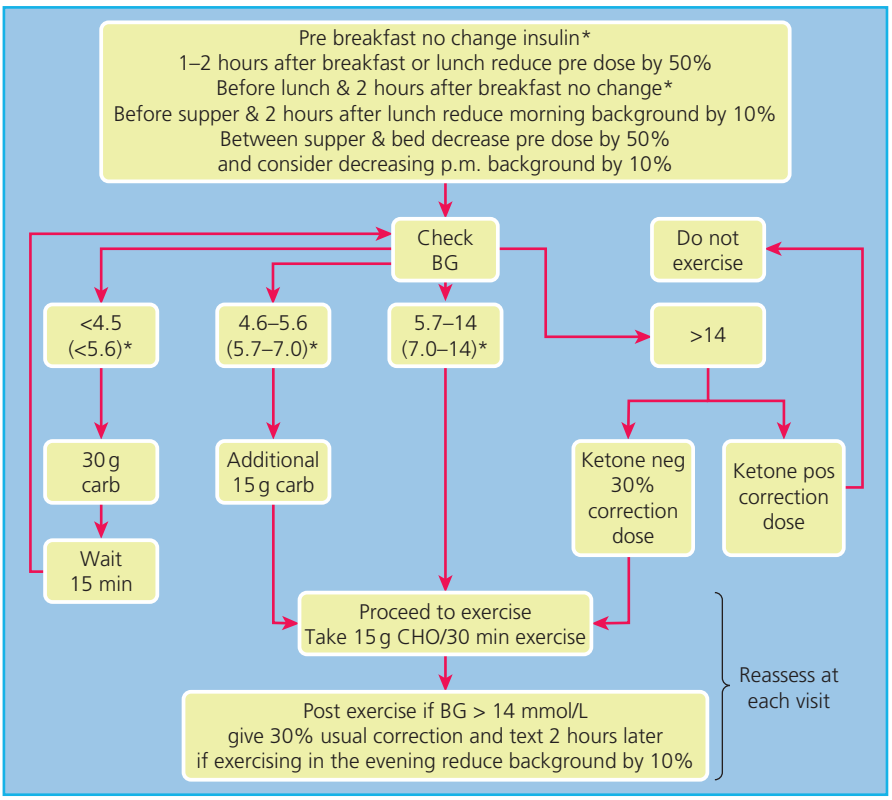

Figure 26.7 Algorithm for people with T1DM suggesting changes to insulin and carbohydrate intake when exercising. Note different blood glucose levels are used in this algorithm if exercising before breakfast or when exercising 2 hours after breakfast and before lunch when no changes in insulin dosages are made, this is denoted by a star. BG, blood glucose.

weight estimate CHO requirements for different exercise intensities [227]. The maximum rate of enteral glucose absorption is 1 g/min. Therefore CHO requirements exceeding 60 g of glucose per hour, would need to comprise a combination of glucose and fructose. In general, once CHO requirements for exercise exceed 60 g/h, we would recommend altering insulin doses.

Several studies have examined insulin dose reductions for exercises of different intensities. This has enabled the development of dose reduction tables (Table 26.7). These tables tend to refer to changes to fast-acting insulin and therefore relate to exercise undertaken within 2 hours of eating (3 hours if on soluble human insulin). To gain the most from these reductions, exercise is best conducted within 30 minutes after eating, and the meal or snack should predominantly contain low glycemic index CHO [228]. Reduction in background insulin can, however, be helpful if people are undertaking prolonged exercise in the morning, or in the afternoon 2 hours after their meal.

Strategies to manage glucose post exercise

Following exercise, carbohydrate is required to replenish muscle and liver glycogen stores. Protein is also needed for post-exercise muscle repair and synthesis. Failure to provide this increases the risk of hypoglycemia in the subsequent hours, and fatigue in subsequent exercise sessions. Initially individuals should be advised to take snacks equivalent to 1 g/kg of carbohydrate and 0.3 g of protein per kg [229]. This snack should be taken with insulin as this increases CHO storage in the exercising muscles and liver [230]. Initially we recommend a third of their normal insulin to CHO ratio.

There is a risk of hypoglycemia several hours after exercise through an increase in insulin sensitivity. If individuals have exercised during the morning or early afternoon, they should monitor their blood glucose and take extra CHO as needed. If exercise has been undertaken in the late afternoon or evening, this may lead to nocturnal hypoglycemia. To prevent this people should reduce their evening background insulin by 10% or take extra carbohydrates before going to bed.

High-intensity aerobic and anaerobic exercise can lead to post-exercise hyperglycemia through increased hepatic glucose output and muscle insulin resistance, brought on by increased production of counter-regulatory hormones [231]. This means that additional insulin may be needed post exercise. Whilst there is currently no evidence to guide an insulin correction dose, we recommend starting with 30% of the usual correction dose for blood glucoses ≥14 mmol/L post exercise. Figure 26.7 shows a simple algorithm that brings together all this advice.

Specific considerations for people with type 2 diabetes

In individuals with T2DM, exercise does not usually cause hypoglycemia and so CHO supplementation is usually unnecessary. If blood glucose declines rapidly during exercise, as may occur in individuals taking oral hypoglycemic agents or insulin, the drug dosage should be reduced or withheld on exercising days.

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27 Monitoring Diabetes

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Key points

- Glycated hemoglobin (HbA_{1c}) levels are now reported using the International Federation of Clinical Chemistry standard expressed as mmol/mol of unglycated hemoglobin. The equivalent of the current HbA_{1c} levels of 6.5% and 7.5% are 48 mmol/mol and 58 mmol/mol.
- For people with type 1 diabetes (T1DM), blood glucose control should be monitored with measurement of HbA_{1c} every 2–6 months depending on the level and stability of blood glucose control and change in therapy.
- People with T1DM should be encouraged to self-monitor blood glucose with capillary blood glucose meters. With treatment regimens intended to produce intensive glycemic control, testing should be frequent (e.g. four or more times a day).
- For people with type 2 diabetes (T2DM), blood glucose control should be monitored using high precision methods for measurement of HbA_{1c} every 3–6 months depending on the level and stability of blood glucose control and change in therapy.
- For people with non-insulin-treated T2DM, self-monitoring of blood glucose is unlikely to be effective for most patients and should therefore not be used routinely and if used, only when training and support is available and a clear purpose for use identified.

Why monitor?

"The overall goal of diabetes management is to achieve as near normal physiological or ideal [glucose] values as possible, without detriment to quality of life and, for glucose control in particular, without causing significant hypoglycemia" [1].

Diabetes is a disorder of glucose homeostasis. It currently affects 415 million people worldwide and is expected to affect 642 million by 2040 [2]. For people without diabetes, glucose levels are maintained in the range of 4–6 mmol/L (80–110 mg/dL). When blood glucose levels increase as a result of glycogen conversion or eating carbohydrate-containing food, insulin is released restoring homeostasis through hepatic conversion of glucose to glycogen, and uptake of glucose into muscle and fat cells. Conversely, if blood glucose levels fall too low as a result of exercise or lack of food, glucagon is released causing hepatic conversion of glycogen to glucose.

The aim of monitoring in diabetes includes:

- allowing people with diabetes to understand the nature of their disorder;
- to determine the optimum times for initiating therapeutic intervention; and
- to guide the day-to-day adjustment of treatment.

Choosing the optimal target for monitoring and assay is important, not only to ensure the best outcomes for an individual, but at a population level, where small differences between the performance of tests, the frequencies with which they are carried out, and their costs may lead to important differences in outcomes and overall costs of care.

The topic of "monitoring in diabetes" could extend across the full range of clinical measurements required for optimal disease management including monitoring of lipids and blood pressure. However, there are specific issues associated with measurement of glycemia in diabetes that require special consideration. People with type 1 diabetes mellitus (T1DM) lack the normal homeostatic mechanism to control levels of blood glucose, while people with T2DM have an impaired or absent response to changing levels of glucose. In addition to insulin, which is the most important of the regulatory mechanisms, corticosteroids, glucagon, growth hormone, thyroxine, and catecholamines are counter-regulatory hormones and lead to increases in blood glucose levels. There is increasing evidence that these hormones are involved in a brain-centered glucoregulatory system [3].

Glycated hemoglobin (HbA_{1c}) and blood glucose are the two most frequently used measures of glycemia in current practice. Glycated hemoglobin provides information about overall control of glucose levels in the previous 6–8 weeks allowing assessment of the need for therapy and therapeutic response with minimal within-person variation in measurement. Blood glucose measurements provide information about the day-to-day level of control,

Textbook of Diabetes, Fifth Edition. Edited by R. Holt, C. Cockram, A. Flyvbjerg and B. Goldstein.

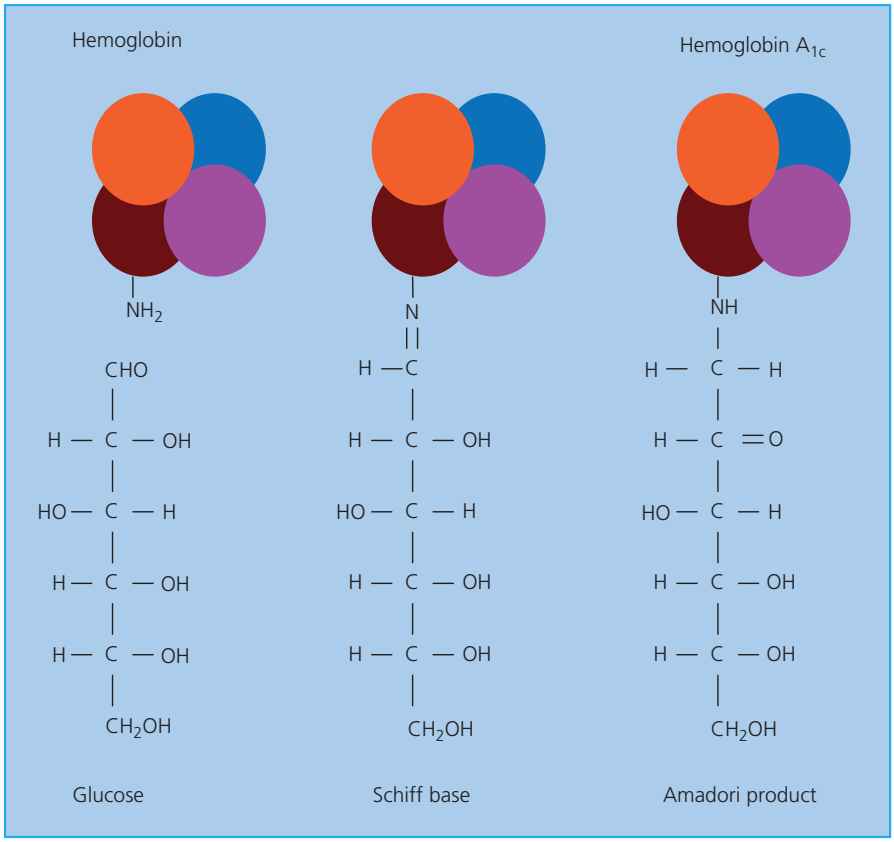

Figure 27.1 The Amadori reaction.

variation in control, and response to therapeutic intervention. This chapter will describe the tests for HbA_{1c} and glucose levels, the characteristics of these tests, the technology used in measuring their levels, and their clinical application in T1DM and T2DM.

Tests and their characteristics

Measurement of glycated hemoglobin

Quality controlled HbA_{1c} measurement has a central role in the management of diabetes, and increasingly a role in diagnosis of T2DM. HbA_{1c} levels are associated with the response to treatment and the risk of developing complications, and therefore provide an evidence-based marker with which to judge the impact of glucose lowering treatment, and prognosis. Its pivotal role derives from its use in reports of the major outcome studies that demonstrated the link between improved glycemic control and important clinical outcomes [4, 5].

Hemoglobin reacts spontaneously with glucose to form glycated compounds (or derivatives) in a non-enzymatic manner. The process occurs slowly, with the extent of glycation determined by the concentration of glucose in blood. Human hemoglobin A undergoes such glycation to form HbA_{1c} from a reaction between the β chain of hemoglobin A0 and glucose (Figure 27.1). Other compounds result from similar reactions on the α and β chains of hemoglobin and these can be measured as the total glycated hemoglobin.

Levels of glycated hemoglobin are measured as the proportion of glycated to total levels of hemoglobin. Formerly expressed as a percentage, the proportion is now increasingly expressed in the units of mmol per mol of unglycated hemoglobin. Work to standardize measurements of glycated hemoglobin to enhance its clinical application has overcome initial problems caused by a range of assays used and lack of agreement over a common reference standard. The publication of DCCT [5] in 1993 led to a number of countries developing national programs to standardize measurement that included external quality assurance schemes ensuring that measurements between laboratories could be compared [6]. As more advanced assays were developed the new reference method based on assaying a specific component of HbA_{1c} (the β-N-terminal hexapeptide) was established.

Despite the increasing standardization of HbA_{1c} measurement, there are over 30 different methods in use for measurement. Manufacturers provide calibration factors for individual machines, and there is a global network of laboratories that maintain and monitor the relationship between the different standards.

The new reference standard for HbA_{1c} agreed by the International Federation of Clinical Chemistry and Laboratory Medicine (IFCC) was introduced slowly over a period of time but is now increasingly accepted. It is expressed in the unit of mmol/mol. The new standard continues to be based on a proportion of glycated

Table 27.1 IFCC aligned values for HbA_{1c} and correlation of HbA_{1c} with estimated average glucose.

DCCT aligned HbA_{1c} (%)	IFCC HbA_{1c} (mmol/mol)	Estimated average glucose*	
		mg/dL	mmol/L
4.0	20	68	3.8
5.0	31	97	5.4
6.0	42	126	7.0
7.0	53	154	8.6
8.0	64	183	10.2
9.0	75	212	11.8
10.0	86	240	13.4
11.0	97	269	14.9
12.0	108	298	16.5

The estimated average glucose numbers are based on data from the ADAG trial [8].
The IFCC reference standard can be converted to the former DCCT aligned standard using the formula: IFCC-HbA_{1c} (mmol/mol) = [DCCT-HbA_{1c} (%) − 2.15] × 10.929.

to unglycated hemoglobin, but specifies the proportion of β-N-terminal hexapeptide that has been glycated.

The conversion equation between the IFCC units and DCCT % is:

$$\text{DCCT result (\%)} = (0.0915 \times \text{IFCC result in mmol/mol}) + 2.15$$

Hence the equivalent of the HbA_{1c} levels of 6.5% and 7.5%, commonly used as targets for glycemic control, are 48 mmol/mol and 58 mmol/mol in the new units (Table 27.1).

For both people with diabetes and clinicians, the new standard for reporting HbA_{1c} values has, in addition to clearly separating old and new assay values for HbA_{1c} levels by increasing the order of magnitude in which the measurements are expressed, also reduced potential confusion between reports of blood glucose levels in mmol/L and HbA_{1c} measurements. With the former reference range for HbA_{1c} it was relatively easy to confuse a blood glucose value given in mmol/L with an HbA_{1c} (%) value of a similar order but having different implications for clinical decision-making. By contrast, in countries that still use mg/dL, the potential for confusion is increased and this is one of the reasons why the American Diabetes Association has not adopted the new units. Nevertheless, a considerable education initiative continues to be needed to inform both people with diabetes and clinicians of the change.

In the United States the American Diabetes Association and the American Association for Clinical Chemistry recommend that HbA_{1c} (often referred to as A1C) can be reported with an estimated average glucose (eAG) result (Table 27.1) when a clinician orders the A1C test [7]. The mean plasma glucose numbers are based on data from the ADAG trial [8].

Table 27.2 Conditions that can affect the measurement of glycated hemoglobin.

Iron deficiency anemia
Hemoglobinopathies
Polycythemia
Blood transfusion
Hemolysis (hemolytic anemia)
Uremia caused by renal failure
High levels of vitamin C
HIV infection
Aging
Ethnicity

Analytical techniques and quality assurance for HbA_{1c} measurement

Accurate interpretation of glycated hemoglobin requires a normal lifespan of erythrocytes. The presence of a shortened lifespan, for example with hemolytic disease or blood loss, can lead to underestimates of the true value. By contrast, iron deficiency anemia, which is associated with a longer lifespan, can be associated with an overestimate of the true value. Other conditions, for example hemoglobin variants, uremia, hypertriglyceridemia, and chronic salicylate ingestion, can also lead to inaccurate results (Table 27.2), but specific assays (e.g. high performance liquid chromatography rather than immunochemistry or affinity chromatography methods) can be used in some cases to avoid the problem and obtain an accurate result. Laboratories still differ in whether a result from a heterozygous person with variant hemoglobin is reported as non-comparable to the Diabetes Control and Complications Trial/UK Prospective Diabetes Study (DCCT/UKPDS) standard, or whether it is not reported at all.

HbA_{1c} levels are higher among racial and ethnic minority groups with impaired glucose tolerance after adjustments for a wide range of demographic and risk factors compared to white Europeans [9]. Therefore, using a fixed threshold of 6.5% for the diagnosis of diabetes in different ethnic groups could lead to differences in proportions of people in different ethnic groups being diagnosed with diabetes when compared to use of an oral glucose tolerance test for diagnosis [10]. In addition, HbA_{1c} levels are associated with increasing age in non-diabetic populations, and so the extent to which age-specific diagnostic and treatment thresholds are needed, remains to be determined [11].

Glycated hemoglobin serves as a retrospective indicator of the average glucose concentration over the previous 6–8 weeks. Approximately 50% of the variance in HbA_{1c} is determined by the average blood glucose concentration over the previous month, 25% by the concentration over 30–60 days, and the remaining 25% by the concentration from 60–120 days [12].

Using a laboratory assay with high precision methods to measure glycated hemoglobin levels is recommended to assess the maintenance of glycemic control. Results should now be reported in IFCC units (mmol/mol) alongside the DCCT aligned (%) units. In addition to laboratory-based analyzers, there is now a range of

Table 27.3 Values for diagnosis of diabetes mellitus.

	Glucose concentration (mmol/L)*			
	Plasma		Whole blood	
Time of measurement	Venous	Capillary	Venous	Capillary
Fasting	≥7.0	≥7.0	≥6.1	≥6.1
2 h after a glucose load	≥11.1	≥12.2	≥10.0	≥11.1

*1 mmol/L = 18 mg/dL.

handheld or desk-based analyzers that can be used in an office or bedside setting. The rationale for using these meters is to allow changes in treatment within the consultation, or to allow measurement of HbA_{1c} levels where transport of blood to a laboratory is not possible or laboratory facilities are not available [13].

Measurement of fructosamine

Albumin is the main component of plasma proteins. Albumin contains free amino groups that can react non-enzymatically with glucose to form fructosamine. Measurement of fructosamine reflects glucose levels over the previous 1–3 weeks. Fructosamine measurement is not appropriate for routine use because the assay is markedly affected by excessive turnover or excretion of albumin in, for example, renal disease. In addition, fructosamine assays are not standardized in the same way as HbA_{1c} assays. Fructosamine testing remains useful in a number of circumstances, for example in pregnancy where glucose requirements change rapidly, or in the preconception period where motivation to improve control is high and the changes can be evaluated at shorter intervals. With the lower cost and increased standardization of HbA_{1c}, however, it is possible that more frequent measurements of HbA_{1c} may be an alternative strategy, particularly if evaluating potentially large improvements in the blood glucose over the preceding 4–6 weeks contributing to a clinically important change from a previous HbA_{1c} result [14].

Measurement of blood glucose

Blood glucose (or the level of glucose to which the body's organs are exposed) is expressed as the plasma glucose concentration. Blood samples for analysis of glucose levels need to be taken under controlled conditions. Red blood cells may continue to metabolize glucose after collection, continuing glycolysis, and thus leading to an apparent reduction in reported glucose levels from those at the time of collection. The continuing glycolysis should be avoided by rapid centrifugation, collection onto ice and storage in a refrigerator. If blood is to be transported at room temperature it should be collected into fluoride-containing tubes that inhibit further glucose metabolism. If a patient has an intravenous line *in situ*, blood should be drawn from the arm opposite to the one with the line to prevent contamination of the sample from any infusion.

Blood glucose measurement is a term that is frequently used without precise definition. Measurement of glucose levels is usually carried out either on capillary or venous samples of blood. Most laboratories measure the level of glucose in plasma, which again differs from measurements made on whole blood. Table 27.3 shows the equivalent measurements from the different sites and samples taken.

Blood glucose levels are expressed in SI units (from the French, *Le Système International d'Unités*) as millimoles/liter (mmol/L). The traditional unit for measuring blood glucose is milligrams/decilitre (mg/dL), although use of these units is now largely confined to the USA. To convert mmol/L glucose to mg/dL, multiply by 18 (Table 27.1).

Sampling and preparation of the sample affect measurement. Whole blood glucose is also affected by the concentration of protein (mainly hemoglobin) in the sample. Whole blood concentrations are therefore 12–15% lower than plasma concentrations. Venous blood glucose levels are normally similar to arterial and capillary levels when fasting. The arterial and capillary levels most closely reflect the glucose concentrations at the organ level. After meals, venous blood will have lower glucose concentrations than arterial blood and can be as much as 10% lower.

Analytical techniques and quality assurance for measuring glucose levels

A range of analytical techniques is used for the laboratory measurement of blood glucose concentration. Chemical oxidation or reduction methods have a low cost for reagents and, although less specific, are still valid. Enzymatic analysis of glucose is more specific, although more expensive. The enzymatic reference method for glucose is the hexokinase/G6PDH method. The glucose oxidase methods are comparable, although the presence of reducing substances may cause error. Glucose oxidase methods are frequently used because of their convenience and lower cost. Measurements are accurate and precise with measurement coefficient of variance of around 2%. Electrochemical techniques now predominate [15] and underpin the technology in handheld glucose sensors. Self-measurement of blood glucose is possible using capillary blood glucose meters with test strip systems. Specific issues associated with their use are considered in the next section. Some meters now incorporate the facility to measure blood ketone levels, of particular importance for people with T1DM.

Other meters have the facility to calculate insulin bolus requirements or to download blood glucose results for charting using a computer.

Most of the currently marketed handheld capillary blood glucose meters give results as an equivalent to venous plasma glucose but this is not always the case. The same type of handheld meter may be calibrated to report whole blood glucose in one country and plasma values in another. The calibration of a meter should be checked and the thresholds for action set accordingly.

Measurement of blood glucose in a hospital setting

In a hospital or "site-of-care" setting, capillary blood glucose measurement can be used to replace venepuncture, with greater comfort and more rapidly available results for monitoring patients in an acute situation. Standards have been laid down to ensure that bedside glucose determinations can be made accurately and include the need for well-defined policies which include adequate training, quality control procedures, and regular maintenance of equipment [16]. Some meters used in hospitals support quality assurance procedures by restricting access to trained personnel and transferring the results directly to the electronic patient record.

Blood glucose meters may require entry of a number or insertion of a coding chip to ensure calibration to the batch of testing strips used—although most meters, particularly those now used as handheld devices by people with diabetes, do not now require this extra step.

Self-monitoring of blood glucose

Self-monitoring of blood glucose (SMBG) is now an integral part of self-care for people with T1DM to maintain levels of blood glucose that minimize risks of complications. In addition it is required for people with T2DM using insulin, and for some people with T2DM who have specific indications [7]. Carrying out regular SMBG requires a high level of motivation from a person with diabetes and so its use needs to be carefully discussed and supported [7]. Effective SMBG technique, awareness of how to interpret the results, and a knowledge of action needed on the results obtained are essential for the procedure to be both clinically and cost-effective.

People with diabetes need to be taught how to perform SMBG testing accurately and how to use the data to adjust therapy in relation to food intake and physical activity. Correct technique involves obtaining the blood sample from the side of the finger pulp, wiping and using the second drop of hanging blood, using the meter correctly and disposing of the lancet (Figure 27.2). Alternative sites for sampling include the base of the thumb, forearm, and thigh. Pre-meal readings will be the same between sites, but at times of rapid glucose change (in the postprandial period or during hypoglycemia) forearm and thigh results will be different from the fingertip results, because glucose changes lag behind the fingertip results.

Figure 27.2 Correct technique for self-monitoring of blood glucose improves accuracy of testing.

Measurement issues associated with point of care meters

Although laboratory methods of blood glucose measurement are more accurate than capillary blood glucose meters, their convenience and rapidity of use can, in some circumstances, outweigh their higher coefficient of variance. Therefore, despite a slight reduction in accuracy compared to laboratory testing, and the possibility of user error, they are in wide use. The majority of meters conform to international standards (www.iso.org), with 95% of readings <4 mmol/L (<72 mg/dL) within 0.83 mmol/L (15 mg/dL) of the true result, and within 20% of the true result for higher glucose readings. The newer meters have minimized the possibility of user error by requirement for smaller volumes of blood for measurement and automated calibration methods. Operator error, however, remains a significant source of error, including failure to calibrate meters (most meters do not now require external calibration), poor hand-washing technique and dirty meters [17].

Careful training and consistent technique in making measurements can minimize measurement error. Allowance for the possibility of error in the reading when calculating an insulin dose on the basis of a meter reading should be made. Regular testing should be carried out so that results that do not fit the usual pattern can be identified, with retesting as necessary.

Despite their imprecision, blood glucose meters remain particularly helpful at higher blood glucose values, where, for example, it is of less importance to distinguish a plasma glucose of 11 mmol/L (198 mg/dL) from one of 14 mmol/L (252 mg/dL). In such circumstances, the aim of management is to achieve a substantial reduction in plasma glucose. At lower plasma glucose levels, however, the consequences of an imprecision of 15% are much greater. For many people with well-controlled diabetes aiming to keep

their glucose levels in the range 4–6 mmol/L (72–108 mg/dL), the majority of readings below 4 mmol/L (72 mg/dL) will result from the variance of the measurement rather than reflecting a true "low" value.

Measurement of urinary glucose

Measurement of glucose in urine has limited arguments in favor of its use for routinely monitoring diabetes. It is rapid, inexpensive, non-invasive, and can provide a quantitative result; however, it does not reflect the changing levels of hyperglycemia with any accuracy and so interpretation may be difficult if not impossible. In addition, the renal threshold varies between individuals and varies during pregnancy and with aging. In any case, glucose is not excreted renally at levels where blood glucose is significantly elevated above that which should be targeted to minimize diabetic complications.

Urine fraction should be analyzed immediately, preserved at pH < 5 to inhibit bacterial metabolism or stored at 4 °C. The enzyme used is glucose oxidase/peroxidase, which may lead to false-positive results with hydrogen peroxide and false-negative test results with the presence of ascorbic acid.

Urine testing should no longer be used in most healthcare settings because of the availability of alternative and more accurate tests. For the moment it may have a role in resource-poor settings where identification and treatment of individuals with poorly controlled diabetes is the highest priority.

Monitoring in clinical practice

Effective monitoring of glycemic control requires a partnership between the healthcare professional and the person with diabetes. Optimal regimen and the balance between use of laboratory testing and self-monitoring require consideration of a range of factors extending from, at the one end wholly clinician-directed testing (e.g. during acute illness in a hospital setting) to self-monitoring for a person with diabetes in the community who is otherwise well. The importance of self-management should not be underestimated; attempts by hospital clinicians to take over monitoring of a patient during an admission otherwise unconnected with diabetes can lead to conflict, as can attempts by a clinician in the community to direct testing in someone whom they might only see once or twice a year, where inappropriate testing may have no useful purpose.

Monitoring in type 1 diabetes

People with T1DM should be encouraged to practice SMBG using capillary blood glucose meters. With treatment regimens intended to produce intensive glycemic control, testing should be frequent (e.g. four or more times a day) [18].

People treated with insulin need to measure, interpret and take appropriate action to adjust their insulin dose on a regular basis at home. Detailed records of blood glucose measurements and actions are needed to allow review by both the person with diabetes and their clinician. Blood glucose measurements are particularly helpful in situations where frequent adjustment of therapy is needed. Fasting blood glucose measurements are important in judging the effectiveness of longer-acting insulin therapies. Pre-prandial blood glucose levels are often equated with, but are not equivalent to, fasting blood glucose levels, which require an 8-hour fast. Pre-prandial measurements may be useful for evaluating the impact of a complex insulin schedule, particularly with fast-acting insulin analogs.

When using a typical basal bolus regimen, including three injections of short-acting insulin and one or more injections of long-acting insulin at least four time-points during the day, blood glucose levels need to be monitored, pre-breakfast, pre-lunch, pre-dinner, and before bedtime. Comparison of pre-prandial readings with 1–2 hour postprandial measurements provides a guide to the response to the short-acting insulin. Frequent glucose testing allows identification of periods during the day when plasma glucose levels are higher or lower than ideal and appropriate adjustment of the short-acting or bedtime injections. If the individual has regular routines and varies little in food intake and physical activity from day to day, then monitoring can take place at a frequency of less than four tests a day; for example, a daily fasting blood glucose with four-point sampling on either 1 or 2 days a week, or each day testing at one or more additional time-points to build a picture over the week. Until the dose of long-acting insulin has been established, a series of paired bedtime and fasting readings are needed to allow it to be adjusted to an optimal dose.

Tight control brings with it the risk of hypoglycemia [19]. Additional checks on blood glucose levels should be made in relation to the risk of hypoglycemia, for example, before exercise or driving and in the presence of symptoms that may indicate hypoglycemia. For some people (limited duration of life, inability to make the adjustments required for tight control) intensive control is inappropriate. Accepting less tight control allows the use of less complicated regimens and less frequent monitoring. For individuals using conventional rather than long-acting insulin analogs, and with biphasic regimens more frequent monitoring may be required because of the less stable time course of the long-acting components of the insulin.

For people with T1DM, the overall level of glycemia should be measured with a HbA_{1c} test every 2–6 months [7, 18] depending on the level and stability of blood glucose control and change in therapy. HbA_{1c} measurement should be provided either at site-of-care or carried out by the laboratory before clinical consultation. Glycated hemoglobin measurement for people with T1DM complements blood glucose measurement. The HbA_{1c} measurements provide additional checks on the extent to which glucose results are giving an accurate picture of overall blood glucose control. A record of recent blood glucose measurements indicating good control may need to be re-examined if a HbA_{1c} measurement does not indicate a corresponding level of good control. For example, timing of blood glucose measurements and measurement technique may need reassessing.

Adults with T1DM should be encouraged to achieve and maintain a HbA_{1c} target of 48 mmol/mol (6.5%) or lower to minimize risk of long-term complications, but individualized targets should be agreed based on lifestyle and previous experience of hypoglycemia [18]. Optimal target ranges for blood glucose monitoring for adults are for fasting blood glucose levels, 5–7 mmol/L (90–126 mg/dL), 4–7 mmol/L (72–126 mg/dL) before meals and 5–9 mmol/L (90–162 mg/dL) after meals [18]. Targets for children (aged 0–12 years) are higher because of the high risk of and vulnerability to hypoglycemia. Adolescents and young adults are at particular risk with developmental and psychological issues, but should nevertheless aim for good glycemic control <58 mmol/mol (<7.5%). Optimal target ranges for blood glucose monitoring for children are for fasting blood glucose levels, 4–7 mmol/L (172–126 mg/dL) (or 5–7 mmol/L (90–126 mg/dL), if intending to drive), 4–7 mmol/L (72–126 mg/dL) before meals and 5–9 mmol/L after meals (90–162 mg/dL) [18].

Monitoring diabetes in a hospital setting

Critically ill patients should have blood glucose levels maintained between 7.8 and 10.0 mmol/L (140 and 180 mg/dL) although in those centers with more experience in glucose control, a lower target of 6.1–7.8 mmol/L (110–140 mg/dL) may be aimed for provided that there is no increase in the incidence of severe hypoglycemia (see Chapter 34). For non-critically ill patients the target glucose level should be between 6.0 and 10.0 mmol/L (108 and180 mg/dL), with a level of 4.0–12.0 mmol/L (72–216 mg/dL) being acceptable for medical patients and for awake surgical patients. Concerns about hypoglycemia mean that some institutions have concern about the safety of these goals as initial targets.

Self-management of diabetes in the hospital setting may be appropriate where adult patients are alert, able to self-manage their diabetes at home, and have stable requirements for insulin. This may also provide an opportunity for providing support in learning techniques of insulin adjustment in line with carbohydrate intake.

Monitoring diabetes in a community setting

Glycated hemoglobin and SMBG testing are the two primary techniques for monitoring success in achieving glycemic goals, adjusting therapy and providing information to support lifestyle change. Meters to test HbA_{1c} are now available in a clinic setting. However, there is as yet insufficient evidence for their use in this way unless there are problems in obtaining laboratory measurement [20, 21].

Continuous blood glucose measurement in type 1 diabetes

The need to provide more frequent SMBG measurements to document glucose excursions and guide insulin therapy has led to the development of innovative technologies that can provide up to 300 measurements a day. Detailed data on the magnitude and duration of glucose fluctuations can be used to guide lifestyle and drug therapy in an attempt to produce a near-physiologic control of plasma glucose.

There are a number of different systems currently available. All require calibration using capillary blood glucose measurement and utilize a subcutaneously implanted sensor that can remain *in situ* for up to 7 days. This usually transmits data to a wireless monitor. All the continuous glucose monitoring (CGM) systems are intended for intermittent use in order to identify periods of hyperglycemia that can be corrected by changing therapy (e.g. increasing the dose of insulin or changing timing of injections), or detecting periods of biochemical hypoglycemia that may be too brief to cause symptoms but may nevertheless cause some impairment in cognitive function. The devices are not as accurate as a conventional blood glucose meter, and so blood glucose levels should be confirmed before a change in treatment.

Other technologies are now available for interstitial glucose measurement. These include the FreeStyle® Libre device that includes a sensor worn for up to 2 weeks. It is designed for continuous use, does not require calibration, but is scanned, giving readings over the previous 8 hours, using a handheld device that avoids the need for a direct connection between a sensor and the recording device.

Evidence for effectiveness of CGM in selected people with T1DM aged over 25 years using intensive insulin therapy comes from a randomized trial with 322 people with T1DM in which those allocated to the CGM arm experienced a 0.5% (6 mmol/mol) reduction in HbA_{1c} from 7.6 to 7.1% (60 to 54 mmol/mol) compared to conventional therapy [22]. Evidence for HbA_{1c} lowering is less strong in children, teenagers and younger adults, although there may be specific clinical circumstances in which CGM might be helpful. Success correlates with adherence to the ongoing use of the device. Many people with T1DM indicate that CGM is a valued addition to diabetes care with a perceived improvement in HbA_{1c} and reduction in hypoglycemia [23].

CGM systems are now being evaluated as a sensor within a closed-loop system in which insulin delivery through a pump device is regulated by the use of a control algorithm that automatically reduces and increases subcutaneous insulin delivery according to sensor glucose levels. Recent short-term studies in young adults with diabetes in a home setting indicate that glucose control is improved during the day and night with fewer episodes of hypoglycemia [24].

Monitoring in type 2 diabetes

For people with T2DM, the overall level of glycemia should be monitored with a test for the level of HbA_{1c} every 3–6 months depending on the level and stability of blood glucose control and change in therapy [7, 18]. An interval of 3 months between tests is usually recommended following changes in therapy or when levels are unstable, although a test after 2 months may provide some additional information [12, 25]. HbA_{1c} measurements should be provided, usually through a laboratory assay before clinical consultation. There is now an increasing range of point of care devices

available that could be used to provide immediate feedback on glucose levels, although the pragmatic value of these devices in optimizing care in comparison to that based on HbA_{1c} laboratory assay has not yet been evaluated. However, in the absence of timely laboratory measurement of HbA_{1c}, then point of care devices are feasible to use and sufficiently accurate to guide treatment.

Setting HbA_{1c} targets for people with T2DM is important to guide decisions about treatment and to provide feedback to patient and clinician about the effectiveness of treatment. The level at which targets should be set for an individual remains widely debated. Although guidelines provide advice about generally accepted targets, individuals need to be involved in decisions about their own HbA_{1c} target. Once available, the results of tests should be used to encourage people to achieve and maintain their target unless they develop hypoglycemia. In addition to pharmacotherapy, attention to lifestyle should be maintained at all stages of treatment. As levels of HbA_{1c} rise above the selected target, then advice about diet, lifestyle, and adherence to medicines should be further stressed, and increase in treatment considered.

The clinical implications of glycemic variability remain uncertain. Although there are claims that long-term variability in glucose levels are associated with an increased risk of complications, the only evidence available is for an increased risk of hypoglycemia. In addition, there is no evidence that targeting glucose variability leads to improved outcomes.

If HbA_{1c} measurement is unavailable, then a fasting plasma glucose measurement can be used to indicate need for, or response to a treatment that leads to a reduction in fasting hyperglycemia (e.g. metformin or a sulfonylurea). A fasting capillary plasma glucose level of 3.9–7.2 mmol/L is recommended as a target for control.

Glucose monitoring is now infrequently recommended for routine monitoring in non-insulin-treated T2DM where HbA_{1c} testing is available. It continues to have a place where there are concerns about hypoglycemia (e.g. use of sulfonylurea) or HbA_{1c} measurements are not possible or do not provide an accurate measure of glycemia. Although some behavioral feedback on the impact of lifestyle and of drug treatment is available to people with diabetes through SMBG, the additional benefit of doing this routinely alongside standard care has not been demonstrated in rigorous clinical trials and the debate around this issue is discussed in the following section.

Self-monitoring of blood glucose in insulin-treated type 2 diabetes

For people with T2DM who are using insulin, SMBG is needed to adjust insulin dose and check that good control is maintained, although optimal use remains to be established. The recommended schedules for monitoring are derived from trials that have sought to achieve reductions in HbA_{1c} to within recommended levels [26]. The intensity of these schedules has not yet been evaluated in wider populations and those more representative of primary care populations. Fasting blood glucose levels carried out twice a week will allow weekly or 2-weekly titration of long-acting insulin to achieve tight control. Additional 4- or 7-point profiles may be helpful every 3–4 weeks to identify patterns of blood glucose control that require further attention, for example, to address the possibility of hypoglycemia or to identify high levels of postprandial glucose that may require the use of pre-meal short-acting insulin.

Continuous glucose monitoring systems are now being used as a research tool among people with T2DM, but the extent to which the procedure is useful to the person with diabetes or to the clinician remains unclear and its use cannot be recommended in routine clinical practice. Advocates of the procedure suggest that it might be useful as a means of helping people to recognize aspects of their lifestyle that lead to hyperglycemia [27].

Self-monitoring of blood glucose in non-insulin-treated type 2 diabetes

SMBG use for people with T2DM was initially explored to see whether patients might use it to gain a greater understanding of their diabetes and how best to control it, for example by weekly or 2-weekly adjustments of the dose of oral glucose reducing treatment. HbA_{1c} measurement was less widely available when SMBG was first used in this way. Additional proposals for using SMBG in management of T2DM have been put forward based on deductions from physiological observations. For example, blood glucose levels are usually high following meals, and thus contribute to overall blood glucose control. Some studies have therefore been interpreted to suggest that postprandial glucose levels correlate with development of complications better than fasting blood glucose levels (or that glycemic variability may be related to poor outcomes). Attempts to titrate oral hypoglycemic medication by taking account of post-meal measures, however, have not been successful [28].

Where HbA_{1c} measurement is not available, then SMBG may be an option for some people with T2DM. For people with non-insulin-treated T2DM, the within-person coefficient of variation of fasting (pre-breakfast) blood glucose levels is low and measurements vary little from day to day. Measurement of blood glucose levels with a personal meter is therefore a means of assessing day-to-day control and making adjustments to therapy or assessing the impact of lifestyle changes. The frequency of fasting blood glucose measurement for non-insulin-treated T2DM has been suggested from once a week to once a day. The evidence for a particular frequency of testing, however, is lacking, and individual variations (familiarity with ensuring measurement techniques, variation in lifestyle, availability of professional help in supporting patients in interpretation of measurements) will require that a judgment be made on the precise purpose of monitoring. However, using SMBG rather than HbA_{1c} measurement in this way is less preferred by many people with diabetes, and is costly.

Clinical trials over the past 20 years or more among people with T2DM comparing management programs based on the use

of SMBG with management programs not using SMBG suggest that, overall, it has a small and clinically unimportant effect. Systematic reviews report the pooled effect sizes from a wide range of trials in differing settings in support of this conclusion [28]; analyses using patient-level data from the major studies of SMBG also confirm the overall effect is small and do not identify groups who may find SMBG of particular help [30]. An additional concern is that, for some individuals, particularly where regular support and guidance is not available, levels of anxiety can be increased and quality of life reduced [31, 32].

Guidelines for treatment of people with T2DM now draw attention to the lack of evidence for effectiveness and cost-effectiveness of routine use of SMBG [7] and recommend that it should not be routinely used [18]. Where there are concerns that the treatment may lead to hypoglycemia (e.g. use of sulfonylureas) or where HbA_{1c} cannot be used, then SMBG may be helpful, but only where the person with diabetes has been trained in its use, where the purpose is clear, and with regular review for continuing need.

Use of HbA_{1c} in the diagnosis of diabetes

Although current guidance continues to support the diagnosis of diabetes based on at least two laboratory measurements of blood glucose ≥7 mmol/L or random samples of ≥11.1 mmol/L (Table 27.3), there is increasing attention to HbA_{1c} as an alternative approach for diagnosis of T2DM in non-acute settings, for example in screening for diabetes. Improved standardization in the measurement of HbA_{1c} and wider availability of the assay led to a recommendation in 2011 by the World Health Organization that HbA_{1c} could be used instead [33]. HbA_{1c} offers a potentially easier, non-fasting and therefore more acceptable test. Furthermore, there appears to be less intra-individual variation with HbA_{1c} than glucose testing.

Previously, there were concerns that despite the variation in results of oral glucose testing within the same person, the alternative of a single HbA_{1c} test would be unsatisfactory because the threshold for screening (previously identified as 53 mmol/mol [7%]) would have missed a substantial number of people with diabetes. There is also considerable potential for confusion, because current guidance for people with diabetes is to aim, if possible, for HbA_{1c} levels of 48–58 mmol/mol (6.5–7.5%). There has been wide debate about the threshold that should be used, including detailed comparisons of the levels of glycemic control, assessed by different measures that are associated with complications [34]. Some organizations have made specific recommendations for a diagnostic level of 48 mmol/mol (6.5%) [35] (with a requirement for the result of a single abnormal test to be confirmed by a second test), but it is likely that judgments about an appropriate threshold may need to differ between countries. A diagnostic test based solely on using HbA_{1c} will not replace the glucose criteria, as in many parts of the world HbA_{1c} is not available and the need for a glucose-based test in T1DM and in an acute setting, where HbA_{1c} may be falsely negative because of rapidly changing glucose, remains [36, 37].

Gestational diabetes mellitus

Women with diabetes should be advised to test fasting blood glucose levels and blood glucose levels 1 hour after every meal during pregnancy (see Chapter 61). They should be able to adjust their insulin dose to maintain target blood glucose levels. Many oral glucose-lowering medicines are not recommended for use during pregnancy, particularly during the first trimester, and so early training in the use of SMBG and insulin therapy is necessary.

Use of continuous glucose monitoring systems has also been evaluated for pregnant women with insulin-treated diabetes. In a randomized trial those women randomized to continuous glucose monitoring had lower mean HbA_{1c} levels from 32 to 36 weeks' gestation compared with women randomized to standard antenatal care. The authors concluded that continuous glucose monitoring during pregnancy is associated with improved glycemic control in the third trimester, lower birth weight, and reduced risk of macrosomia [38].

Monitoring of diabetes in special situations

Policies and practice for monitoring diabetes, and particularly T2DM may need to change in special situations. HbA_{1c} testing may be unavailable because of difficulties in transport to the laboratory or because laboratory facilities are not available. HbA_{1c} measurement with point of care meters or use of blood glucose testing may be appropriate as an alternative. However, consumables for these meters are expensive. Fasting blood glucose assays are required to assess blood glucose control accurately for people not using insulin.

The costs of SMBG using handheld meters remain high in relative terms, and using it in a resource-poor setting may not be appropriate. Particularly for people with T1DM, there is an urgent need for lower cost test strips, although a requirement for rigorous quality control procedures to maintain accuracy of the assay limits the potential for lower cost equipment.

Urine glucose testing remains an alternative to blood testing or HbA_{1c} measurement for people with diabetes in a country where healthcare resources are limited, or in a healthcare setting where costs of testing equipment are borne directly by the individual with diabetes. There are few data on self-monitoring using urine glucose testing. A meta-analysis from 2005 [33] included two studies that compared SMBG and self-monitoring of urine glucose and reported a non-significant reduction in HbA_{1c} of 2 mmol/mol (0.2%) in favor of SMBG. Although some people do not find the procedure acceptable or helpful [34], a recent study compared SMBG with urine testing and found no added advantage from SMBG, with 80% of participants finding urine testing acceptable and continuing with it [39]. Measurement of urine glucose should therefore not be seen as a substitute for SMBG, but can be used as an alternative where SMBG is not accessible, affordable, or desired. Interpretation of information needs to be focused on the period between last voiding and the production of the current urine specimen. Most people have a renal threshold for glucose of around

8 mmol/L, so information about glucose levels is limited below this threshold. The renal threshold can drop during pregnancy, and so glycosuria is more likely in this situation.

The future of monitoring in diabetes

Current research is focusing on a number of non-invasive methods to enable continuous monitoring. Methods being considered include using infrared, electric currents, and ultrasound. Currently available continuous monitoring systems require calibration, but are then able to record blood glucose levels at 5-minute intervals for up to 72 hours. Efforts are currently being made to improve and further develop integrated systems with glucose meters linked by wireless communication to insulin pumps and with computer algorithms recommending infusion rates. Computerized algorithms for controlling insulin pumps on the basis of blood glucose levels have been developed and have already been evaluated in the setting of intensive care. There is increasing emphasis on integrating novel approaches to monitoring with digital health initiatives. For example, mobile phones have also been linked to blood glucose meters to allow easy review of charted data, real-time feedback of support, and integration of data with medical records [40]. Linkage of monitoring devices, systems for decision support and Internet-linked communication promises better and more efficient use of results, alongside better communication. A series of proof-of-concept studies have indicated the potential for Internet-linked digital devices to improve care, although evidence for implementation at a wider scale, with integration into routine care remains limited [41, 42]. However, despite the increasing availability of technology, optimal strategies for monitoring, and how it can best be used to support behavioral change requires more work [43].

In some clinical areas uptake of telehealth has already been rapid. For example, the period of monitoring required for gestational diabetes is relatively short and many women who are pregnant have access to smartphones. As a result, systems intended to support better monitoring are being developed and evaluated. A recent example has demonstrated that remote monitoring of glycemia by a midwife is acceptable [44], and can lead to more frequent review of insulin treatment than would otherwise be possible with routine hospital visits [45].

Conclusions

Glycemic control should be monitored regularly for all people with diabetes. The optimal method of determining risk of long-term complications is through HbA_{1c} measurement, although if this is not available, then examination of a series of blood glucose measurements, including fasting tests, may provide guidance. Decisions about treatment depend on the clinical setting and the type and stage of the individual's diabetes. People with non-insulin-treated T2DM have little scope for adjusting therapy on the basis of routine SMBG measurements, although some may benefit from exploring the extent of their glycemic variability, monitoring impact of changes in physical activity and diet, self-titration of glucose-lowering medication or checking whether symptoms are related to low blood glucose readings. For adults with T1DM and pregnant women treated with insulin, the evidence for active and regular blood glucose testing (including use of continuous glucose monitoring) to achieve intensive blood glucose control through adjustment of insulin dose in relation to lifestyle is strong. There is also good evidence for the routine use of SMBG for people with insulin-treated T2DM.

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28 Drug Therapy: Special Considerations in Diabetes

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Key points

- Many drugs interfere with glucose homeostasis or interact with antidiabetes agents and thus can disturb glycemic control in people with diabetes. Specific diabetic complications, such as nephropathy and neuropathy, may require particular drugs to be used with care.
- Hyperglycemia can be caused or worsened by numerous drugs. Those that induce insulin resistance include glucocorticoids, certain oral contraceptives, antipsychotics, HIV protease inhibitors, the fluoroquinolone gatifloxacin, and β-adrenoceptor antagonists. Diabetogenic drugs that damage the β cell include pentamidine and cyclosporine (ciclosporin).
- Sulfonylureas and related agents commonly cause hypoglycemia by interacting with other drugs that block their metabolism in the liver, for example ciprofloxacin inhibits CYP2C9, which degrades glyburide (glibenclamide), or that impair renal function and decrease their elimination (e.g. non-steroidal anti-inflammatory agents).
- Hypoglycemia can be induced by drugs that stimulate insulin secretion (e.g. quinine, especially in children with cerebral malaria) and sulfamethoxazole, which binds to the sulfonylurea receptor. Pentamidine can induce transient hypoglycemia, by causing passive loss of insulin from the β cell, as a prelude to permanent diabetes.
- Hypoglycemia can complicate overdosage with acetaminophen (paracetamol), following hepatic necrosis; or aspirin, which blocks hepatic glucose output and stimulates peripheral glucose uptake. Alcohol inhibits hepatic gluconeogenesis and can provoke, prolong, or exacerbate hypoglycemia.
- Non-selective β-adrenoceptor antagonists inhibit insulin secretion and can impair glucose tolerance. They also decrease certain catecholamine-mediated symptomatic and metabolic responses to hypoglycemia; awareness of hypoglycemia may therefore be reduced, and recovery of normoglycemia delayed. These adverse effects are much less pronounced with cardioselective β_1-adrenoceptor antagonists.
- Angiotensin-converting enzyme inhibitors and angiotensin receptor blockers, relative to other antihypertensive drug classes, are associated with a lower risk of new-onset diabetes and are useful in heart failure and nephropathy.
- Certain drugs require special consideration in people with diabetic complications. Metformin and several sulfonylureas are cleared through the kidney; they are therefore contraindicated in advanced nephropathy and should not be co-administered with nephrotoxic drugs. Vasodilators and ganglion-blocking agents may exacerbate postural hypotension.

Introduction

This chapter discusses the problems posed by drug therapy in the management of people with diabetes. Numerous drugs can affect diabetic control, causing hyperglycemia or hypoglycemia, by interfering with insulin secretion or action or both, or by interacting with antidiabetes agents. Some important examples are illustrated in Figure 28.1. The special considerations that apply when using other drugs in people with diabetes and in the presence of specific diabetic complications are also discussed.

Drugs that raise blood glucose concentrations

Drug-induced diabetes is recognized as a distinct etiologic category, and diabetogenic drugs are discussed in detail in Chapter 19. The main culprits are shown in Table 28.1. Most of these drugs—notably glucocorticoids (a common and important cause of iatrogenic diabetes), contraceptive steroids, and β-adrenoceptor antagonists—act by inhibiting insulin action. By contrast, insulin secretion is inhibited by diazoxide, while pentamidine can cause permanent β-cell damage. More recently, antipsychotic drugs,

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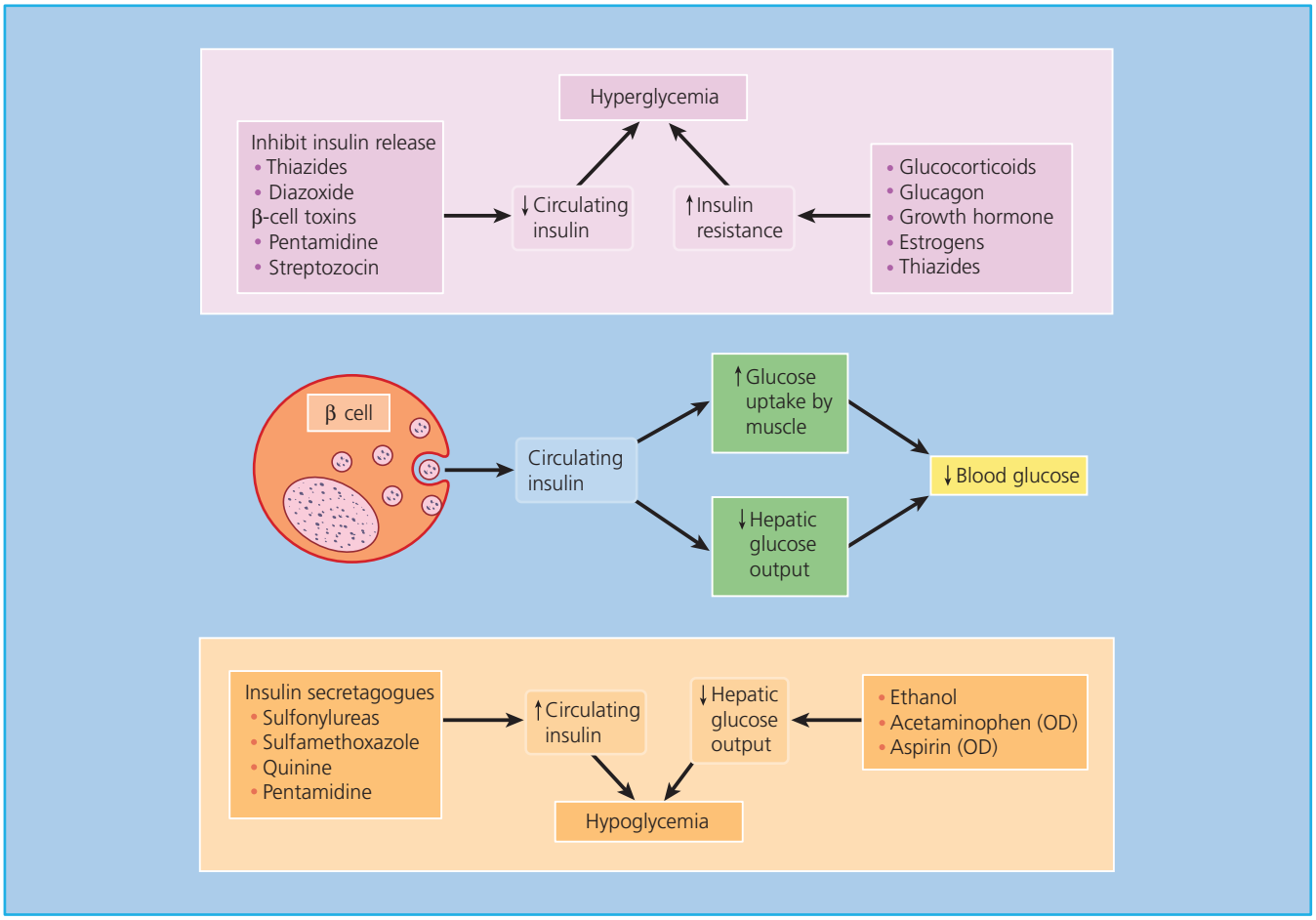

Figure 28.1 General mechanisms of drug-induced hyperglycemia and hypoglycemia. OD, overdose.

HIV protease inhibitors, and the fluoroquinolone antibiotic gatifloxacin have emerged as important causes of hyperglycemia.

Drugs that lower blood glucose concentration

Many drugs can cause hypoglycemia (Table 28.2) [1–11]. These include some that interact with and enhance the action of glucose-lowering drugs. Others act in their own right as insulin secretagogues, or to enhance or mimic the effect of insulin in suppressing glucose production by the liver and stimulating glucose uptake into peripheral tissues. Some drugs (e.g. non-selective β-adrenoceptor antagonists) specifically block the warning symptoms or the neuroendocrine counter-regulatory responses that are normally triggered by hypoglycemia, and so can prolong and intensify hypoglycemic episodes.

Drugs should always be suspected whenever people with previously well-controlled diabetes experience unexplained hypoglycemic episodes, or if dosages of insulin or oral antidiabetes agents decline. As well as prescription drugs, patients should be asked about herbal, traditional, and other alternative medicines. These are now widely used by people with diabetes, up to one-third of participants in one study [12], and some products may contain naturally occurring or synthetic glucose-lowering agents (Table 28.3).

Sulfonylureas

Sulfonylureas are an important and sometimes unrecognized cause of symptomatic hypoglycemia (see Chapter 35). They are also affected by numerous interactions with other drugs (Figure 28.2).

The older long-acting sulfonylureas glibenclamide and chlorpropamide are especially troublesome. In one outpatient survey, 20% of people treated with glibenclamide experienced hypoglycemia in the previous 6 months [13], while other surveys suggested that tolbutamide caused fewer episodes of severe hypoglycemia than either glibenclamide or chlorpropamide [14, 15]. A Swiss study [16] defined the risk of severe hypoglycemia as two episodes per 1000 persons per year in those given glibenclamide, over twice as high as in those taking shorter-acting sulfonylureas such as tolbutamide, gliclazide, or glipizide. The newer sulfonylurea, glimepiride, is said to carry a relatively low risk of

Table 28.1 Drugs that may cause or exacerbate hyperglycemia.

Potentially potent effects	Minor or no effects
Glucocorticoids	Growth hormone (physiologic doses)
	Somatostatin analogs†
	Androgen deprivation therapy for prostate cancer
Oral contraceptives	Oral contraceptives
High-dose estrogen	Progestogen-only pills
	Levonorgestrel in combination pills
Thiazide diuretics (especially high dosages)*	Loop diuretics
Non-selective β-adrenoceptor antagonists	α_1-Adrenoceptor antagonists
β_2-Adrenoceptor agonists	Calcium-channel blockers
Salbutamol	
Ritodrine	
Antipsychotics	Selective serotonin reuptake inhibitors and other antidepressants
HIV protease inhibitors	Lamivudine
Indinavir, nelfinavir, ritonavir and others	
Others	
Pentamidine	Isoniazid
Gatifloxacin	Nicotinic acid
Streptozotocin	
Diazoxide	
Cyclosporine ciclosporin)	
Tacrolimus	
Temsirolimus	
Interferon-α	
L-Asparaginase	

* "High" dosages of thiazides correspond to ≥5 mg/day bendroflumethazide or >25 mg/day hydrocholorothiazide.
† Somatostatin analogs may induce hyperglycemia in type 2 diabetes but not type 1 diabetes.

Table 28.2 Drugs that may cause or exacerbate hypoglycemia.

Anti-diabetes drugs
Insulin
Sulfonylureas
Meglitinides
DPP-4 inhibitors
GLP-1 receptor agonists
SGLT2 inhibitors

Drugs that interact to enhance the actions of sulfonylureas (see also Table 28.4)
Quinolone antibacterials: Levofloxacin, Gatifloxacin [4]
Corticosteroids, including inhaled corticosteroids (when withdrawn may lead to adrenal insufficiency) [5, 6]

Other drugs
Aspirin (in overdosage)
Cibenzoline
Disopyramide
Doxycycline [7, 8]
Etanercept
Ethanol
Hydroxychloroquine
Imatinib
Mefloquine
Non-selective β-adrenoceptor antagonists
Paracetamol (in overdosage) – Acetaminophen
Pentamidine
Quinidine
Quinine
Sulfamethoxazole (in co-trimoxazole)
Valproate (in neonates exposed *in utero*) [9]
Venlafaxine (in overdosage) [10]

hypoglycemia because it binds to a different site on the sulfonylurea receptor from classic sulfonylureas and also has distinct pharmacokinetic properties. Nonetheless, 10–20% of people receiving this drug still experience at least one mild episode each year [17].

Several factors other than the drug itself can increase the risk of hypoglycemia from sulfonylureas, notably increasing age and renal impairment [14, 15, 17–19]. Reduced food intake during intercurrent illness can also contribute [18, 19]. Drug interactions that enhance the action of sulfonylureas are considered below.

Not all those who have sulfonylurea-induced hypoglycemia are people with type 2 diabetes (T2DM); "bystanders" have included toddlers who ate a grandparent's tablet [20], nursing-home residents given the treatment of other patients [21], and people whose prescriptions for other drugs have been misread [22].

Sulfonylurea-induced hypoglycemia can be profound and prolonged, and difficult to manage. People with sulfonylurea-induced hypoglycemia may require admission and treatment with glucose until the effect of the sulfonylurea has worn off. Insulin hypersecretion induced by sulfonylureas can be suppressed effectively with either diazoxide (which opens the β-cell K_{ATP} channel that is closed by sulfonylureas) [23, 24] or by the somatostatin analog octreotide [25].

Other antidiabetes agents

These are described in Chapter 31.

- *Metformin* used alone is not expected to cause hypoglycemia in therapeutic use; but the UK Prospective Diabetes Study (UKPDS) reported instances of unconfirmed hypoglycemia during metformin treatment [26].
- *Thiazolidinedione* (e.g. pioglitazone) potentiates the peripheral actions of insulin. It does not induce hypoglycemia alone, but can enhance hypoglycemia caused by sulfonylureas or insulin when used in combination with them.
- *Meglitinides* (e.g. repaglinide) stimulate insulin release by a mechanism distinct from that of the sulfonylureas and so causes hyperinsulinemic hypoglycemia. A case of factitious hypoglycemia from repaglinide has been reported [27].

Table 28.3 Some herbal medicinal products and food supplements that can potentially interact with antidiabetes drugs to affect blood glucose concentrations.

Name	Effect on blood glucose
Alfalfa	↓
Aloe vera	↓
Basil	↓
Bee pollen	↑
Bitter melon	↓
Burdock	↓
Celandine	↓
Celery	↓
Coriander	↓
Cornsilk	↓
Damiana	↓
Dandelion	↓
Devil's claw	↑
Elecampane	↑
Eucalyptus	↓
Fenugreek	↓
Figwort	↑
Garlic	↓
Ginseng, Eleutherococcus	↓
Ginseng, Panax	↓
Gotu kola	↑
Guar gum	↓
Horehound	↓
Hydrocotyle	↑
Juniper	↓
Licorice	↑
Marshmallow	↓
Melatonin	↓
Myrrh	↓
Myrtle	↓
Nettle	↓
Night-blooming cereus	↓
Onion	↓
Sage	↓
St. John's wort	↑
Tansy	↓

Source: Data from Ernst E. The Desktop Guide to Complementary and Alternative Medicine. An Evidence-Based Approach. Edinburgh: Mosby, 2001.

- *Acarbose* inhibits intestinal disaccharidase, and so reduces the hydrolysis of sucrose and thus glucose absorption. It does not cause hypoglycemia when used as monotherapy. People treated with acarbose who develop hypoglycemia from other glucose-lowering drugs should be warned that oral glucose, not sucrose, is needed to treat the episode.
- *Incretin mimetics* (e.g. exenatide, liraglutide) are agonists of the glucagon-like peptide-1 (GLP-1) receptor. They enhance the pancreatic insulin response to glucose in the gut. They slow down stomach emptying and stimulate insulin secretion. Unlike insulin, they do not tend to cause hypoglycemia. They promote weight loss and in rodent models and increase pancreatic β-cell mass. The major disadvantages are nausea, the need for subcutaneous injections, and the high cost.
- *DPP-4 inhibitors* increase the circulating levels of incretins by inhibiting dipeptidyl peptidase 4 (DPP-4), the enzyme that breaks down incretins and other peptides. The oral route of administration is an advantage, with low risk of hypoglycemia and no weight gain. Furthermore, their efficacy and overall safety has been demonstrated in several large multi-center randomized clinical trials [28–30].
- *Sodium/glucose cotransporter 2 (SGLT2) inhibitors, or gliflozins,* inhibit glucose reabsorption in the kidney and thereby increase glucose loss in the urine. This reduces blood glucose levels in people with T2DM. The calorific loss also leads to decrease in body weight and blood pressure. There is an increased incidence of urinary tract infection and vulvovaginitis. Hypoglycemia is uncommon, but euglycemic ketoacidosis, although rare, needs to be recognized. This class should be avoided in people with insulin deficiency. Although trials in type 1 diabetes (T1DM) are ongoing, until these are reported, SGLT2 inhibitors should not be used in people with T1DM.

Other drugs

Antimicrobials

- *Quinine and quinine derivatives*. People with falciparum malaria are often extremely ill, and may have hypoglycemia because of the effects of cytokines and malnutrition, both of which diminish hepatic gluconeogenesis. In this context, it is easy to overlook quinine-induced hypoglycemia, which can be profound, especially in children [31, 32]. It is caused by insulin hypersecretion, as quinine has insulin secretagogue activity [33]. Octreotide (a long-acting somatostatin analogue) has been used successfully to inhibit insulin release and raise blood glucose concentrations under these conditions [34]. Quinidine and mefloquine may occasionally cause hypoglycemia, while chloroquine does not [32].
- *Sulfamethoxazole*, which is combined with trimethoprim in co-trimoxazole, has a sulfonylurea-like action and can stimulate insulin secretion; several cases of severe hypoglycemia have been described [35]. This tends to be long-lasting, especially when excessive amounts of glucose solution infused can paradoxically worsen hypoglycemia by further stimulating insulin secretion. Elderly individuals receiving high dosage, and those in renal failure (which causes the drug to accumulate) are at particular risk [36], as are people infected with HIV who receive high doses of co-trimoxazole to treat *Pneumocystis jirovecii* pneumonia (formerly known as *Pneumocystis carinii*) [37].
- *Pentamidine*, a drug used to treat and prevent *P. jirovecii* pneumonia, can also damage pancreatic β cells. This initially leads to the passive leakage of insulin out of secretory vesicles, causing hypoglycemia, but diabetes may develop subsequently [38]. In two series of people with HIV treated with pentamidine, 25% [39] and 14% [40] developed symptomatic hypoglycemia; they invariably developed renal damage from the drug as well. Even inhaled pentamidine can cause hypoglycemia [41].

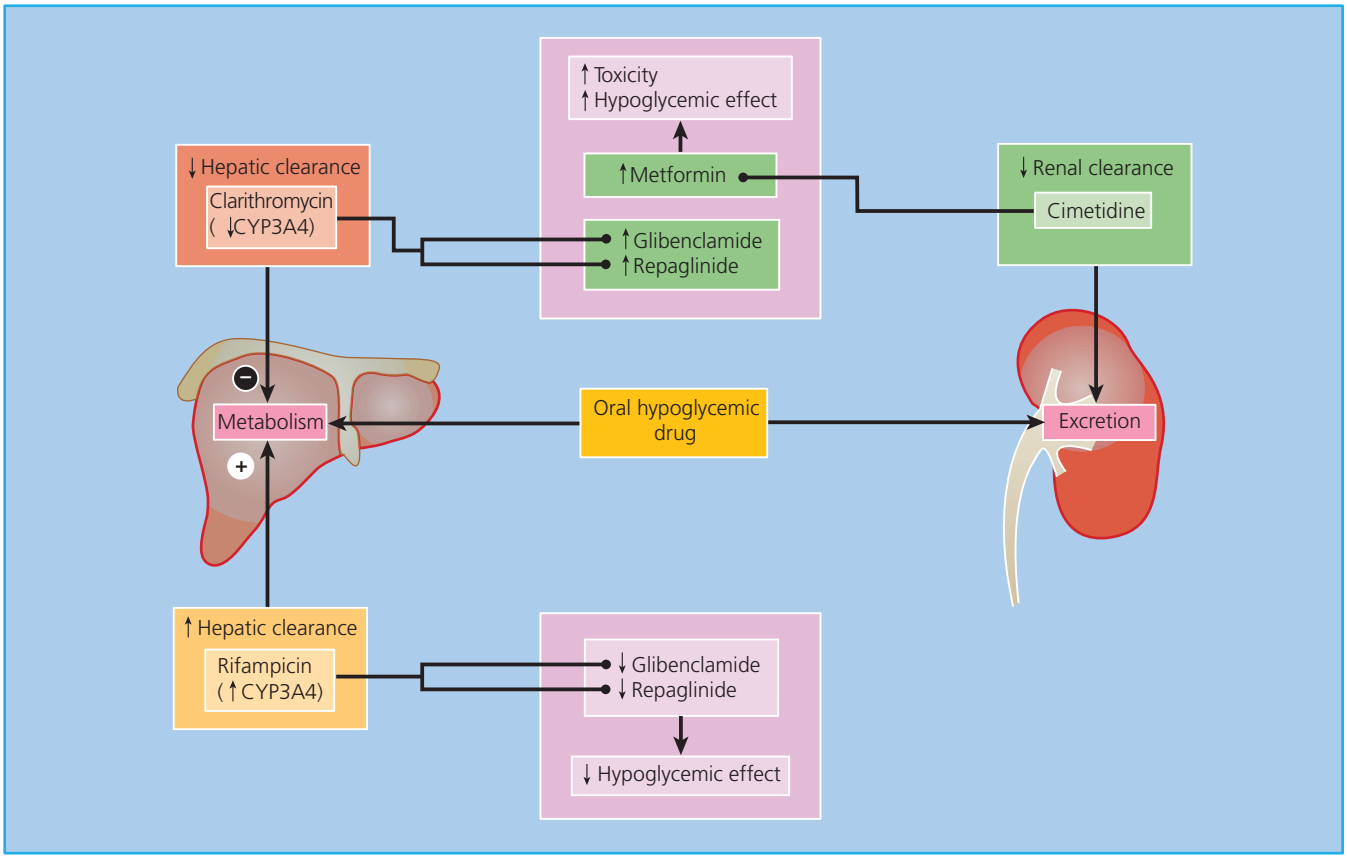

Figure 28.2 Interactions between oral antidiabetes agents and other drugs.

• *Doxycycline* has been suggested to cause hypoglycemia, but the reaction is infrequent and no mechanism has been identified [42].
• *Quinolones*, particularly gatifloxacin, can cause hypoglycemia (and also hyperglycemia). A case–control study defined an adjusted odds ratio for hypoglycemia with gatifloxacin treatment of 4.3 (95% confidence interval [CI]: 2.9–6.3) compared with macrolide treatment [4]. There is also a small increase in risk with levofloxacin.

Miscellaneous drugs

• *Disopyramide* and *cibenzoline* (*cifenline*), class Ia antiarrhythmic agents, can rarely cause symptomatic hypoglycemia; this can occur either with or without hyperinsulinemia [43], suggesting that peripheral effects contribute. In healthy people, disopyramide produces a small but statistically significant fall in fasting glucose concentration [44]. In a Japanese case-control study, cibenzoline treatment was associated with an eightfold increased risk of hypoglycemia; disopyramide did not significantly increase the overall risk, but the confidence intervals were wide [45]. The effect of disopyramide appears to be dose-dependent. In one case, a man developed severe hypoglycemia while taking disopyramide only after starting treatment with clarithromycin, a known inhibitor of hepatic enzymes, for an intercurrent infection [46].
• *Antidepressants*, including monoamine oxidase inhibitors, selective serotonin reuptake inhibitors and nefazodone, have been reported to reduce blood glucose concentrations [47].

Drugs in overdose

• *Acetaminophen* (*paracetamol*), in overdose, can cause hypoglycemia as a complication of acute hepatic necrosis. Overdosage of *aspirin* and other salicylates inhibits hepatic glucose production and also increases peripheral glucose utilization, leading to hypoglycemia, especially in children. Paradoxically, for unknown reasons, hyperglycemia can be encountered in adults.
• *Ethanol* inhibits gluconeogenesis and so it can cause hypoglycemia in children or fasting adults and exacerbate hypoglycemia from another cause even when consumed in relatively modest amounts (see Chapter 58). Results of experimental studies are unclear: modest concentrations of ethanol impaired the growth hormone response to insulin-induced hypoglycemia in volunteers with T1DM, but did not affect glucagon response [48]. The same dose of ethanol impaired the glucagon, but not growth hormone (GH), response to the same degree of hypoglycemia in people with diet-treated T2DM [49]. Rebound hypoglycemia can follow 2–3 hours after drinking alcohol with a glucose load in the form of sweet drinks or foods—so-called "gin-and-tonic hypoglycemia" [50]. Alcohol ingestion also increases the risk of severe

brain damage or death in people who take an intentional overdose of insulin [51].

Non-pharmacopoeial drugs

Some "herbal," "traditional," and "folk" remedies contain compounds with glucose-lowering properties that are generally weak (Table 28.3) [52]. Some preparations, however, have caused severe hypoglycemia and have been found on analysis to contain an undeclared sulfonylurea [53].

Drug interactions that affect blood glucose concentrations

Drug–drug interactions can cause hyperglycemia or hypoglycemia through several mechanisms. Pharmacokinetic interactions can influence the effective concentrations of a glucose-modifying drug; examples are the increased concentrations of disopyramide following co-administration of clarithromycin, as described earlier, and the large number of drugs that increase or decrease circulating concentrations of sulfonylureas (see following section).

Pharmacodynamic interactions occur when the observed action of one drug is modified by the action of another, without a change in the circulating concentration of either. The drugs can act at the same site (e.g. sulfamethoxazole is a ligand at the SUR-1 sulfonylurea receptor) or at different sites. Examples of the latter include β-adrenoceptor antagonists and other drugs that influence the physiologic response to hypoglycemia, and so alter the duration or severity of hypoglycemia from another cause.

Drugs that interact to enhance the actions of insulin secretagogues

Many drugs have pharmacokinetic or pharmacodynamic interactions with sulfonylureas that can cause clinically important disturbances in glycemic control. Some of the more important examples are shown in Table 28.4 and Figure 28.2. The commonest outcome is hypoglycemia, brought about by reduced metabolic or renal clearance. Transient effects from displacement of protein-bound drug may occasionally also be important. Major dangers include the potentiation of the effects of tolbutamide, and possibly of chlorpropamide, glibenclamide, and glipizide, by azapropazone (apazone), chloramphenicol, and fluconazole. Miconazole interacts with glibenclamide and glipizide as well as tolbutamide. All these interactions are caused by the inhibition of sulfonylurea metabolism in the liver. Several oral hypoglycemic agents, including glimepiride, glipizide, glibenclamide, tolbutamide, and nateglinide, are metabolized by CYP2C9. Thus, ciprofloxacin increases the plasma concentrations and therefore enhances the hypoglycemic action of glibenclamide by inhibiting the hepatic CYP2C9 enzyme that metabolizes glibenclamide [54]. Clarithromycin has also been reported to interact with glibenclamide and glipizide, leading to hypoglycemia [55]. A meta-analysis confirms that hypoglycemia is more likely with glibenclamide than other insulin secretagogues (relative risk (RR) 1.52; 95% CI: 1.21–1.92) [55].

Table 28.4 Drugs that interact with sulfonylureas.

Drugs that may enhance the hypoglycemic effect of sulfonylureas
Azapropazone, phenylbutazone
Salicylates
Probenecid
Sulfonamides
Clarithromycin
Nicoumalone
Fluconazole, ketoconazole, miconazole, voriconazole
Fluoxetine
Drugs that may reduce the hypoglycemic effect of sulfonylureas
Rifampicin
Chlorpromazine

By contrast, rifampicin reduces the action of glibenclamide by inducing CYP2C9 and enhancing the hepatic clearance of sulfonylurea. Chlorpromazine also decreases the glucose-lowering effect of sulfonylurea, possibly by inhibiting insulin secretion.

Another important interaction with chlorpropamide (and, to a much lesser extent, with other sulfonylureas) is the cutaneous vasodilatation of the face and occasionally the trunk that is induced by ethanol, the chlorpropamide–alcohol flush (see Chapter 31).

Some individuals may be more susceptible to drug-induced hypoglycemia than others. For example, a Japanese case-control study suggested that people taking levothyroxine and who also had liver disease were at substantially increased risk of mild hypoglycemia, with an odds ratio of 14.7 (range 1.6–137) [56]. Individuals with genetically determined low CYP2C9 activity are at an increased risk of sulfonylurea-associated severe hypoglycemia [57].

Surreptitious ingestion of sulfonylureas such as glibenclamide in alternative medicines can cause hypoglycemia [58].

Interactions with metformin

Metformin is excreted in the kidneys through the organic cation transporter 2 (OCT2). Cimetidine reduces the renal clearance of metformin, and causes it to accumulate (Figure 28.2). Drugs that impair renal function, such as non-steroidal anti-inflammatory agents and aminoglycosides, should be used with care, as they can also raise metformin concentrations, increasing the risk of lactic acidosis. Metformin should be stopped 24 hours before prolonged fasting (e.g. before surgery) and 48 hours before procedures requiring intravenous radiocontrast media. People receiving metformin are advised to avoid alcohol or to drink in moderation as hepatic damage poses a risk of hypoglycemia and lactic acidosis.

Interactions with other antidiabetes agents

- *Rosiglitazone* is metabolized by the hepatic microsomal enzyme CYP2C8, raising the theoretical possibility of interaction with other agents metabolized by this enzyme such as paclitaxel [59].

- *Repaglinide* is metabolized by CYP3A4, which also metabolizes glibenclamide and several other important drugs, and is then excreted in the bile. Clarithromycin, which inhibits CYP3A4, has been reported to increase repaglinide concentration and the risk of hypoglycemia [60]. Rifampicin, which induces the same enzyme, reduces the effective concentrations of repaglinide by 25% in healthy volunteers, and could potentially worsen glycemic control in those with T2DM [60]. Repaglinide is also metabolized by CYP2C8, and so its plasma concentration can be increased by inhibitors of CYP2C8 such as gemfibrozil or clopidogrel. Such an interaction can result in hypoglycemia [60].
- *Glimepiride* is broken down by CYP2C9 and so its metabolism can be inhibited by fluconazole and its hypoglycemic action enhanced [61].
- Among the DPP-4 inhibitors, *sitagliptin* has low potential to interact with CYP3A whilst *vildagliptin* and *linagliptin* are not metabolized by cytochrome P450 (CYP450). *Alogliptin* is metabolized by CYP2D6 to one active metabolite and through acetylation to one inactive metabolite. *Saxagliptin* is metabolized by CYP3A4/5 in liver to an active metabolite and therefore a dose reduction is recommended to avoid hypoglycemia when co-administered with strong CYP3A4 inhibitors such as ketoconazole and clarithromycin, whilst glycemic control may deteriorate if CYP3A4 inducers such as carbamazepine, rifampicin, and phenytoin are prescribed [62].
- The new class of agents, SGLT2 inhibitors, are also in general less affected by drug–drug interactions. Both *dapagliflozin* and *canagliflozin* are metabolized through glucuronidation by uridine diphosphate-glucuronosyltransferase (UGT) 1A9. Since potent inhibitors of UGT1A9 are rare, clinically relevant interactions are infrequently reported [63]. Clinical studies so far have also noted absence of any relevant drug–drug interactions with *empagliflozin* [64].

Hazards of general drugs when used in people with diabetes

The presence of diabetes can influence the choice of agent for treating several important conditions. Drugs to treat cardiovascular diseases, hypertension, angina, arrhythmias, and heart failure, and hyperlipidemia are of particular importance, because these conditions are common in people with diabetes.

Drugs with cardiovascular actions

Antihypertensive agents

Calcium-channel blockers

In vitro and *in vivo* studies have suggested that calcium-channel blockers may impair glucose metabolism, possibly because of impaired insulin secretion. Very few cases of clinically significant hyperglycemia, however, have been reported, and most of these were associated with excessive dosages of the drugs. When used appropriately, calcium-channel blockers are as safe in people with and without diabetes (see Chapter 42). In people of Asian or African origin, calcium-channel blockers are relatively more efficacious in lowering blood pressure. This is especially relevant in populations that have a high incidence of stroke.

Angiotensin-converting enzyme inhibitors

ACE inhibitors are now widely used to treat hypertension and heart failure in both people with and without diabetes. The evidence of benefit of ACE inhibition after myocardial infarction, in systolic ventricular dysfunction and chronic heart failure is strong [65–67]. Similarly, ACE inhibitors reduce proteinuria and the endpoint of doubling of serum creatinine, or the need for dialysis or transplantation [68]. This protective effect on the kidney is encouraging their use in normotensive people with early nephropathy (see Chapter 39). By contrast, the use of ACE inhibitors in people with coronary heart disease without systolic ventricular dysfunction remains controversial. Two large randomized controlled trials showed reductions in cardiovascular events [69, 70], but this was not confirmed in a third trial [71].

ACE inhibitors do not cause hyperglycemia, and neither do they adversely affect lipid metabolism [72, 73]. Indeed, there is some evidence from the HOPE study that ACE inhibitors may reduce the likelihood of new-onset diabetes [74]. The DREAM study, which specifically addressed this issue, did not confirm this. In comparison with diuretics and beta-blockers, the effect is striking. ACE inhibitors can improve insulin sensitivity and lower blood glucose concentrations, occasionally causing severe hypoglycemia [75, 76]. Case-control studies in the Netherlands and Scotland have demonstrated a threefold increase in the risk of severe hypoglycemia (requiring hospital admission) in people with diabetes taking ACE inhibitors [77, 78].

In people with or without diabetes, ACE inhibitors are contraindicated if the renal arteries are stenosed because of the high risk of renal impairment, which is usually reversible but sometimes permanent. There may be significant renal artery stenosis in up to 20% of individuals with both hypertension and T2DM [79].

Angiotensin receptor blockers

Like ACE inhibitors, ARBs are also indicated for hypertension, heart failure, post-myocardial infarction, and diabetic nephropathy [80]. One study showed a marked reduction in stroke and mortality in people with diabetes on an ARB-based regimen [81]. There is also evidence from meta-analysis that ARBs reduce the risk of new-onset diabetes [82]. There are no trials demonstrating that ARBs are superior to ACE inhibitors in terms of outcome. On the other hand, ARBs do not cause the characteristic dry cough associated with ACE inhibitors. Combining an ACE inhibitor and an ARB has no demonstrable value in coronary heart disease or diabetic nephropathy, other than reducing urinary albumin excretion further [83, 84]. Furthermore, it may be associated with significant hyperkalemia.

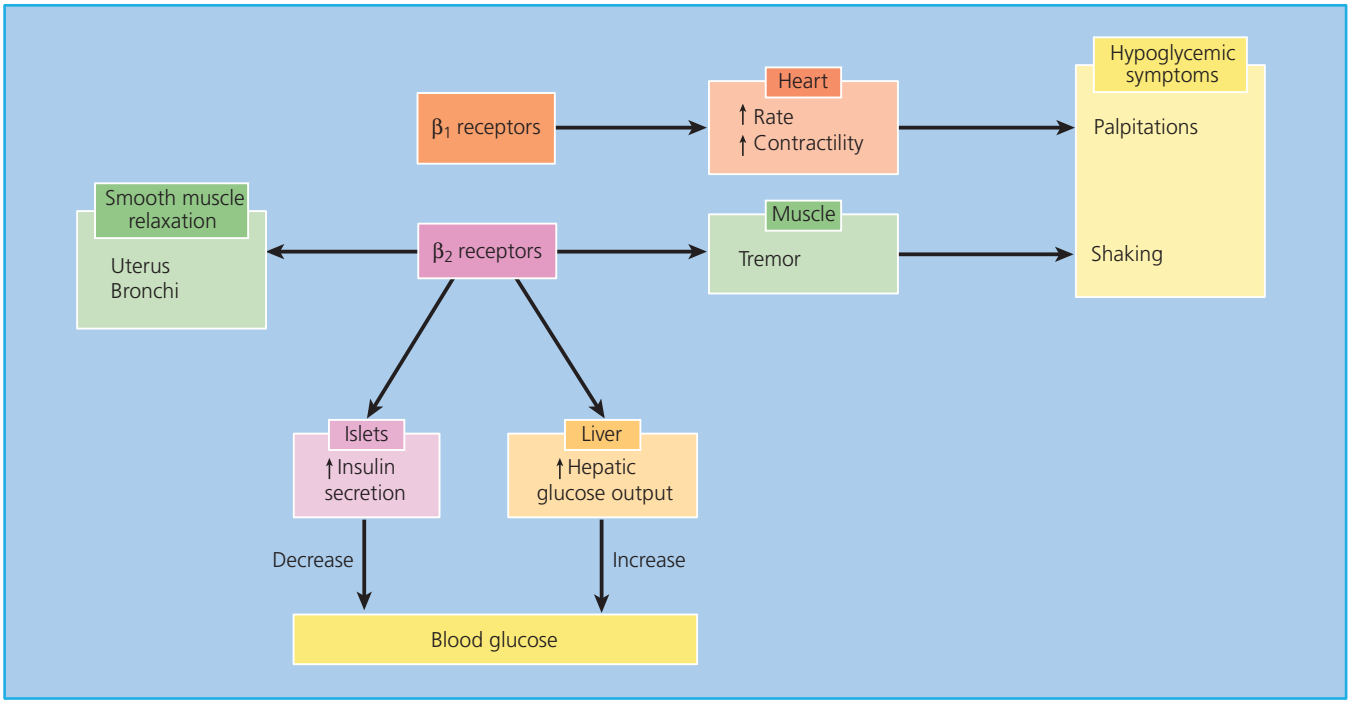

Figure 28.3 Effects mediated by β-adrenoceptors.

β-*Adrenoceptor antagonists*

These are useful in the treatment of hypertension, angina, arrhythmias, and heart failure. They are effective cardioprotective agents that reduce mortality following myocardial infarction in people with and without diabetes [85, 86]. β-Adrenoceptor antagonists are indicated in those with chronic heart failure as they improve left ventricular function and reduce mortality [87]. The β-adrenoceptor antagonists should be started in stable patients, at a very low dose and escalated gradually.

β-Adrenoceptor antagonists can interfere with several aspects of glucose homeostasis (Figure 28.3). In the islets, insulin secretion is enhanced by β_2-adrenoceptor stimulation, while the β_2-adrenoceptor-mediated response to hypoglycemia in the liver promotes hepatic glycogenolysis and increases hepatic glucose output, a crucial part of the counter-regulatory response that restores blood glucose to normal.

Long-term treatment with β-adrenoceptor antagonists, especially in combination with high-dose thiazide diuretics, has been shown to be diabetogenic. This is discussed further in Chapter 19. β-Adrenoceptor antagonists were used in combination with thiazide diuretics in most of the early large clinical trials of hypertension treatment. In clinical trials testing a β-adrenoceptor antagonist on its own, its effect on stroke was less favorable than comparative drugs. This led to its relegation to fourth-line treatment in the fourth British Hypertension Society guidelines [88]. In people with diabetes, their effect on insulin resistance may make them a less suitable choice than an ACE inhibitor or ARB. People with diabetes require good blood pressure control to reduce macrovascular complications, so multiple drugs might be needed to achieve this. In such instances, a beta-blocker could be added. People with diabetes frequently have ischemic heart disease, which is another indication for β-adrenoceptor antagonists.

β-Adrenoceptor stimulation is responsible for major hypoglycemic symptoms: the pounding heart and palpitation are secondary to β_1-adrenoceptor-mediated increases in heart rate and contractility, while tremor and sweating are both β_2-mediated (sweating also has a cholinergic component) (Figure 28.3). Non-selective β-adrenoceptor antagonists that antagonize both β_1- and β_2-receptors can reduce the awareness of hypoglycemia and also delay recovery from hypoglycemia.

Cardioselective β_1-adrenoceptor antagonists are less likely to interfere with awareness of or recovery from hypoglycemia, and so are preferable in those treated with insulin or sulfonylureas. Even low doses of cardioselective β_1-adrenoceptor antagonists can modify some of the symptoms and signs of hypoglycemia (e.g. tachycardia), while other symptoms that are robust indicators of hypoglycemia (e.g. sweating) are unchanged or even more pronounced in the presence of β_1-blockade [89, 90]. Overall, cardioselective β-adrenoceptor antagonists rarely impair recognition of hypoglycemia. The incidence of hypoglycemia is not increased during treatment with β_1-selective adrenoceptor antagonists, even in those prone to the condition [91, 92]. By contrast, the non-selective drugs can impair recovery from hypoglycemia [89, 93, 94].

Concerns about the adverse metabolic effects of β_1-selective adrenoceptor antagonists have probably been exaggerated and the

potential benefits of their cardioprotective effects underplayed [85]. Moreover, studies in heart failure have now provided extensive data showing that low-dose β-adrenoceptor antagonists are safe in the elderly [95].

α_1-*Adrenoceptor antagonists*

α_1-Adrenoceptor antagonists are effective hypotensive agents. They are generally thought to have beneficial metabolic effects, including improved insulin sensitivity, with falls in blood insulin, glucose and lipid concentrations [96–98], although one report [99] has suggested that the use of doxazosin may worsen glycemic control in people with diabetes. Despite their potential advantages, these drugs are not currently in extensive use, perhaps because of the side effect of postural hypotension. In the Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT), the α-blocker arm of the study was prematurely terminated because of an increased incidence of congestive heart failure compared to the diuretic arm [100]. This probably reflects the benefit of diuretics in treating the symptoms of heart failure rather than worsening of heart failure by α-adrenoceptor antagonists.

Thiazides

It has become unfashionable to use thiazide diuretics in people with diabetes, even though they are generally well tolerated, inexpensive, and at least as effective as newer agents in preventing stroke and myocardial infarction. The concerns are the reversible impairment of glucose tolerance that can occur with thiazides, unfavorable changes in serum lipid profile and the worry that they may cause erectile dysfunction [101–118]. Many of these concerns stem from old trials in which high doses of thiazide diuretics (e.g. 5 mg bendroflumethiazide) were used.

The diabetogenic potential of the thiazides is discussed in detail in Chapter 19. The consensus is that low dosages (e.g. 2.5 mg bendroflumethiazide), which are just as effective as higher dosages in lowering blood pressure, cause little if any deterioration in glycemic control [119]. The effects on lipids of low dosages are minor, and outweighed by the benefits of blood pressure reduction [116, 117, 120]. Finally, one large study (Treatment of Mild Hypertension Study) found no excess of erectile dysfunction attributable to thiazide treatment among middle-aged hypertensive men, who had a high prevalence incidence of this complaint [118]. Overall, the thiazides have a useful place in the treatment of hypertension in people with diabetes [121].

Loop diuretics

Loop diuretics, such as furosemide (frusemide), ethacrynic acid, and bumetanide, seem to have less impact on glucose homeostasis than thiazide diuretics, although several reports suggest that they can cause hyperglycemia [122, 123]. Recent *in vitro* studies have shown that furosemide inhibits enzymes in the glycolytic pathway [124], leading to poor glucose utilization and hyperglycemia. In practice, however, few problems are encountered in using loop diuretics in people with diabetes; it has been argued that any insulin resistance and hyperglycemia are not actually drug-induced, but instead are the consequence of the conditions that require potent diuretic therapy.

Antihyperlipidemic agents

The relationship between diabetes mellitus and dyslipidemia is discussed in detail in Chapter 43. Hypertriglyceridemia is often ameliorated by the effective treatment of hyperglycemia; conversely, some evidence indicates that lowering lipids (including free fatty acid concentrations) can improve blood glucose control. In practice, drugs are often prescribed independently for diet-resistant hyperglycemia and hyperlipidemia and so interactions between agents used to treat the conditions are potentially important.

Statins

People with diabetes have elevated cardiovascular risk. Statins (hydroxymethyl-glutaryl coenzyme A inhibitors) are therefore usually indicated, even before there is overt cardiovascular disease. Meta-analysis has shown that people with diabetes benefit from statin therapy [125], but has also revealed a small increase in the risk of developing diabetes in people without diabetes, particularly when high-dose statins are used [126]. Overall, the cardiovascular protection outweighs the slight increase in the risk of developing diabetes.

Fibrates

People with diabetes tend to have a dyslipidemic lipid profile characterized by raised triglycerides and low HDL cholesterol. Studies of fibrates showed some benefit in cardiovascular event prevention [127], but fibrates do not lower LDL cholesterol as effectively as statins and the combined use of a fibrate and a statin increases the risk of myositis. The Fenofibrate Intervention and Event Lowering in Diabetes (FIELD) study tested if fenofibrate was beneficial in people with diabetes [128]. Although fenofibrate was safe, even when used in combination with a statin, it did not significantly reduce the risk of the primary outcome of coronary events. It appeared to reduce non-fatal myocardial infarctions and revascularizations [128]. In the Action to Control Cardiovascular Risk in Diabetes (ACCORD) Lipid Trial, adding fenofibrate to simvastatin did not reduce the rate of major cardiovascular events compared with simvastatin alone [129]. These two important trials suggest that a fibrate should not be routinely added to a statin in those with diabetes. Myalgia and more serious muscle damage (with rhabdomyolysis and myoglobinuria) are rare but well-established complications of both statins and fibrates and the risks are increased by co-administration, albeit the risk is lower for combination of fenofibrate with statins. There is emerging evidence that fibrates may slow the progression of diabetic maculopathy and so they may still have a role in people with diabetes.

Nicotinic acid and its derivatives

Nicotinic acid (niacin) has been used for treating low HDL-C, which is commonly found in those with diabetes. It causes

Table 28.5 Drugs requiring caution in specific diabetic complications.

Complication and drug	Problem	Action to be taken
Nephropathy		
Sulfonylureas	Accumulate in renal failure; increased risk of hypoglycemia and toxicity	Use insulin or a sulfonylurea not cleared through the kidneys (e.g. gliquidone, gliclazide)
Metformin	Accumulates in renal failure; increased risk of lactic acidosis	Avoid if eGFR <30 mL/min/1.73 m^2
DPP-4 inhibitors	Accumulate in renal failure	Reduced dose needed for sitagliptin, vildagliptin, saxagliptin, and alogliptin. No dose adjustment required in renal impairment for linagliptin.
SGLT2 inhibitors	Reduced efficacy in renal impairment	Avoid if eGFR <60 mL/min/1.73 m^2
ACE inhibitors or ARBs	Initial rise in plasma creatinine; risk of hyperkalemia	Use with caution and appropriate monitoring of renal function
NSAIDs or COX-2 inhibitors	Further compromise renal function	Avoid if possible
Radiocontrast media	Reduce renal function	Adequate hydration before procedure
Oral sodium phosphate solution for bowel cleansing	Acute renal failure	Close monitoring of fluid status and renal function or use alternative bowel preparation such as polyethylene glycol (PEG)
Cardiovascular disease		
β-Adrenoceptor antagonists	Accentuate hypoglycemia May cause modest VLDL elevation	Consider alternative antihypertensive Antianginal or antiarrhythmic drugs (e.g. ACE inhibitors, calcium-channel blockers)
Thiazide diuretics (high dose)	Worsen glycemic control in type 2 diabetes Exacerbate hyperlipidemia	Reduce dose, or use loop diuretic or alternative antihypertensive drugs
Retinopathy		
Mydriatics (eyedrops or systemic atropinic drugs)	In those with rubeosis or previous eye surgery, glaucoma may be precipitated	Seek ophthalmologic advice before dilating pupils
Anticoagulants	May predispose to vitreous hemorrhage in patients with proliferative changes	Avoid if possible
Abciximab	May predispose to vitreous hemorrhage in patients with proliferative changes	Avoid if possible
Somatropin	Can worsen proliferative retinopathy	Avoid
Autonomic neuropathy		
Phosphodiesterase inhibitors (e.g. sildenafil)	Aggravates postural hypotension	Avoid, especially in the elderly and those taking nitrates
Ganglion-blocking agents and vasodilators	Aggravate postural hypotension	Use with caution
Erectile dysfunction		
Ganglion-blocking agents β-Adrenergic blockers Clonidine α-Methyldopa	Aggravate erectile failure	Use alternative antihypertensive drugs (e.g. ACE inhibitor, calcium-channel blocker or α-adrenergic blocker)

ACE, angiotensin-converting enzyme; ARB, angiotensin receptor blocker; COX, cyclo-oxygenase; NSAID, non-steroidal anti-inflammatory drug; VLDL, very-low-density lipoprotein.

flushing, which can be ameliorated to some extent by using a slow-release formulation or an inhibitor of prostaglandin D2, laropiprant. It can also cause hyperglycemia [130]. Niacin is no longer recommended for dyslipidemia because its efficacy in reducing vascular events could not be demonstrated in two large randomized controlled trials, the Heart Protection Study 2–Treatment of HDL to Reduce the Incidence of Vascular Events (HPS2-THRIVE) [131] and the Atherothrombosis Intervention in Metabolic Syndrome with Low HDL/High Triglycerides: Impact on Global Health Outcomes (AIM-HIGH) [132].

Anion-exchange resins

Anion-exchange resins such as cholestyramine could theoretically reduce the absorption of antidiabetes drugs from the gut, although clinically significant interference has not been reported.

Other drugs

The UK Summaries of Product Characteristics of many products contain contraindications to using the product in people with diabetes or diabetic complications. Some of the less obvious examples are oxymetazoline hydrochloride nasal spray and verruca gels

containing salicylic acid [133]. In addition, there is a wide range of warnings that medicines should be used with caution in diabetes; for example, oral rehydration solutions and ribavirin [133]. Oral sodium phosphate bowel preparation is also best avoided in those with diabetes, with use of alternatives such as polyethylene glycol (PEG) being preferred [134].

Special precautions in diabetic complications

Some drugs are relatively or absolutely contraindicated in the presence of certain diabetic complications. These include oral contraceptives or hormone replacement therapies in women with diabetes and severe vascular disease, the antiplatelet agents abciximab and cilostazol, growth hormone in people with proliferative retinopathy, and propranolol by injection in those prone to hypoglycemia [133]. Important examples are shown in Table 28.5.

Given the increasing proportion of people with diabetes and chronic kidney disease (CKD), particular attention should be paid to the adjustment of medications in CKD. Metformin is contra-indicated for those with eGFR <30 mL/min/1.73 m^2. The DPP-4 inhibitors in general need dose reduction in the setting of CKD, except for linagliptin. For the SGLT2 inhibitors, efficacy is reduced in the setting of CKD, and this class of agents are in general not recommended for people with eGFR <60 mL/min/1.73 m^2.

There has been controversy about the risks of inducing vitreous hemorrhage with thrombolytic treatment (e.g. streptokinase) for myocardial infarction in those with proliferative retinopathy. Current advice is to give thrombolytic drugs according to the usual indications, as the likely benefits far outweigh the potential threat to vision.

Drug interference with monitoring of diabetic control

Urine testing for glucose is no longer recommended for screening or monitoring of diabetes but is subject to interference by several drugs [135], including ascorbic acid, which can give false-negative urine glucose readings with glucose oxidase strips (see Chapter 27) [136], and by the SGLT2 inhibitors, which lower blood glucose by inducing glycosuria.

Blood glucose measurements, using dry-reagent glucose oxidase test strips, can potentially be affected by drugs such as aspirin if present in very high concentrations [137]. Readings can also be misleading if fingers are contaminated with alcohol from swabs (which inactivates glucose oxidase) or with glucose (e.g. from sugary drinks) [138]. The complex sugar icodextrin, used as a peritoneal dialysate, can give spuriously high glucose concentrations; this can mask underlying hypoglycemia [139]. Paracetamol has been reported to interfere with continuous glucose monitoring sensing and results in falsely elevated readings [140].

Conclusions

Rational prescribing is a difficult task that demands the integration of data about the drugs being used, the patient, and the conditions that affect the patient. There are three major areas of difficulty when prescribing for people with diabetes. First, a large number of drugs affect glucose tolerance. They include important agents, such as oral corticosteroids, which can be life-saving but confound attempts to achieve euglycemia. Second, people with diabetes are now commonly asked to take several medicines to control glycemia, and to treat the complications of diabetes. The number of potential interactions between pairs of drugs increases rapidly with the number of different drugs prescribed. As the number of prescribed medicines increases from 5 to 10, the number of possible pair-wise interactions increases from 10 to 45 (and the number of three-way interactions from 10 to 120). Third, those with diabetes are at high risk of other disorders that require the prescribing of other medicines. For example, treatment after myocardial infarction, five times more likely in the presence of diabetes, would commonly involve one or more antiplatelet agents, a statin, an ACE inhibitor, and a β-adrenoceptor antagonist.

Rational prescribers will consider, in consultation with the person with diabetes, therapeutic purpose, and the potential benefit and the possible harm of any additional treatment to the individual prior to prescribing. They will also review long-standing prescriptions from time to time to revisit previous decisions in the light of changes in the patient, the reason for prescribing, and the pharmacopoeia.

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6 Treatment of Diabetes

29 Insulin and Insulin Treatment

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Key points

- Insulin is a potent anabolic hormone essential for life. Insulin has a circulating concentration of 15–20 mU/L in the fasting state, and 60–80 mU/L postprandially.
- Early insulins were extracted from the pancreases of pigs and cows but good glycemic control was difficult to achieve due to impurities in the preparation. The newer and purer animal insulins are better tolerated and can potentially achieve a level of glycemic control similar to synthetic human insulins. Significant hypoglycemia rates between the human and animal insulins appear to be similar.
- The challenge of insulin replacement therapy is to reproduce a normal physiological insulin profile without incurring significant hypoglycemia. A range of insulin preparations with differing durations of actions are available to achieve this: rapid-acting insulin analogs (about 3 hours), soluble insulin (about 6–8 h), neutral protamine Hagedorn (NPH) insulin (12–18 h), Lente insulins (about 12–24 h), long-acting insulin analogs (about 24 h), and ultra-long-acting insulin analogs (about 40 h).
- Current recommendations for the injection of insulin are to use the abdomen, upper buttocks, upper back of the arms and upper thighs, and to rotate injection sites to avoid lipohypertrophy. The needle should be injected at right angle to the skin and left there for 10 sec before removing the needle. Injection needle lengths should be as short as possible to minimize trauma and to avoid intramuscular delivery. For those using insulin pens, 4 mm needles are available. Syringe needles remain at 8 mm. Alternative routes of insulin delivery such as continuous subcutaneous insulin infusion can also be highly effective.
- Multiple dose insulin therapy is an appropriate initial approach to reproducing the physiological insulin profile in people with absolute insulin deficiency such as those with type 1 diabetes. This consists of a long-acting insulin preparation administered once or twice a day to meet the basal insulin requirement, with the injection of a short-acting insulin preparation with each meal.
- A number of different insulin injection regimens are available for people with type 2 diabetes who may already be treated with non-insulin-based therapies. These include a once daily injection of a long-acting insulin, a once daily injection of a long-acting insulin with an injection of a short-acting insulin with the main meal, twice a day injections of insulin mixtures, and multiple dose injections. In addition insulin can be administered with other injectables such as GLP-1 receptor agonists.

Life (and death) before insulin

Insulin is a potent anabolic hormone, and its absence induces a profound catabolic state that affects fat, carbohydrate, and protein stores. Absolute insulin deficiency, such as that characterized by type 1 diabetes (T1DM), will result in death if left untreated (Figure 29.1). What the study of people with diabetes in the pre-insulin era taught us is the surprisingly long period that can be survived without insulin. Leonard Thompson was the first person to have effective insulin treatment. He was 12 years old when he was diagnosed with diabetes in 1919 and had survived over 2 years when at 11 am on January 22, 1922 he received his first injection of insulin. That said it was a miserable existence without insulin. Other than the weight loss, the constant tiredness, thirst, urination, and frequent infections, there was the certain knowledge that a death sentence had been passed, and that death would be an agonizing and slow process. The most effective therapy available at that time appeared to be severe nutritional restriction, perhaps most popularly expounded by Frederick Allen from the Rockefeller Institute in New York [1]. This, however, was a difficult regimen that did not appear to prolong life expectancy significantly, and when death came it was not clear whether it was the result of diabetes or starvation.

The discovery of insulin

Though there had been previous attempts at identifying a pancreatic agent that could control blood glucose, most notably by the Romanian physiologist Nicolas Paulescu, the story of insulin may be considered to start in autumn of 1920 when Frederick

Textbook of Diabetes, Fifth Edition. Edited by R. Holt, C. Cockram, A. Flyvbjerg and B. Goldstein.

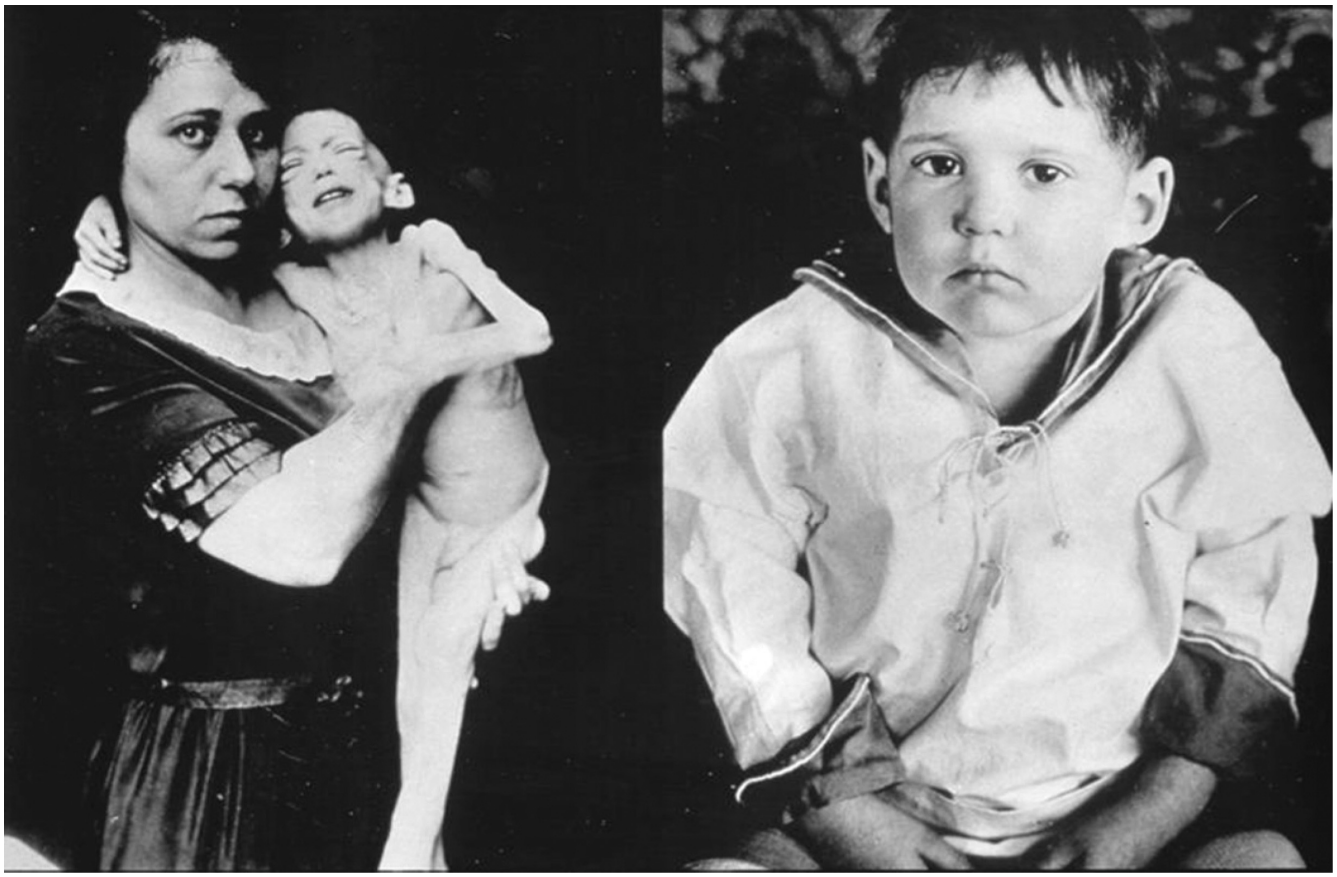

Figure 29.1 A boy with diabetes before and after insulin therapy.

Grant Banting who, while preparing a lecture on carbohydrate metabolism, considered a way to isolate the internal secretion of the pancreas. By the summer of the following year he had arranged with John Macleod, Professor of Physiology at the University of Toronto, for facilities and the support of a science student Charles Best to start experimentation (Figure 29.2). They showed that tying off the pancreatic ducts induced atrophy of the exocrine glands of the pancreas thus allowing the "internal" secretions to be isolated. They tested the effect of this internal secretion on blood sugar by injecting it into dogs rendered diabetic through pancreatectomy. With the help of a biochemist, James Collip, they were able to purify this abstract sufficiently for the early experiments on patients. For this work, Banting and Macleod shared the Nobel Prize in Medicine in 1923.

This discovery was by no means a straightforward process, and according to one particularly harsh commentator "the production of insulin … originated in wrongly conceived, wrongly conducted and wrongly interpreted series of experiments …" [2]. The discovery of insulin nevertheless was a defining moment in the history of diabetes and the molecule has gone on to be well studied, with work on it contributing to three further Nobel prizes: Frederick Sanger in 1958 for determining its primary amino acid sequence, Dorothy Hodgkin in 1964 for X-crystallographic studies, and Rosalyn Yalow et al. in 1977 for contributing to the development of the radioimmunoassays.

The first insulins

Commercially available insulin was initially extracted from porcine and bovine pancreases. The tissue would undergo acid-ethanol treatment to solubilize insulin, which would then be salted out with sodium chloride, precipitated, and crystallized [3]. This procedure resulted in insulin with a purity of 80–90%, the contaminants largely being pancreatic polypeptides and glucagon. Though this insulin was effective, it was often complicated by immune-mediated side effects, in particular lipoatrophy and antibody-mediated insulin resistance [4], both factors which can profoundly influence the kinetics of insulin action. These impurities also contributed to an allergic reaction that sometimes resulted in swelling and pain at the site of injection.

Animal insulin continues to be porcine and bovine derived. The amino acid structure of beef insulin differs from that of human by three amino acids (position 30 of the B chain, and 8 and 10 of the A chain) and that of pork from human by just one amino acid (position 30 of the B chain) [5, 6]. These differences

Figure 29.2 Charles Best and Frederick Banting on the roof of the medical building at the University of Toronto, summer 1921.

aside, it was the purity of the insulin preparation that appeared to influence its immunogenicity. Additional purification steps in the 1970s resulted in an insulin, called mono-component or single-component insulin, with fewer side effects and which was better tolerated (Table 29.1). The incidence of lipoatrophy and allergy decreased as these purer insulins became more widely available. It was a logical step, therefore, to move on to treatment with human insulin in an effort to reduce immune-mediated complications and improve glucose control further.

Human insulin has been obtained using three techniques. The earliest attempts were to isolate and purify it directly from human cadaveric pancreases. However, the supply of human tissue was never sufficient to enable this technique to provide sufficient quantities. The technique of "semi-synthesis" chemically converts porcine insulin to the human sequence through substituting the one amino acid difference in the primary sequence. It was not until 1980 with the introduction of recombinant DNA technology that human insulin therapy became widely available. The technique involves the insertion of the human DNA sequence into a host cell, usually baker's yeast or the bacteria *Escherichia coli*, allowing it to

Table 29.1 Insulin therapy milestones.

1922	Isolation of insulin and treatment of the first patient (January 22nd)
1936	Protamine insulin
1946	NPH isophane insulin
1951	Zinc lente insulin
1959	Biphasic insulin
1977	Continuous subcutaneous insulin infusion
1980	rDNA human insulin
1981	Insulin pens
1987	Monomeric short-acting insulins
1987	Soluble prolonged action insulin
1996	Rapid-acting insulin analogs
2001	Long-acting insulin analogs
2013	Ultra-long-acting insulin analogs
2015	Biosimilar insulins

synthesize the insulin molecule [7]. The protein would then be purified usually via chromatography columns to achieve a 99.5–99.9% insulin purity. The quality of the human insulin preparation achieved with this technique, as indeed with the purified pork insulin, has virtually eliminated problems associated with immune-mediated side effects.

Counter to expectations, rigorous and well-designed studies comparing purified animal insulin with recombinant human insulin have yet to demonstrate a significant benefit in glycemic control. A meta-analysis of 45 randomized controlled trials involving a total of 2156 participants comparing animal and human insulin failed to show a significant difference between these two therapies [8]. Most (36 of the 45) of these studies used highly purified porcine insulin.

The move from animal to human insulin was associated in some patients with higher incidences of severe hypoglycemia, largely due to changes in hypoglycemia warnings [9, 10], but systematic reviews have failed to substantiate this finding [8, 11].

There has been a large-scale uptake of recombinant human insulin such that less than 7% of global insulin sales are now animal insulin. The phasing out of animal insulins by the leading insulin manufactures has certainly contributed to this. Several companies, however, continue to provide this alternate source, and both beef- and pork-derived insulin remain available in many countries.

Modifying the duration of action of insulin without altering its molecular structure

The biological action of soluble insulin lasts about 5–6 hours. The early preparations were often associated with pain and swelling at the site of injection, and the needles and syringes were not optimized for painless injection. Attempts were, therefore, made in the 1920s and 1930s to provide the daily insulin requirement in just one injection. To this end, modifying agents such as lecithin, oil, and cholesterol [12] were used. However, their duration of

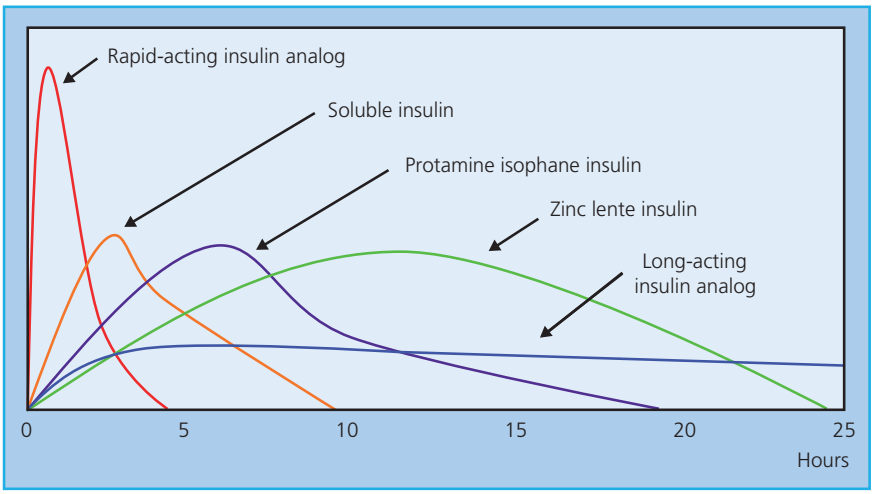

Figure 29.3 Time action profiles of the different insulin formulations.

action varied significantly from injection to injection which limited their clinical utility.

In 1936 a method for incorporating insulin into a poorly soluble complex, thus slowing its absorption, was reported [13]. This technique involved the addition of a highly basic protein, protamine, derived from the sperm of salmon or trout. The complex was further stabilized by the addition of a small amount of zinc such that it lasted about 24 hours. This insulin was called protamine-zinc insulin. It was difficult to make consistent batches and absorption again tended to be erratic. In 1946 the technique was further refined such that protamine and zinc were added in stoichiometric proportions (so that there was no free protamine or zinc), which resulted in a preparation that was absorbed at a more consistent rate and lasted between 12–24 hours. This insulin was called Isophane or neutral protamine Hagedorn (NPH), and became clinically available in 1940. In 1951 a development which prolonged the action of insulin without the need for protamine was reported. This required that zinc be added in excess and in acetate buffer resulting in crystals of relatively insoluble zinc-insulin complexes, called the Lente insulins [14]. The size of the crystals could be adjusted by changing the pH such that larger crystals, which were more slowly absorbed (Ultralente), and smaller crystals (called Semilente), could be produced. A preparation containing a 70 : 30 ratio of the Ultralente and Semilente insulins, called Lente insulin, was the most popular form of the zinc insulins and was used widely in clinical practice.

Modifying the duration of insulin action through altering its molecular structure

Insulin circulates as single molecules in the blood at concentrations of about 10^{-9} mol/L. At higher concentrations such as in commercial preparations, insulin molecules tend to associate non-covalently into dimers, tetramers, and hexamers [15]. The presence of zinc further stabilizes the hexamer association. Following injection, fluid is drawn into the injected insulin depot through osmosis. This leads to dilution of the insulin and dissociation of the insulin molecules; a spontaneous but gradual process that must occur before insulin crosses the capillary walls as monomers into the blood circulation [16, 17]. People with diabetes are, therefore, advised to inject their soluble insulin 15–20 minutes before a meal so that circulating insulin levels are optimal at the time their meal is being absorbed (Figure 29.3). A significant proportion of people with diabetes find it hard to follow this advice because of the planning required. Even when they do, the calculated doses may be inaccurate, particularly if the preparation and presentation of the meal is not under the individual's control.

The association between insulin molecules can be reduced by specific changes to insulin's amino-acid sequence [18], many of these centering on the B28-29 amino acids. These changes result in faster absorption of insulin into the blood stream, and allow it to be injected closer to the mealtime, and often just before starting to eat. To date, three such rapid-acting analogs have become available. Insulin lispro (Humalog®, Lilly) differs from human insulin in that amino acid proline at position B28 is replaced by lysine, and the lysine in position B29 is replaced by proline. Insulin aspart (NovoRapid®, Novo Nordisk) again has a substitution at B28, where proline is replaced with an aspartic acid. Insulin glulisine (Apidra®, Sanofi-Aventis) differs from human insulin in that amino acid lysine in position B29 is replaced by glutamic acid, and asparagine at position B3 is replaced by lysine. These analogs act more quickly (within 10–20 min) and have a shorter duration of action (3–5 h) than soluble insulin [19] (30–60 min, and 6–8 h, respectively) (Figure 29.3). A number of studies have now demonstrated the safety of rapid-acting analogs in both T1DM and T2DM, as part of a "basal bolus" insulin injection regimen combined with intermediate-acting insulins, and in continuous subcutaneous insulin infusion (CSII) [20]. The time action profile of rapid-acting analogs is well suited to mimicking the requirement at mealtimes and, therefore, they probably control postprandial hyperglycemia more effectively than soluble insulin. As a result, individuals can achieve better glycemic control with fewer episodes of hypoglycemia with rapid-acting analogs than with

soluble insulin. The benefits of rapid-acting analogs over soluble insulin appear to be clearer in studies involving people with T1DM than T2DM, and using CSII than for multiple dose injections [19].

Though delayed action insulin such as insulin Lente and Isophane (NPH insulin) can cover the 12–24-hour period, they do not display this extended duration of action in all people with diabetes. Furthermore, absorption from subcutaneous tissue can vary significantly [21]. Therefore, attempts at stringent glucose control can be associated with an increased risk of hypoglycemia. As for rapid-acting analogs, modification of the insulin molecule primary amino acid sequence can also result in a longer and more reproducible duration of action. Again there are currently three such insulin analogs. Glargine (Lantus®, Sanofi) achieves a prolonged insulin action through amino acid substitutions that make the insulin molecule less soluble. Glargine insulin forms microcrystals following subcutaneous injection that dissolve slowly over an 18–26-hour period [22]. In non-inferiority studies, insulin glargine achieves similar glycemic control to isophane insulin, and appears to do so with less hypoglycemia [23]. Insulin detemir (Levemir®, Novo Nordisk) has a fatty acid side-chain addition to the insulin molecule that promotes binding to circulating albumin, which then slowly dissociates giving it a duration of action just a little short of glargine insulin. Detemir is as efficient as isophane insulin at improving glycemic control, but appears to do so with less hypoglycemia and weight gain [24]. The most recent addition to the long-acting insulin analogs has been insulin degludec (Tresiba®, Novo Nordisk). Degludec also has a fatty acid side-chain but structured in such a way as to encourage it to form long multihexamer chains following subcutaneous injection. This chain disassembles very slowly and gives degludec a very long duration of action (half-life exceeding 25 h) such that it has been termed an ultra-long-acting insulin analog [25]. This long duration of action allows a very flat insulin profile, and a more reproducible duration of action that is not significantly affected by variations in the time of day-to-day administration. Non-inferiority studies have shown that insulin degludec is able to achieve similar levels of glycemic control to insulin glargine, but with less overall and nocturnal hypoglycemia [26].

Comparative studies of the long-acting analog insulins, have been designed to demonstrate equivalence rather than superiority in terms of glycemic control [27]. They do, however, demonstrate that the same level of glycemic control can be achieved with less hypoglycemia, and possibly with less weight gain. These benefits come at a cost. NPH insulin in the UK costs about £8, compared to £30 for the long-, and ultra-long-acting insulin analogs.

Biosimilar insulins

Biosimilar insulins have recently entered clinical practice and a mention of them is pertinent in this edition of this textbook [6]. Several patent protections for many analog insulin preparations have expired, and the pharmaceutical industry has explored these opportunities to develop "copy cat" insulins to compete with original formulations. Because insulins are currently produced biologically (i.e. through expression in living cells), they are more correctly termed "biological" or "biosimilar" drugs than "generic" drugs. Biosimilars (such as peptide hormones and monoclonal antibodies) are already in clinical practice and are required to undergo a more rigorous testing than standard generic drugs. This testing includes a direct comparison of the biological activity, pharmacology, clinical safety, and efficacy of the biosimilar with the reference insulin. Whilst the development of biosimilars will be more expensive than development of a generic drug, it will not be as expensive as developing the original insulin, and any cost savings will likely be magnified through long-term prescription. Therefore, these insulins will likely be cheaper, thus expanding market competition and increasing availability for people with diabetes. Currently only one biosimilar insulin (based on insulin glargine) has been approved (September, 2014) [28].

Different insulin concentrations

Injecting large volumes of insulin, as is required in those who are insulin-resistant, slows absorption kinetics and reduces the effectiveness of the insulin. Furthermore, it can be more painful. Splitting the dose across different injection sites can reduce the volume. However, in some people, the use of more concentrated insulin is more appropriate. Insulin preparations are currently standardized to 100 U, that is, 100 units of biological activity per mL of insulin. U200, U300, and U500 formulations are available (or becoming available) for clinical use and have been demonstrated to be clinically effective [29–31]. Their exact place in management still needs to be evaluated as they are currently generally reserved for those with very high insulin requirements, but may also benefit those on lower doses.

Reproducing physiological insulin delivery—the size of the problem

In health, the background insulin secretion is low and stable between meals, with significant prandial surges (Figure 29.4) [32]. What is important to appreciate is that in health, pancreatic-derived insulin acts directly on the liver via the portal circulation. In the fasting state, this insulin is at concentrations of 15–20 mU/L, and is sufficient to suppress hepatic glucose production. Fifty to eighty percent of the insulin is metabolized by the liver [33] such that much lower and tightly regulated insulin levels enter the systemic circulation. Peripheral tissues such as muscle also take up glucose but this is at higher insulin concentrations (60–80 mU/L) and tends to occur predominantly postprandially.

The administration of insulin by subcutaneous injection delivers it to the systemic circulation, with relatively lower levels reaching the liver. Therefore, glucose uptake by muscle and adipose tissue is preferential to liver. The lower exposure of the liver to insulin

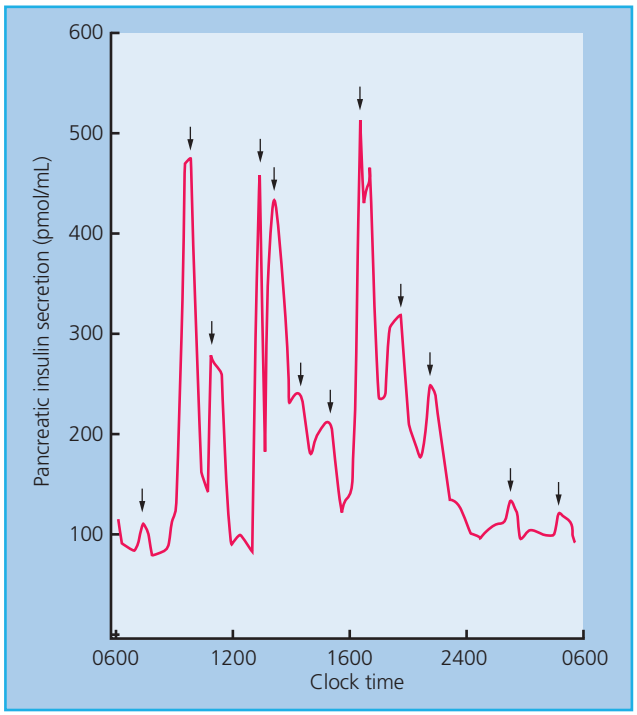

Figure 29.4 Pancreatic insulin secretion in a healthy non-obese individual. Meals were consumed at 0900, 1300, and 1800. Statistically significant pulses of secretion are shown by the arrows. Source: Polansky KS, et al. 1988 [32]. Reproduced with permission from the American Society for Clinical Investigation

also results in greater hepatic glucose production, making the control of blood glucose even more challenging.

The challenge of insulin replacement therapy is to reproduce the physiological insulin profile even though it is being delivered at an "unphysiological" site, and without incurring hypoglycemia. One approach to targeting insulin action to the liver is through the development of hepatoselective insulin [34], including the technique of making the insulin molecule larger through PEGylation to favor it leaving the circulation at the hepatic sinusoids.

Oral, inhaled, intraperitoneal and intramuscular routes of insulin administration

The early experiments of Frederick Banting quickly revealed that the oral route of insulin administration was not an effective means of insulin delivery, as the insulin molecule was functionally degraded by gut peptides. Subcutaneous injection of insulin has become the most popular route of insulin delivery because of its relatively reproducible kinetics of absorption, and the ease with which it can be administered, but it is worth visiting some of the other routes.

Intramuscular injection is more painful, and absorption more rapid, than subcutaneous injection and is, therefore, not recommended for any of the insulin formulations [35]. However, this route can be useful, for example, in the emergency situation when intravenous access is difficult. Inadvertent intramuscular administration should be considered in the slim individual with diabetes who complains of pain on insulin injection, and who may experience erratic glucose control and hypoglycemia. The correct choice of insulin needles can help address this problem (see later).

The delivery of insulin directly into the peritoneal space, for example, with implantable pumps or directly via a port [36] mimics physiological insulin secretion in that insulin bypasses the systemic circulation and directly enters the portal circulation. The theoretical advantages of portal delivery include rapid insulin absorption, near physiological carbohydrate and lipid metabolism, and avoiding peripheral hyperinsulinemia [37]. Clinically, the advantages of intraperitoneal insulin delivery have been explored in a number of clinical trials (reviewed in [38]). Whilst large randomized controlled trials are awaited, current studies suggest some evidence for improvement in HbA_{1c} and improved quality of life in selected people with T1DM [39].

The oral administration of insulin is another route through which this drug can enter the portal circulation, thus avoiding high levels of peripheral insulin. Clinical trials of oral insulin preparations are currently ongoing. These insulins avoid degradation in the gut either through encapsulation, or through modification of the insulin molecule to engender resistance to degradation [40–42]. Concerns about accuracy of insulin dosing, and the anabolic effect of insulin on lower gut tumors will need to be addressed as these insulins come to the market.

Administration of insulin via the respiratory mucosal surface avoids degradation by gut peptides and can be an effective route for insulin delivery, particularly for those who are needle phobic [43]. Inhaled insulin was made available in the UK (Exubera, Pfizer) in 2006, but was withdrawn within a year due to poor uptake by patients and healthcare professionals. A newer device that is smaller, and with a potentially more effective insulin was approved in the USA for marketing in 2015 (Afrezza®, Mannkind-Sanofi) for use as a meal-time rapid-acting insulin. With both formulations, there is a reduction in lung function that reverses when the therapy is stopped, and there is the potential risk of lung cancer in heavy smokers. Afrezza is also not recommended in people who are current smokers, because safety and efficacy has not been demonstrated in this population. It is also contraindicated in people with reactive airway diseases such as asthma or chronic obstructive pulmonary disease. Whilst trials of newer inhaled insulins are awaited, systematic reviews of previous formulations suggest it is as clinically effective, but not as cost-effective as short-acting injectable insulin, in unselected people with diabetes [44].

Technique for subcutaneous injection of insulin

Subcutaneous insulin administration is the most popular route of insulin therapy. The recommended sites for injection are the abdomen centered around the umbilicus, back of the upper arms below the deltoid region, upper lateral thighs, and upper buttocks. The area should be clean and free from signs of infection

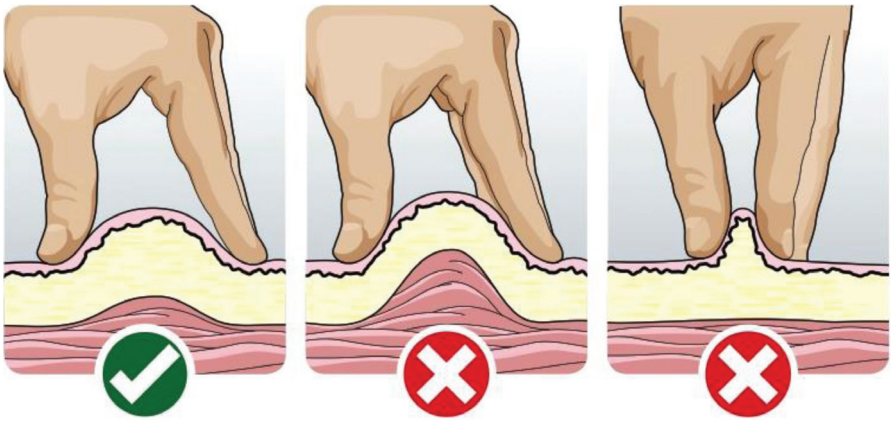

Figure 29.5 The recommended technique for lifting skin folds for the subcutaneous injection of insulin. Source: The Forum for Injection Technique Guidelines 2011. Reproduced with kind permission of BD Medical Diabetes Care.

or lipohypertrophy (see "Complications of subcutaneous insulin therapy" later).

Insulin can be directly dialed up on a pen device, or drawn up using a disposable syringe. If the insulin preparation is cloudy (e.g. pre-mixed insulin), it should be gently rolled and inverted 10 times. This will allow the insulin crystals to disperse and for the mixture to turn to a milky-white suspension. If using a pen device for insulin delivery, the device should be properly primed and a drop of insulin should be visible at the tip of the needle. Similarly, if an insulin syringe is being used, the barrel should be tapped and any air excluded by squeezing the plunger. These maneuvers ensure that air is not contributing to the volume of insulin that has been dialed/drawn, and that an accurate dose of insulin is delivered.

The needle should enter the skin at right angles to the surface in a smooth process, the plunger squeezed gradually and completely, and left there for 10 seconds to allow the insulin to enter the tissue. The needle should then be removed and discarded appropriately. Pen needles and disposable syringes should be replaced at each injection. Rubbing of the skin following injection is discouraged because this increases the rate of insulin absorption, and may increase the risk of hypoglycemia.

Syringe needle lengths are currently restricted to 8 mm. Pen needles come in a variety of lengths from 4, 5, 6, and 8 mm. There is no clinical reason for needles longer than 8 mm. Longer needles increase the risk of injecting directly into muscle, with the associated rapid absorption and risk of hypoglycemia. Currently 4 mm needles are recommended for many adults and most children and these can be often used without the need for lifted skin folds. Injecting into lifted skin folds is appropriate in children, slim adults, and when there is a risk of injecting into muscle. The correct technique for lifting skin folds needs to be taught; it should not lift up underlying muscle, nor be so tight as to cause blanching of the skin (Figure 29.5). The use of lifted skin folds is recommended for all people who use 8 mm needles. Injecting through clothing is to be discouraged because as needle lengths get shorter, there is a risk of intradermal injection.

Studies of absorption of subcutaneously administered insulin have used a variety of techniques including measuring the rate of loss of I^{125} labelled insulin from the site of injection using a gamma counter [45]. They show that the rate can vary significantly between individuals, but also from one injection to another within the same individual [21]. Absorption rates in obese individuals are slower than in people without obesity, and there does not appear to be any clear differences in the rate of absorption between the different injection sites. In lean individuals, the absorption of analog insulins (both rapid- and long-acting analogs) does not appear to vary by injection site [46, 47]. However, in these individuals, absorption of human insulin from the abdomen appears to be faster than the arm or leg [48], and the upper abdomen faster than the lower abdomen [49]. This difference can be utilized to good effect, for example, injecting isophane NPH insulin into the thigh or buttock ensures a slower absorption, and soluble mealtime insulin in the abdomen, a more rapid absorption.

Repeated injection of insulin at the same site results in local hypertrophy of adipose tissue, resulting in slower and more erratic insulin absorption. Patients should always be advised to rotate their insulin injection sites to avoid this complication, and should be shown an easy to follow rotation scheme (Figure 29.6). Other local factors such as edema or local inflammation can influence rates of absorption. Exercise results in greater blood flow to the skin and can result in faster uptake of insulin, particularly when injected into an area close to the muscle groups being exercised. Individuals who are planning to run, for example, should be advised that injection into the leg may be less favorable than injecting into the arm or abdomen [50]. Similarly temperature influences cutaneous blood flow and can influence insulin absorption [51]. Hot climates or sitting in the sauna may result in a rapid surge in insulin levels whereas the converse, travelling to cooler climates can result in a slower uptake. There are also reports that hypoglycemia and smoking can reduce the rate of insulin absorption [52, 53].

Standard insulin preparations have a shelf life of 4–6 weeks when stored at under 25 °C. Storage for longer periods will require that they be kept in a fridge (4 °C), which then allows them to be stored until their expiry date. Exposure of insulin to high temperatures or to microwaves can render them inactive.

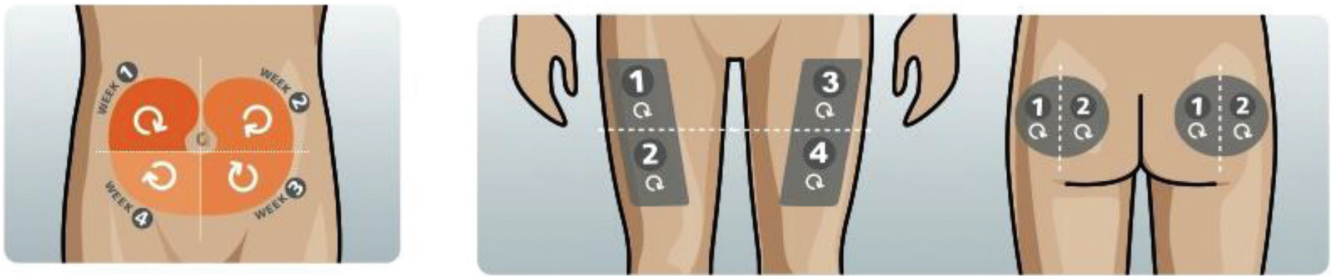

Figure 29.6 Rotation of insulin injection sites. Source: The Forum for Injection Technique Guidelines 2011. Reproduced with kind permission of BD Medical Diabetes Care.

Complications of subcutaneous insulin therapy

The major and most feared complication of insulin injections, for most people, is hypoglycemia. The causes, avoidance, consequences and management of hypoglycemia are discussed in Chapter 35. The fear of hypoglycemia may be a major barrier to insulin initiation.

Insulin not only restores fat and muscle mass in newly or suboptimally treated insulin-requiring patients but can lead to excessive weight gain [54]. This remains a major concern for many people, particularly for the already overweight individual with T2DM who can no longer be controlled on oral antidiabetes agents. Weight gain can be reduced by concomitant advice from the dietician, and an insulin regimen tailored to the requirement of the individual, which wherever possible provides most insulin when needed, that is, at meal times. Over-aggressive insulin titration regimens leading to low blood glucose and stimulation in appetite can lead to excessive weight gain. Some people, particularly but not exclusively young females, can pose a management challenge when they reduce their insulin dose to suboptimal levels to manipulate body weight (See Chapter 57).

Immune responses to the older animal insulins have been well reported but such responses to current human and analog insulins are less common [55]. Allergies may rarely develop in response to the insulin molecule (this may become a more common issue with the introduction of biosimilar insulins where folding may differ) or to components of the insulin preparation (such as the protamine or metacresol). Most commonly, allergic reactions manifest as local acute urticarial reactions. These are best managed with intradermal skin testing of 1 : 20 dilutions of different insulin preparations, and then switching to that which is best tolerated [56]. Antihistamines may be of benefit in such patients as too may be the use of high-dose steroids in exceptional circumstances. More rarely, widespread systemic reactions develop as a reaction to the insulin and patients may benefit from referral to clinical immunology services.

Lipoatrophy in which subcutaneous tissue at the site of injection disappears or atrophies is also an allergic response seen predominantly with the older animal insulins. It is rarely seen today. In contrast, lipohypertrophy is not uncommon, and is not an allergic response at all but develops because of an increase in adipose tissue as a trophic response to insulin. It is most commonly seen in those with a poor injection technique and usually in people who do not rotate their insulin injection sites. The patient usually finds the appearance unsightly and further injections into sites of hypertrophy can lead to poor and delayed insulin absorption with consequent effects on blood glucose levels [57]. Lipohypertrophy generally resolves within 2 months if injecting into that area is avoided. Occasionally mild ulceration, pitting and, more commonly, bruising can occur at injection sites. Rotating injection to another site, and selecting a shorter needle may be indicated.

Insulin regimens

As insulin preparations have evolved from the early animal insulins to both human and analog insulins we have also seen the development of more versatile and indeed flexible treatment regimens that enable the doctor and nurse to provide the person with diabetes requiring insulin with a bespoke treatment that fits in better with their individual needs and lifestyle.

In people without diabetes it is well known that the β cells of the pancreas have the ability to produce insulin both between meals and at meal times to maintain blood glucose values within a narrow physiological range. In people with T1DM, who are no longer producing endogenous insulin, the administration of exogenous insulin is required to try, as far as is possible, to mimic physiological insulin release using a combination of both fast- or rapid-acting insulin to deal with the glucose challenge presented at meal times and more longer acting or basal insulin to provide a background control of glucose between meals. In people with T2DM, the principle is the same although as the β cells may still be producing some insulin the addition of exogenous insulin to existing oral antidiabetes agents can also be used to try and achieve control of blood glucose levels.

We will discuss how each of the individual insulins mentioned earlier can be used either alone although more often in combination in conjunction with lifestyle and diet and other treatments to control blood glucose.

Basal only regimen

In excess of 50% of people with T2DM will require insulin injections at some point in their life [58]. Often as T2DM progresses

the transition from oral antidiabetes agents to insulin injections can be a time of great stress and anxiety to many people for a number of related reasons [59]. Whilst healthcare professionals employ a whole variety of skills and techniques to minimize what people see as a life-changing event, we remain very aware of the many anxieties insulin injections can induce. These may include a sense of personal failure in not being able to control blood glucose levels with lifestyle, diet, and oral therapy; a feeling that the diabetes is now much more serious than it was as it now requires injections rather than tablets; apprehensions, fears and, very occasionally, real phobias over the need to self-inject a treatment [59]; worries of hypoglycemia leading to coma and death; concerns over weight gain; and also the fact that the use of insulin may severely affect an individual's occupation and certain lifestyle activities.

One way in which insulin injections can be introduced to people who are no longer able to manage their blood glucose with diet, lifestyle, and oral therapy alone is to start with only one injection a day. This is usually added on to existing oral therapies rather than as a replacement therapy. An increasing number of studies have now been published demonstrating that a once a day basal insulin can be used as an add-on therapy to metformin, a sulfonylurea, thiazolidinedione, pioglitazone and as an add-on to these agents when used as a dual or triple oral therapy [60]. National and international guidelines in the UK, Europe, and the USA also recommend the use of a basal insulin with oral therapy as a way of initiating insulin in people with T2DM [61–63]. Some of the newer incretin-based therapies including the DPP-4 inhibitors and the GLP-1 receptor agonists have also recently gained licenses for use with insulin therapy in people with T2DM. The concomitant use of insulin and a sodium glucose co-transporter 2 (SGLT-2) inhibitor, where indicated, is also supported by recent clinical trials.

The initiation of insulin therapy, whether in the hospital, or now more commonly in the community should only take place within a structured programme employing active insulin dose titration. The program should include appropriate education, ongoing telephone/text/email support, the use of self-monitoring to help with dose titration to an agreed target, an understanding of diet, avoidance and management of hypoglycemia, and support from appropriately trained and experienced healthcare professionals.

A number of guidelines continue to recommend initiation with a human NPH insulin taken once or twice a day according to need [61]. However, many healthcare professionals are opting for long-acting insulin analogs particularly in people who require assistance with injections from a carer or healthcare professional and where the use of an analog would reduce the number of injections from twice to once a day. Long-acting analog insulins may also be preferred in people whose lifestyle is restricted by recurrent, symptomatic hypoglycemia, those who would otherwise need twice daily insulin injections in combination with oral therapy, and those who have difficulties with the device required for injection of NPH insulin [60]. Similarly indications for switching from NPH insulin to a long-acting basal analog include failure to reach agreed HbA_{1c} target because of hypoglycemia regardless of HbA_{1c}.

Once started on a basal insulin it is important to adjust insulin doses appropriately to achieve an agreed target. A number of algorithms have been developed to assist with this with almost all based upon the fasting blood glucose measured in the community and usually by the person with diabetes themselves [60, 64, 65]. Whilst self-monitored readings are important in the dose titration process, the ultimate measure that determines the success or otherwise of the basal insulin is the HbA_{1c} value. If this is proving difficult to control with satisfactory fasting plasma glucose values the next step including a prandial fast or rapid-acting insulin component may be required.

Combinations of prandial and basal insulins

In people with T2DM a rising HbA_{1c} in the face of normal or near normal fasting glucose values suggests significant postprandial glucose excursions and the need for a meal-time insulin. This can be achieved in different ways including the addition of a prandial insulin with the main meal followed as needed with the addition of a prandial insulin before every subsequent meal [60]. Alternatively patients can be switched from a basal insulin to a premixed insulin which traditionally has been given twice at the time of breakfast and the evening meal but which increasingly is also being given initially once a day with the main meal and increased up to three times a day [63, 66].

Clearly for people with T1DM a basal insulin alone is inadequate and either a complete basal bolus regimen is required with prandial insulin before each meal alongside a basal insulin or alternatively a twice or thrice daily insulin premix can be used.

Basal plus

The addition of a fast-acting human insulin or rapid-acting analog insulin prior to the main meal of the day can be a useful next step in intensification after starting a basal insulin in people with T2DM [63, 67]. Increasingly healthcare professionals are using rapid-acting insulin analogs over fast-acting human insulins, for convenience, as they can be given immediately before, during, and even immediately after a meal [68, 69]. The dietary intake of the individual will determine which their main meal of the day is and, therefore, with which meal the single injection of fast-/rapid-acting insulin will be given. Once again it is important to titrate the prandial insulin to a glucose target. The ideal time to test the impact of the prandial insulin, and certainly a rapid-acting insulin analog, is 90 minutes to 2 hours after the meal. As with basal insulin adjustment it is advisable not to make too frequent a change in insulin dose and ideally no less than inside 3 days or twice a week. The person with diabetes may vary the amount of insulin administered based upon the size of the meal, although as the insulin is given with the main meal of the day, the dose is usually fairly stable from one day to another. As glycemic control becomes more difficult to achieve a second prandial insulin injection may be necessary taken before the second main meal of the

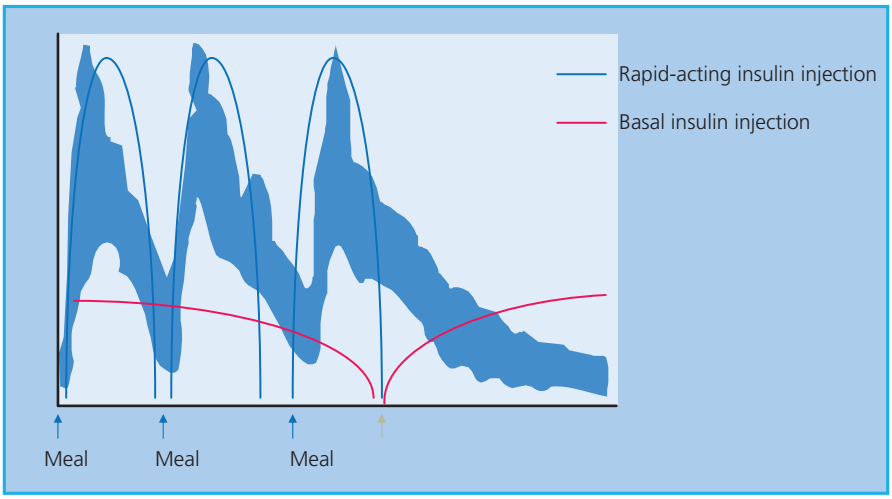

Figure 29.7 Schematic representation of the attempt to mimic physiologic insulin release following three main meals using a basal bolus regimen.

day using a similar dose titration procedure to that for the single prandial injection [67].

Basal bolus

The use of the basal bolus regimen in people with T1 and T2DM attempts to mimic as closely as possible the normal physiological secretion of insulin by providing a background 24-hour coverage of insulin along with a bolus injection at each meal time (Figure 29.7). In most people with diabetes, with the development of long-acting analog insulins, the basal injection is administered once a day. However, based on the results of pre-meal self-monitored blood glucose values some people may require two basal injections approximately 12 hours apart to achieve satisfactory before meal glucose values without hypoglycemia. Traditionally with animal and then human insulins, basal injections are given in the evening, often before bed. However, this is less important with the basal analog insulins and indeed many people benefit from having their once a day basal injection at the same time each morning. As discussed earlier, it is important that insulin doses are adequately titrated to achieve target glucose and HbA_{1c} values, and for the basal bolus regimen the dose of the basal insulin is determined by measurement of fasting (pre-meal) glucose values and the most appropriate fast human or rapid-acting analog insulin dose is best determined by 2-hour postprandial glucose values.

Insulin mixtures

Whilst a few people with diabetes still self mix either animal or human fast-acting and long-acting insulins prior to injection, most people using insulin mixes inject premixed insulin preparations. In recent years we have seen a whole spectrum of insulin premix insulins ranging from a 10 : 90 to 50 : 50 short-/long-acting insulin ratios. In reality many of these premixes were not required and consequently through lack of use the range of premixes has contracted down to 25 : 75, 30 : 70, and 50 : 50 mixes of short- and long-acting, respectively. Most people with diabetes use premixed insulin twice a day before breakfast and the evening meal.

In people with T2DM insulin initiation may start with a once a day premix insulin with the main meal increasing up to two injections a day when needed based on self-monitored blood glucose values and the HbA_{1c} [63, 67]. Some people with T1DM but more frequently people with T2DM move to three injections a day by also administering an injection before lunch. For those escalating to three injections a day, the 50 : 50 mixture providing more rapid-acting insulin at meal times may be more appropriate than the more commonly used 25 : 75 or 30 : 70 mixture usually given twice a day.

Selecting the most appropriate insulin regimen

Most people who have had either T1DM or T2DM try a number of treatment regimens throughout their lives. There are many factors that influence the decision to opt for a specific regimen and ultimately the most important is individual choice rather than evidence from clinical trials.

Type 1 diabetes

All people with T1DM, unless they have been fortunate to become insulin-independent following a pancreas or islet cell transplant, will require exogenous insulin to provide 24-hour background and meal-time coverage. For many this is provided by the basal bolus regimen. The advantage of such an approach is that it is generally better at providing a more physiological insulin replacement with a greater degree of 24-hour flexibility than less frequent premix insulin. Whilst it has the disadvantage of involving more daily insulin injections and requiring many more frequent home blood glucose monitoring which is not popular with some people with T1DM, particularly young and teenage children, it does provide a much greater degree of flexibility throughout the day. Importantly, for example, it allows the individual to vary the meal time dose at up to three different time points during the day to accommodate different daily activities and meal sizes. For some, this "freedom"

is less important and the administration of only two injections a day sways them towards an insulin premix.

Type 2 diabetes

Whilst in some people with T2DM insulin requirements are similar to those with T1DM, for many insulin initiation and intensification is a more gradual process. Views differ on the insulin of choice for initiation, particularly as an add-on to oral hypoglycemic therapy. Prior to the introduction of the long-acting basal analogs many people with T2DM requiring insulin were started on a twice a day premix insulin often as an add-on to metformin. If they were also on a sulfonylurea this was usually stopped. Supported by clinical trials, which demonstrated lower rates of hypoglycemia with long-acting basal analogs as an add-on to existing oral therapy compared to NPH insulin, once a day long-acting basal insulins are now recommended in T2DM treatment guidelines and have found significant popularity, particularly in the community as a means of introducing the person with T2DM to insulin [60, 64]. Anecdotally, however, whilst this is a popular way of starting insulin, many healthcare professionals struggle to achieve satisfactory glycemic targets with this regimen and many people with T2DM will require a second insulin injection with a meal time component within 6–12 months. Trials comparing twice daily premixed insulins compared to a long-acting basal analog when added to metformin in insulin-naïve individuals appear to show a benefit in favor of twice daily premixed insulin with respect to the numbers achieving target HbA_{1c} values [70, 71]. The relative merits of basal only, prandial only, and premix insulin [72] have been evaluated [73]. Clearly there are advantages and disadvantages associated with each approach. A pragmatic response is to consider the person sat in clinic in front of you and consider their lifestyle, social circumstances, and comorbidities and, taking into account what their insulin needs are likely to be in the longer term, make a clinical judgment. If it seems likely that if started on a basal insulin they are likely to remain on this as a single injection or as part of a basal bolus regimen in the future, the basal insulin may be the best option. However, if it seems likely that the individual will be switched to a premixed insulin if a long-acting bolus does not achieve target, then initiating with a premixed insulin would seem sensible. Starting the premixed insulin as a once a day injection increasing to two and sometimes three injections is also an option with some clinical evidence to support it.

Starting insulin for the first time

In the past insulin initiation, particularly for people with T1DM, was conducted either as an inpatient or as a day case in a hospital diabetes center. As confidence grew with the development of purer animal insulins and most recently with human and analog insulins and also with the introduction of disposable syringes, pen injectors and needles, more insulin starts are performed as an outpatient. Lately, with an increased emphasis on community-based diabetes care, insulin initiation, particularly in people with T2DM, is taking place in health centers and GP surgeries [74]. Whilst older algorithms for helping to decide when and where insulin should be initiated have been published, national and local guidelines now seem more appropriate as varying levels of expertise, infrastructure, and service delivery are present.

Wherever insulin is initiated it is vital that for it to be successful a good insulin initiation programme must be in place, with a qualified and competent diabetes nurse specialist. A number of programs are available most with appropriate training courses for healthcare professionals. Insulin initiation involves much more than teaching a patient how to use a needle and syringe and the process of starting and successfully stabilizing them on insulin will require a number of structured contacts with the nurse and also a 24-hour emergency contact number for any urgent problems that may arise (Table 29.2).

Table 29.2 Out-patient/community pathway for people starting insulin for the first time.

Session 1

- The need for insulin has already been discussed with the person with diabetes by a doctor or diabetes nurse specialist and the person with diabetes has been seen by dietician
- A regimen will have been agreed upon and the first prescription has been obtained by the person with diabetes
- A review of "what is diabetes" including what insulin does and the need for insulin injections usually takes place
- Nurse demonstrates the basics and use of insulin injection device and the person with diabetes gives first injection
- Further discussions including:
  - **i** sites for injection/site rotation
  - **ii** timing of injections
  - **iii** where and how to obtain equipment (insulin, pens, needles, self-monitoring equipment, sharps disposal equipment)
  - **iv** recognition and management of hypoglycaemia and hyperglycaemia
  - **v** self-blood glucose monitoring
  - **vi** driving and legal issues surrounding insulin 24-hour contact details provided

Session 2 (around 2 weeks after insulin initiation)

- Prior to session 2 the person with diabetes and nurse will usually have had telephone contact over insulin injections and blood glucose readings
- Review of information provided in session 1
- Review of insulin injection technique

Session 3 (around 4 weeks after insulin initiation)

- Review of session 1 and 2
- Further information provided about:
  - **i** insulin on holiday and when travelling
  - **ii** insulin injections when travelling through time zones (e.g. transatlantic travel)
  - **iii** insulin management during periods of acute sickness
  - **iv** foot care, other diabetes related complications and in women of child-bearing potential – pregnancy

Session 4 (around 10 weeks after insulin initiation)

- Review of previous sessions
- Assessment of glycemic control and need for further doctor/nurse follow-up
- Book follow-up clinic/surgery appointment

For those presenting acutely ill with nausea and vomiting with or without ketosis, admission to hospital for insulin initiation and, where needed, intravenous fluids, is a necessity.

Use of animal, human, and analog insulins

The evolution from animal to human and then analog insulins has been discussed at the start of this chapter. We have subsequently outlined above some of the advice included in national guidelines regarding the use of human and analog insulin. In clinical practice all three types of insulin are in regular use. At the present time, people on animal insulin wishing to stay on animal insulin should, wherever possible, be allowed to do so. There are also advantages associated with the use of the analog insulins although generally they are more expensive to prescribe than human insulin and concerns have been raised over cost–benefits when prescribed routinely. Whilst some of the individual benefits appear small, collectively these benefits are likely to have an impact on many people with diabetes [68]. Whilst those responsible for healthcare budgets seek persuasive clinical trial data it is most unlikely that we will ever see direct head to head studies that provide incontrovertible data one way or another. Ultimately, it will come down to clinical judgment and a decision involving the person with diabetes.

Assessments of glycemic control

Whilst national and international guidelines have made recommendations on glycemic targets based predominantly on the HbA_{1c} [61–63], self-monitoring of blood glucose not only helps people with diabetes achieve HbA_{1c} targets by adjustment of insulin doses but also helps them better understand their own diabetes and blood glucose levels (See Chapter 27). The timing of glucose tests and their role in determining the most appropriate insulin dose in discussed earlier under insulin regimens. Generally speaking people with diabetes should be advised to test at different times on different days including pre-meal and 2 hours postprandial testing to obtain 24-hour glucose profiles over a number of days rather than performing a large number of tests every day. To achieve strict glycemic control, as seen in the T1DM [54], pre-meal blood glucose readings should fall between 4 and 7 mmol/L and post-meal levels from 4–10 mmol/L with a value >7 mmol/L before bed. Whilst individual specialists often follow their own dose adjustment algorithms, in general terms, a change in dose of 2 units or 10% of a dose (whichever is the greater), is a sensible adjustment for most people taking insulin.

Similar targets may be sought for people with T2DM although recent trials based on achieving very tight HbA_{1c} values, with some aiming for <6%, serve to highlight the dangers of hypoglycemia [75]. The frequency of blood glucose testing is extremely variable with patients being recommended to test anything from seven times a day down to four or five tests a week. The most important aspect of regular self-monitoring by people on insulin, is that the test result should be used as part of a management plan to help decide prospectively on insulin dose. There are, however, other points that should be considered when advising on when to self-test, including times of intercurrent illness to adjust insulin dose, symptoms and treatment of hypoglycemia, and foreign travel. Whilst more frequent testing generally provides more information, it is also important to remember not to recommend unnecessary testing as pricking the finger is painful and for most people with diabetes is worse than injecting insulin.

Declaration of interest

At time of writing, Dr Stephen Gough was employed at the University of Oxford but has since taken a position as Senior Principal Clinical Scientist with Novo Nordisk in Copenhagen.

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30 New Technologies for Glucose Monitoring and Insulin Administration

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Key points

- Self-monitoring of blood glucose is evolving to meet new accuracy standards, and data processing tools are enabling individuals and physicians to use the data better.
- Real time continuous glucose monitoring has led to improved glucose control when used regularly.
- Continuous subcutaneous insulin infusion with an insulin pump can lead to improved glycemic control in selected individuals.
- Considerable progress has been made in developing closed-loop systems, using a stepwise approach to incremental feedback control.
- Insulin pens and inhaled insulin are providing alternative means of insulin administration, and may have some clinical benefits.

Introduction

A primary goal of insulin therapy in diabetes has been to optimize glycemic control by reproducing the physiological insulin release that is seen in response to glucose and other stimuli when the pancreatic islets are functioning normally. Recent developments in glucose measurement, insulin delivery, algorithms that relate these two processes, and data management software to demonstrate glycemic patterns have shown the potential to improve the lives of people with diabetes. This chapter reviews the current status of these developments, and their use in the management of insulin-treated diabetes.

Episodic blood glucose monitoring

Self-monitoring of blood glucose (SMBG) has been considered an essential component in the treatment of type 1 diabetes mellitus (T1DM) since the Diabetes Control and Complications Trial [1]. SMBG is also indicated for persons with type 2 diabetes mellitus (T2DM) on insulin therapy and may, when prescribed as part of a broader educational context, be helpful for other people with T2DM when used to guide treatment decisions or self-management [2, 3]. The accuracy of SMBG technology has come into question, however [4]. Because of concerns over the accuracy of monitoring systems, the ISO standard for such systems was changed in 2013 [5]. The previous standard from 2003 required 95% of values to be within 20% of a reference standard (or, for glucose values less than 100 mg/dL [5.6 mmol/L], within 20 mg/dL [1.1 mmol/L] of a reference value). The newer standard requires that 95% of values be within 15% of a reference value (within 15 mg/dL [0.8 mmol/L] for values less than 100 mg/dL). A draft guidance from the United States Food and Drug Administration (FDA) in 2014 proposed the stricter requirement that 95% of all values within the claimed measuring range of the system be within 15% of the reference value and that 99% of all values be within 20% of the reference [6]. The FDA recognizes that not all systems may be able to meet this requirement, particularly at lower glucose ranges, and the proposed standard states that, in this case, the manufacturer may need to raise the proposed lower end of the measuring range. The expectation is that the device will be accurate in the 50–400 mg/dL range [7]. This standard has not yet been implemented.

SMBG data may be used in various ways. With multiple daily insulin (MDI) therapy, individual values are used to determine the next dose of insulin and to teach people the effects of specific foods, exercise, and other activities on blood glucose levels. For people on all types of therapy, SMBG data may be used by the physician to make treatment decisions based on the overall pattern of results. Because of the large volume of data that may be generated, and the often haphazard record-keeping by individuals, recognizing glycemic patterns may be difficult. For this reason, there has been a movement to incorporate new

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technology to simplify this task and make it more accurate. Such developments have come from manufacturers of blood glucose monitoring systems, from suppliers of mobile phones and other telemedicine systems, and from various start-up companies. Many of these were summarized in a recent review [8]. Mobile applications (apps) for downloading SMBG data are available from many sources on both iOS and Android platforms, but many have not had definitive studies to demonstrate their safety or their impact on overall glycemic control. In the Mobile Diabetes Intervention Study, a mobile diabetes software application was used to enter glucose data, carbohydrate intake, and medication and other information. Participants received automated real-time educational, behavioral, and motivational messaging specific to the entered data. A web portal augmented this with a secure messaging service and other information, including a personal health record. In one group, providers had access to a decision support system based on analyzed patient data linked to standards of care and evidence-based guidelines, and in another group providers had access only to unanalyzed data. After 12 months, participants receiving usual care had a decline in HbA_{1c} averaging 0.7%, whereas those in the group using mobile technology without decision support had a decline of 1.2% and those with decision support a decline of 1.9% [9]. Telemedicine diabetes support systems have also been shown to improve quality of life [10] and patient and physician satisfaction [11].

Systems have also been designed to produce graphical results of glucose patterns and have been shown to improve glycemic control. The graphical output can be either on the meter itself [12] or using software that downloads SMBG data from the meter [13]. Figure 30.1 represents an example of download software that

Patterns

! Low Pattern: Overall, 6 glucose readings were below target (13.6%).

! Low Pattern: Overnight, 2 glucose readings were below target (25.0%). Low Pattern: After Lunch, 2 glucose readings were below target (25.0%).

! Low Pattern: 4 glucose readings tagged After Meal were below target (19.0%).

Additional patterns have been detected and may be viewed by selecting different reports to view

Comparative Statistics

	Current Date Range	Previous Date Range	
	1/2/2015 - 1/15/2015	12/19/2014 - 1/1/2015	Change Δ
Blood Glucose (SMBG)			
Overall Avg.	**142.0 mg/dL**	-	
Standard Deviation	**76.5 mg/dL**		
No. of Readings	**44**	0	
Avg. No. of Readings per day	**3.1**	0.0	
% of Readings w/ Meal Tags	**77.3%**	-	
Before Meal Avg.	**179.2 mg/dL**	- mg/dL	
After Meal Avg.	**118.8 mg/dL**	- mg/dL	

Glucose Excursions

	Below Target	Above Target	% Below Target	% In Range	% Above Target
No. of Excursions (SMBG)	6	13	13.6%	56.8%	29.5%
Tagged Before Meal	0	8	0.0%	38.5%	61.5%
Tagged After Meal	4	2	19.0%	71.4%	9.5%
Severe	0	1			
Lowest / Highest Readings	49 mg/dL	369 mg/dL			

Glucose by Time of Day

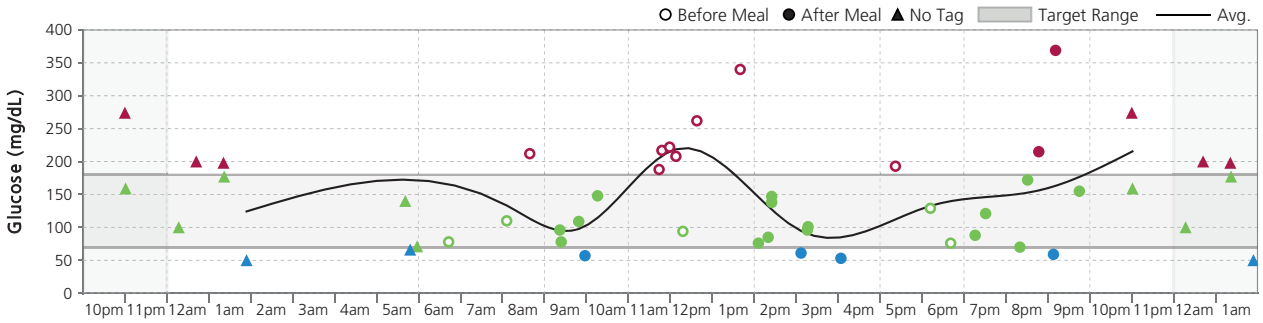

Figure 30.1 Meter downloads provide a rapid means of identifying patterns of glycemic control, such as the overnight and postprandial hypoglycemia seen in this individual. Source: Screen shot from Lifescan, Inc. Reproduced with permission.

Sensor Transmitter Receiver

Figure 30.2 Three components of a continuous glucose monitoring (CGM) device: sensor/probe, transmitter, and receiver. Source: Dexcom, Inc. Reproduced with permission.

can help identify patterns, such as episodes of hypoglycemia, that would be more difficult to detect or take longer to detect by simply reviewing a handwritten logbook.

A new approach to episodic glucose monitoring was recently announced by Abbott Diabetes Care [14]. Given the name FreeStyle Libre Flash® glucose monitoring, the system involves a sensor that is worn on the arm for up to 14 days without any need for calibration by the individual, according to Abbott, and is scanned by a reader to obtain a glucose reading. The device provides a subcutaneous fluid glucose value, unlike meter and strip methods that measure capillary blood glucose. At the time of release it was available in Europe but not the United States. Although similar in concept to continuous monitors, it is labeled only for episodic glucose monitoring and it does not indicate glucose trends.

Real-time continuous glucose monitoring

A number of real-time continuous glucose monitoring (RT-CGM) devices are currently available, including the Medtronic Guardian® REAL-time CGM System and the Dexcom G4 Platinum. The components of a typical CGM system are shown in Figure 30.2, and consist of a subcutaneous sensor that contains the glucose detection chemistry, a receiver that analyzes and displays results, and a transmitter that sends data from the sensor to the receiver. These devices have a transcutaneous glucose oxidase-based electrochemical sensor that measures glucose every 1 min, smooths the data, and displays the glucose concentration in the interstitial fluid every 5 min. Data can be downloaded into a graphical display, as shown in Figure 30.3. There can be a lag between the time a blood glucose level rises or falls and the time when the new concentration is recognized on the CGM. The lag is composed of three components: a physiological lag affected by blood flow to the skin, a sensor reaction time lag for data acquisition, and a sensor processing lag time for signal processing and data smoothing. The total lag can be as short as 5 min or as long as 15 min if the glucose levels are changing rapidly. Because of accuracy limitations [15, 16], the current generation of CGM devices do not have regulatory approval for use as stand-alone devices, and users are required to perform adjunctive capillary blood glucose measurements; however, this limitation is compensated by the additional detailed information provided by the CGM about glucose patterns, the rate and direction of change in the glucose level, and adjustable alarms that are triggered by both hyper- and hypoglycemia (Figure 30.4) [17].

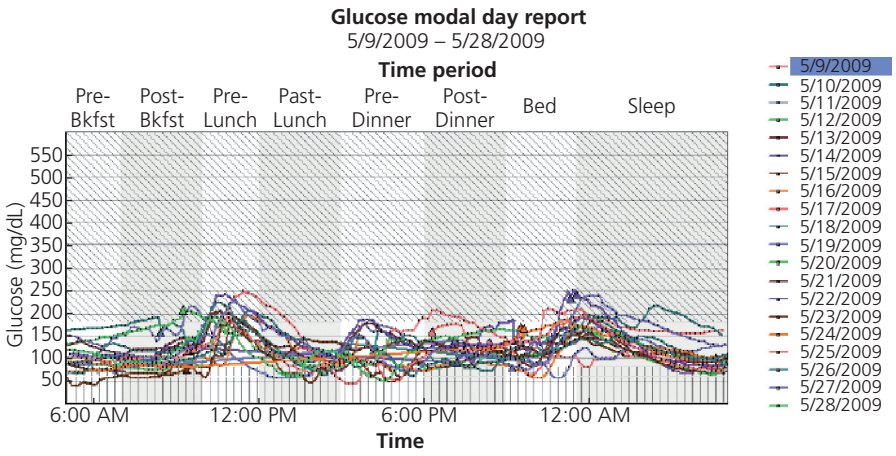

Figure 30.3 Modal day report from an individual who eats breakfast at 9:00 a.m. and supper at 10:00 p.m. daily. It indicates a rapid spike in glucose levels post-meal that had not been detected with intermittent fingerstick blood glucose monitoring. Treatment recommendations focused on changing to more slowly absorbed lower glycemic index carbohydrates (e.g. oatmeal) and/or injection of bolus insulin earlier before the meal.

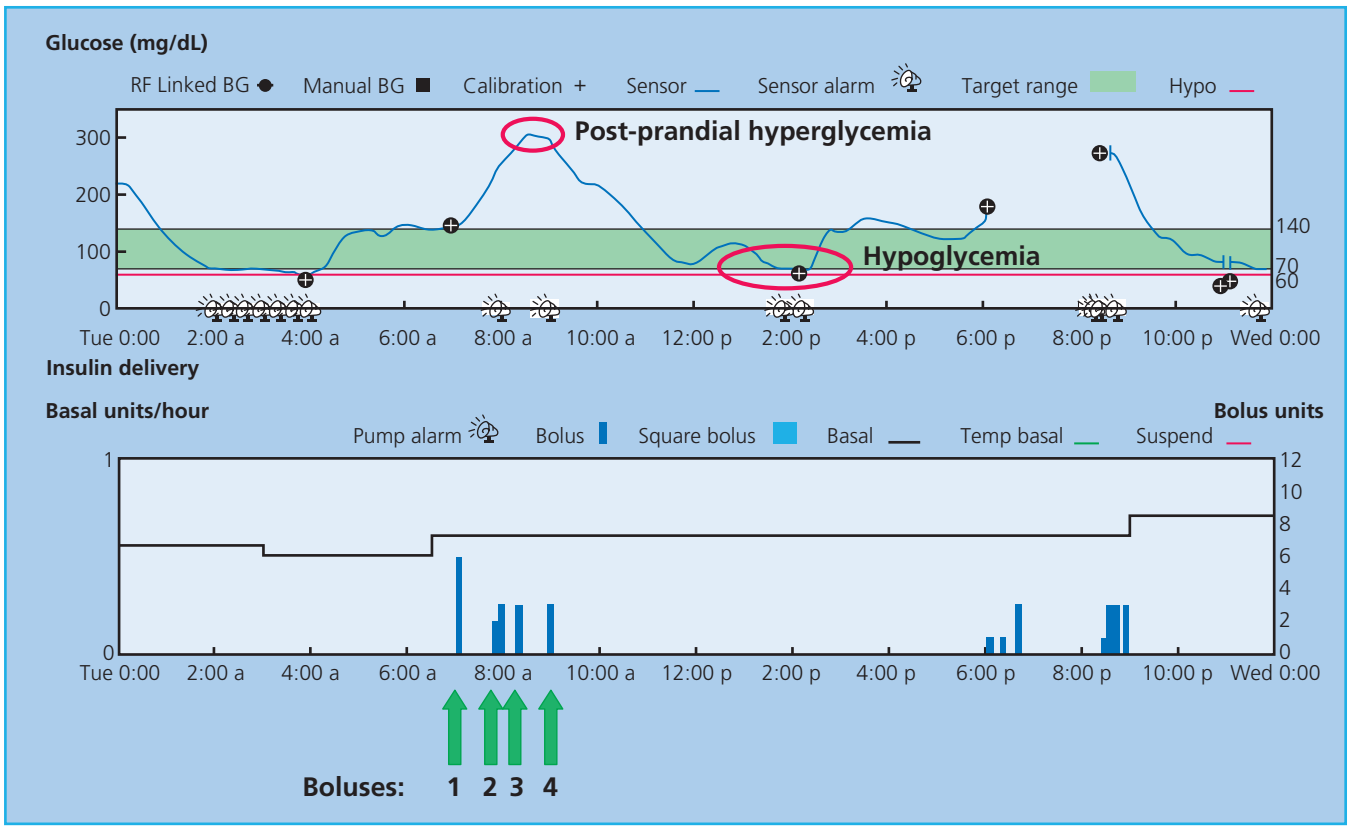

Figure 30.4 Device download: the top panel shows continuous glucose tracing and the bottom panel insulin delivery (each blue bar represents an insulin bolus with units of insulin shown on the vertical axis on the right). Following breakfast, the glucose level increased to 300 mg/dL (16.7 mmol/L), prompting the individual to take multiple boluses with resultant hypoglycemia. The display shows the times when the device produced an alarm to indicate hypo- or hyperglycemia. RF, radio frequency.

Clinical efficacy of RT-CGM

Many randomized controlled trials have been performed to evaluate the clinical benefits of CGM. The initial reported studies, the durations of which were only a few days, showed that the use of RT-CGM leads to a reduction in both hyper- and hypoglycemic excursions with more time in the target glucose range [18, 19]. The GuardControl trial using the Medtronic Guardian was the first longer duration study of RT-CGM. This study enrolled 156 adults and children with T1DM using both pumps and MDI therapy [20]. At 3-month follow-up, the group randomized to RT-CGM use showed a 1.0 ± 1.1% (11 ± 12 mmol/mol) reduction in HbA_{1c} (down from 9.5 ± 1.1% [80 ± 12 mmol/mol] at baseline) compared with a 0.4 ± 1.0% (5 ± 11 mmol/mol) reduction in the control group ($p = 0.003$). In addition, at 3 months, 50% of participants in the CGM group had HbA_{1c} reductions of ≥1% compared with 15% of those in the control group, and 26% in the CGM group had HbA_{1c} reductions of ≥2% compared with 4% in the control arm. Reported results from this industry-supported study did not include any specific information on the treatment protocols used in the trial or data on the effect of CGM on hypoglycemia.

The results of two large-scale multicenter randomized controlled trials of 6 months' duration have been published: the industry-supported STAR-1 trial and the Juvenile Diabetes Research Foundation (JDRF)-sponsored CGM trial. The STAR-1 trial enrolled 146 participants aged 12–72 years with T1DM treated with CSII pumps [21] who were randomized to pump therapy with RT-CGM using the Medtronic 722 pump system or pump therapy with fingerstick self-monitoring of blood glucose. The primary endpoint was not achieved; there was a similar reduction in HbA_{1c} (0.71 ± 0.71% in the sensor group vs. 0.56 ± 0.072% in the control group; p = non-significant) over the 6-month trial. Importantly, in those using RT-CGM, the improvement in glycemic control was accomplished without any change in biochemical hypoglycemia ($p < 0.0002$), whereas in the control group who were using fingerstick glucose monitoring there was an increase in biochemical hypoglycemia (documented with blinded CGM devices). More severe hypoglycemic events occurred in the group using RT-CGM than in the control group (11 vs. 4; $p = 0.04$). During six of the 11 severe events in the RT-CGM group, the individuals were not using a sensor. The Data Safety Monitoring Board determined that in the remaining five severe hypoglycemic events there was evidence of the following:

1 failure of the individuals to respond to alarm warnings of hypoglycemia;

2 multiple insulin boluses without use of the pump bolus calculator, resulting in dose stacking; or

3 "blind boluses" (i.e. treatment decision based on sensor readings showing hyperglycemia without confirmatory fingerstick capillary blood glucose measurements).

This clinical experience from the Star 1 trial was incorporated into the treatment protocols and patient education materials used in the JDRF CGM trial.

The JDRF CGM trial enrolled 451 people with T1DM aged 8–74 years and HbA_{1c} <10% (86 mmol/mol) to an RT-CGM group or a group that continued with capillary blood glucose monitoring [22, 23]. This study involved people using both insulin pumps and injection therapy and used three different CGM devices (Abbott Navigator®, Dexcom Seven®, and Medtronic Guardian/722®), with assignment based on patient preference with investigator guidance. By design, the cohorts with HbA_{1c} at randomization of <7.0% (<53 mmol/mol; $n = 129$) and 7–10% (53–80 mmol/mol; $n = 322$) were analyzed separately.

For individuals with T1DM who have already managed to achieve HbA_{1c} levels in the optimal target range with intermittent capillary blood glucose monitoring, the main therapeutic challenge is minimizing the risk for hypoglycemia that accompanies intensive glucose control. Accordingly, for the cohort enrolled in this trial with baseline HbA_{1c} <7.0% (<53 mmol/mol), the prespecified primary endpoints were focused on changes in hypoglycemia rather than HbA_{1c} per se. At 26 weeks, biochemical hypoglycemia ≤3.9 mmol/L (70 mg/dL) was less frequent in the CGM group than in the control group using intermittent fingerstick monitoring (median 54 vs. 91 min/day), but this was not statistically significant. The median time spent with glucose level ≤3.3 mmol/L (60 mg/dL) was 18 vs. 15 min/day, respectively ($p = 0.05$). There were similar numbers of severe hypoglycemic events in the two groups; however, the trial was not adequately powered to detect a treatment group difference. More people in the CGM group than the control group had a decrease in HbA_{1c} of ≥0.3% without having a severe hypoglycemic event (28% vs. 5%; $p < 0.01$) [24].

For the cohort with baseline HbA_{1c} 7–10% (53–86 mmol/mol), the prespecified primary endpoint was HbA_{1c} reduction. A significant between-group difference in change in HbA_{1c} from baseline to 26 weeks was seen in those aged ≥25 years old, favoring the continuous monitoring group (mean difference in change –0.53%; $p < 0.001$), but not in the younger participants. Biochemical hypoglycemia evaluated by CGM was similar in the two treatment groups and there were no significant differences in the incidence of severe hypoglycemic events between the study groups. In the adult cohort, the frequency of the combined outcome of 26-week HbA_{1c} <7.0% (<53 mmol/mol) and no severe hypoglycemic events was 30% in the CGM group and 7% in the control group ($p = 0.0006$). A follow-up 6-month extension to this study in 83 adults showed, after 12 months, a reduction of HbA_{1c} of –0.4%. The incidence of severe hypoglycemia, in events per 100 person-years, dropped from 21.8 to 7.1 [25]. The finding that RT-CGM leads to an improvement in glycemic control without an associated worsening in hypoglycemic events is in direct contrast to other intervention studies such as the DCCT, in which intermittent capillary glucose monitoring had been used to guide intensification of metabolic control, and points to the promise hat this technology offers for people with T1DM.

The American Diabetes Association, in its clinical guidelines, concluded that CGM in conjunction with intensive insulin therapy is a useful tool to lower HbA_{1c} in selected adults aged ≥25 years with T1DM (level of evidence A: clear evidence from randomized clinical trials), that it may be helpful in younger adults, teenagers, and children, depending on adherence with the device (level of evidence C: supportive evidence from poorly controlled or uncontrolled trials), and that it may be a supplemental tool to SMBG in those with hypoglycemia unawareness and/or frequent episodes of hypoglycemia (level of evidence E: expert opinion or clinical consensus) [26].

Practical issues with the use of RT-CGM

The randomized controlled trials that have demonstrated the benefits of RT-CGM have involved individuals with a high level of engagement in their diabetes self-care (the mean number of daily capillary blood glucose measurements performed by people enrolling in the JDRF trial was six). Furthermore, to use this technology successfully, individuals need to have advanced diabetes self-management. In the following sections, we discuss several key issues that need to be addressed in the training of people starting on CGM.

Physiological lag between blood and interstitial glucose

The lag in the equilibration of glucose levels between the capillary blood (measured using a home blood glucose monitoring device) and the interstitial fluid in the subcutaneous tissue (measured by the CGM device) [27, 28] has important practical implications. In general, increases or decreases in the glucose concentration will first be apparent in the blood followed by the interstitial fluid. Currently available CGM devices are calibrated using fingerstick capillary blood glucose measurements, and to optimize sensor accuracy it is important that the device be calibrated only when the glucose level is relatively stable, and there is steady-state equilibration between glucose concentrations in the blood and interstitial fluid. In practice, calibrations should be performed preprandially or at least 3 h after a bolus (Box 30.1). Each manufacturer's instructions should be consulted to determine the timing and frequency of calibration for a specific CGM device.

The physiological lag has implications with regard to the detection and treatment of hypoglycemia. Because of the lag of interstitial glucose behind blood glucose, when the glucose level is declining the interstitial (sensor) glucose can be in the normal range even though the actual blood glucose is low [29]. Users should be instructed to perform a fingerstick blood glucose measurement before driving if the sensor glucose reading is normal and the trend graph or rate-of-change arrows on the sensor display indicate that the glucose level is declining (Box 30.2). As shown in

Box 30.1 Patient teaching points: calibration dos and don'ts.

- *Do* follow the manufacturer's instructions regarding the time and frequency of calibration to achieve the greatest possible accuracy.
- *Do* use only very recent blood glucose measurements for calibration.
- *Do not* calibrate when the blood glucose is changing at a significant rate, as indicated by trend arrows on the display. Some times when rapid blood glucose change may occur include:
  - within 3–4 h of a meal or an insulin bolus
  - during exercise
  - after recovering from hypoglycemia.

Box 30.2 Patient teaching points: circumstances where fingerstick capillary glucose must be checked.

- If the sensor indicates that the glucose is elevated, the reading must first be confirmed with a fingerstick capillary blood glucose measurement before the person takes a corrective bolus.
- When subjective symptoms are not in keeping with the sensor reading, such as a low CGM reading in the absence of hypoglycemic symptoms, a fingerstick reading should be taken to confirm the glucose level.
- Before or during driving, if the sensor reading is normal and the continuous glucose monitoring rate of change indicator or tracing indicates that the glucose level is falling, the person must measure fingerstick blood glucose.
- Following treatment of a low glucose level, if the sensor still shows a low reading, the person should check fingerstick blood glucose and use this measurement to decide whether to take in more carbohydrate. Reliance on the sensor reading to assess response can lead to overtreatment.

the study by Wilson et al. [30], when the glucose is falling rapidly, the physiological lag can also lead to underestimation of the true rate of fall of the blood glucose by the rate-of-change indicator of the CGM device. The practical implication is that if the person feels hypoglycemic or has reason to suspect that the glucose is declining, but this is not corroborated by the sensor, they should disregard the sensor data and carry out a fingerstick glucose measurement.

This lag phenomena also has practical implications for the treatment of hypoglycemia. During the recovery from hypoglycemia, the increase in the interstitial glucose will often lag behind the blood glucose [31], and when blood glucose has already normalized the sensor/interstitial glucose may still be in the low range. Individuals should be informed of the need to perform fingerstick glucose measurements to assess the response to treatment of hypoglycemia accurately. Those who rely on the RT-CGM to judge whether the glucose level is improving following ingestion of carbohydrates may mistakenly assume that they need to consume more glucose than necessary.

Setting glucose alarms

The alarms for hypoglycemia and hyperglycemia are an important feature of RT-CGM devices. There are trade-offs in the adjustment of alarm thresholds, and settings need to be individualized based on specific clinical considerations [32]. If the alarm thresholds are set at target or ideal glucose levels (e.g. low = 5 mmol/L [90 mg/dL]; high = 10 mmol/L [180 mg/dL]), there will be increased sensitivity for the detection of high and low glucose; however, the frequent false alarms can be a source of irritation and disrupt sleep, leading to "alarm fatigue" in some individuals, with a related tendency to ignore the alarms. There is also a risk of people sleeping through alarms. Buckingham et al. [33] found that people who were videotaped while sleeping awoke to only 29% of individual alarms and 66% of repeated alarms.

The adjustment of alarm thresholds is a stepwise process:

1 deciding on initial thresholds when initiating use of the sensor;
2 optimizing alarm thresholds over time based on retrospective review of continuous glucose tracings.

For persons with hypoglycemia unawareness or a history of severe hypoglycemic reactions, where the overriding imperative is on reducing hypoglycemia, the low glucose alarm threshold should be set at 4.5 mmol/L (80 mg/dL) or higher. Because of the physiological lag between blood and interstitial glucose, when the sensor alarm is triggered the blood glucose level will often be lower than the sensor measurement.

For individuals without a history of problematic hypoglycemia, it is a common practice to set the initial glucose thresholds at 3–3.5 mmol/L (55–60 mg/dL) and ≥14 mmol/L (250 mg/dL). This ensures that during the initial period after starting the use of CGM, while the individual is mastering the use of the technology, there will be fewer intrusive and irritating alarms, and less risk for alarm burnout. Over time, as the patient uses the information from the sensor to reduce glucose excursions, the alarm settings can be brought closer to target glucose levels, and this can assist with further tightening of glycemic control. A snooze alarm prevents the CGM from sounding continuously for a prolonged episode. Typically, this alarm will be set for 15–30 min for hypoglycemic events and for 2–3 h for hyperglycemic events (which take longer to resolve than hypoglycemic events). In some CGMs, a predictive alarm can be set to sound when the glucose level is predicted to reach a preset threshold. During follow-up visits, the clinician should enquire whether the sensor alarm alerted the individual to low or markedly elevated glucose levels, and whether they were troubled by frequent false alarms. If there are frequent high glucose levels (especially during the overnight period) and the person is not being appropriately alerted by the sensor to take

corrective action, the high alarm threshold should be reduced. Conversely, if the individual has experienced hypoglycemic reactions without being alerted by the CGM alarm, the low alarm threshold will need to be set at a higher level.

Risk for hypoglycemia from excessive postprandial bolusing

Although the glucose alarms and trend indicators on CGM devices can be helpful in minimizing hypoglycemia, some individuals will overreact to the postprandial glucose spikes revealed by the continuous sensor by taking excessive doses of insulin [34], leading to an increased risk for hypoglycemia. Minimizing this tendency for postprandial overbolusing (known as stacking—not considering remaining insulin from prior injections) should be a major focus in the training of the individual using CGM. People need to factor in the amount of residual insulin on board from the previous bolus before taking additional insulin to treat postprandial hyperglycemia. "Insulin-on-board" (IOB) calculators to help in this determination are available on insulin pumps (discussed later in this chapter) and for non-pump users bolus calculators that include an IOB estimation are being developed both as a feature of a glucose monitor or as a mobile app. In 2014, the Roche ACCU-CHEK® Aviva Expert system became the first and only freestanding blood glucose meter system with a built-in insulin bolus calculator to be approved by the FDA.

Continuous subcutaneous insulin infusion pumps

Continuous subcutaneous insulin infusion (CSII) pumps were first introduced almost 40 years ago [35, 36]. They consist of an insulin reservoir and a delivery catheter that infuses insulin continuously into the subcutaneous tissue. In recent years, there has been growing adoption of this technology in diabetes care. Several factors have contributed to this increased use, including the focus on intensive therapy triggered by the Diabetes Control and Complications Trial (DCCT), improvements in the reliability and usability of pumps, patient preferences, and also the growing recognition by clinicians that CSII delivery is associated with reduced risk for hypoglycemia. Recent literature has pointed out the potential advantages of pumps as a tool for insulin administration and newer developments in pump technology such as bolus calculator software and square-wave delivery have made these devices easier to use.

Glycemic control with insulin pumps compared with multiple daily insulin injections

Several published meta-analyses have examined the role of CSII pumps as a tool for intensifying glycemic control [37–39]. These meta-analyses of the randomized controlled trials in the published literature indicate that CSII use in people with T1DM is associated with 0.4–0.5% (5–6 mmol/mol) lower HbA_{1c} than for multiple daily injection (MDI) therapy. The improvements in HbA_{1c} with the change to pump therapy appear to be greater in individuals who have poorer glycemic control [40, 41]. Most of the studies examined in these meta-analyses involved MDI regimens using neutral protamine Hagedorn (NPH) or ultralente insulins; however, more recent randomized controlled trials suggest that CSII is also superior to MDI regimens using the newer long-acting insulin analogs insulin glargine and insulin aspart [42, 43].

Although CSII has been studied primarily in T1DM, a recent study in individuals with T2DM who did not achieve adequate glycemic control on MDI compared participants randomized to either MDI using analog insulin or MDI, and found that mean HbA_{1c} declined by 1.1% in the CSII group and by 0.4% in the MDI group ($p < 0.0001$). The mean total insulin dose was 97 units on CSII and 122 units on MDI, with no significant difference in weight change in the two groups [44]. Two adverse events requiring hospitalization occurred in the CSII group: hyperglycemia and ketosis without acidosis. One episode of severe hypoglycemia occurred in the MDI group and none in the CSII group. Device malfunction and problems with either the infusion set or the infusion site may occur with modern pump technology, which points to the importance of providing education on proper catheter site care and ketoacidosis prevention to all individuals using pumps. In addition, a small-scale crossover study in obese individuals with T2DM and insulin resistance also demonstrated a significant reduction in HbA_{1c} and postprandial glucose excursion with the use of pump therapy [45]. On the other hand, the studies by Raskin et al. [46] and Herman et al. [47] showed similar HbA_{1c} changes with both modes of insulin delivery.

Because of the more controlled delivery of insulin, CSII can be an effective tool for reducing glycemic variability, and this can be of benefit for reducing the risk for hypoglycemia brought about by insulin replacement therapy [48]. Clinical guidelines from several national and international organizations recommend consideration of pump therapy for individuals with T1DM with suboptimal glycemic control and problematic hypoglycemia, as summarized in Box 30.3 [25, 49, 50]. Although earlier studies gave conflicting results, the meta-analysis of randomized controlled trials by Pickup and Sutton [51], which was restricted to studies published since 1995 (i.e. since the introduction of more reliable pump technology) with a baseline (pretrial) rate of severe hypoglycemia of >10 episodes per 100 patient-years and ≥6 months of CSII use, showed that there was a 2.9-fold (95% confidence interval [CI] 1.45–5.76) reduction in severe hypoglycemia during CSII compared with MDI. The analysis also indicated that the benefit from pump therapy was greater in individuals with higher rates of severe hypoglycemia ($p < 0.001$) and those with longer duration of diabetes ($p = 0.025$). A meta-analysis commissioned by the Endocrine Society reached different findings, and concluded that in comparison with MDI, CSII was not associated with a significant reduction in severe or nocturnal hypoglycemia [52]. The validity of these conclusions is limited by the inclusion of studies of relatively short duration with low incidence rates of severe hypoglycemia that would be underpowered to detect any significant decrease in the incidence

of hypoglycemia and would therefore bias against recognition of benefit from insulin pump therapy. In addition, the rates of minor and nocturnal hypoglycemia were determined using intermittent fingerstick glucose monitoring, which can be unreliable in detecting nocturnal hypoglycemic events [53] and would therefore be relatively insensitive to detecting treatment-related differences. Furthermore, it should also be noted that the studies examined in the Endocrine Society analysis were performed using almost entirely older pump types that did not incorporate the bolus calculator software now available in updated pumps, which can help to limit hypoglycemia related to doses stacking up from repeated boluses. These factors limit the generalizability of the conclusions from this analysis to clinical practice. The weight of evidence from published studies suggests that clinicians caring for motivated individuals with T1DM with recurrent hypoglycemia and especially a history of severe hypoglycemic reactions should recommend a trial of insulin pump therapy. The STAR 3 study in children and adolescents demonstrated that sensor-augmented pump therapy improved HbA_{1c} and glucose area under the curve with no increased risk of hypoglycemia compared with MDI therapy [54]. An interesting ancillary finding in the STAR 3 study was that improving overnight and post-breakfast glucose levels had the greatest effect on lowering HbA_{1c} levels [55].

Box 30.3 Pump therapy: indications and considerations.

- Severe hypoglycemia and hypoglycemia unawareness.
- HbA_{1c} above goal.
  Caution: Intentional insulin omission (to facilitate weight loss) is a not uncommon cause of poorly controlled diabetes, especially in young women [56]. Before initiating pump therapy, it is important to rule out this problem. Because these individuals habitually underdose insulin and are frequently hyperglycemic, they do not routinely troubleshoot for insulin non-delivery by the pump and can therefore be at increased risk for developing ketoacidosis.
- Diurnal variations in basal insulin requirements caused by the dawn phenomenon [57] and steroid therapy [58] have been reported to be more readily managed using the multiple basal rates provided by the pump than by long-acting injected insulins. However, Bouchonville et al. reported that people who programmed their pump to counteract the dawn phenomenon did not reduce the dawn phenomenon and also had more frequent hypoglycemia [59]. A potential reason for the failure to improve therapy with programming, the authors proposed, was the unpredictable occurrence of the dawn phenomenon. Continuous subcutaneous insulin infusion can be of special benefit for the person with diabetes post-renal transplant on steroid therapy who is striving for intensive glycemic control.
- Preconception and pregnancy.

Box 30.3 (*Continued*)

- Practical advantages of pumps for bolus insulin delivery include:
  - *Dosing precision:* The extra precision of insulin dosing with pumps can be an important advantage for young children (especially infants and neonates) [60] and adults who are on very low insulin doses. In addition, accurate dosing of insulin boluses in fractions of a unit allows the patient to correct hyperglycemia more precisely without overshooting and causing hypoglycemia. For those patients in whom fear of hypoglycemia is an impediment to tight glycemic control, this added assurance can be critical in overcoming reluctance to intensification. In practice, it can be helpful to reduce missed food boluses, facilitate interprandial "correction" bolusing, and help simplify eating at restaurants and social occasions (with the use of extended/square-wave boluses and multiple bolusing).
  - *Optimizing postprandial insulin coverage:* Facilitates dosing for higher fat, complex carbohydrate, and/or larger meals. Dietary fat delays gastric emptying [61] and induces postprandial insulin resistance [62], so high-fat meals cannot usually be adequately covered using a single injection of rapid-acting insulin [63]. Use of the extended/dual bolus [64] and increased temporary basal can help optimize postprandial glycemic control following these meals [65].
  - *Gastroparesis:* Use of the extended/dual-wave bolus can allow for better matching of carbohydrate absorption and insulin action.

When people are unable to achieve adequate glycemic control, several practical issues should be considered (Box 30.4). A number of publications, oriented to both people with diabetes and health-care providers, can provide detailed strategies [66, 67].

Box 30.4 Practical issues to consider in people on pump therapy with erratic glucose control.

- *Infusion site issues including scarring, hyperpigmentation, lipohypertrophy, and lipoatrophy:* Infusion sites should be routinely examined in pump users with unexplained glucose fluctuations.
- *Infusion catheter kinking or dislodgement:* Plastic catheters may kink or become dislodged, especially with activity or perspiration. Solutions include changing to sets with a shorter cannula, or other types of plastic infusion sets that are less prone to kinking, and sets that insert obliquely.
- *Failure to change the pump reservoir and infusion system on a regular basis:* This may manifest in a tendency for

Box 30.4 (*Continued*)

elevated and erratic glucose in the period preceding infusion set changes.

- *Review of pump downloads can be helpful:*
  - Check priming history to assess how frequently the infusion system is being changed.
  - Check bolus history to detect possible missed meal boluses.
  - Check percentage of basal to bolus insulin. A high percentage of basal insulin in the person with frequent hyperglycemia may indicate that bolus doses are frequently being missed. A high percentage of basal insulin in the person with frequent hypoglycemia may indicate that high basal rates are contributing to hypoglycemia, and would point to a need to re-evaluate basal rate settings. A low percentage of basal insulin can result in high preprandial glucose levels followed by large correction doses at mealtime followed by occasional resultant postprandial hypoglycemia.
  - Check for a history of pump suspension or basal rate reduction. Even temporary removal of the pump to bathe can lead to elevations in the glucose levels; people need to be reminded to bolus to replace the missed basal when reconnecting the pump. Some individuals using the pump will get into the practice of reducing the basal rate or suspending the pump when they are hypoglycemic; the end result will often be exaggerated rebound hyperglycemia
- *Insulin instability in the pump infusion system:* This can manifest as increases in the glucose levels in the period preceding infusion set changes or even precipitation in the infusion system [68].
- *Pump malfunction.*
- *Air bubbles in the infusion system* resulting from poor filling technique.
- Temperature of pump and insulin exceeds the storage range recommended by the manufacturer of each short-acting insulin, which is no lower than 36 °F and no higher than 75–86 °F, depending on the product.

Quality of life benefits and patient expectations

Many people describe improvements in quality of life when they change to pump therapy [69]; however, there have been few carefully designed studies that have examined patient perspectives of pump therapy and differences in psychosocial functioning with CSII compared with MDI. People will vary in their perceptions about the potential quality of life benefits (including increased lifestyle flexibility, dietary freedom, and reduced fear for hypoglycemia) relative to some of the potential drawbacks of CSII (including body image concerns and the need for frequent blood glucose monitoring) [70]. Wolpert and co-workers conducted a focus group investigation of 30 people followed at the Joslin Diabetes Center to examine how psychosocial factors impacted the use of the pump [71]. Those with better glycemic control viewed the pump as a tool for diabetes self-management rather than as a panacea. In contrast, individuals on pump therapy with poorer HbA_{1c} had more unrealistic expectations, including the perception that the use of technology was a substitute for attentiveness to self-care and that pump therapy allowed them to do whatever they wanted, particularly with regard to eating. Before initiating pump therapy, healthcare professionals need to assess patients' expectations of the pump, dispel unrealistic notions (often promoted by marketing materials) and ensure that they recognize that although the pump allows life with diabetes to be more flexible and convenient, it is not a vehicle for total freedom from diabetes.

Bolus calculators and insulin-on-board

Software programs that assist people with bolus calculations have been incorporated into insulin pumps. The insulin : carbohydrate ratio (the number of grams of carbohydrate covered by 1 unit of insulin) and correction/sensitivity factor (a measure of the glucose-lowering effect of 1 unit of insulin) is programmed into the pump software. Based on planned carbohydrate intake of the pump user and the blood glucose level, the bolus calculator will recommend a bolus dose. Although this dose calculation software can simplify the daily self-care routines of the pump users, patients should receive appropriate education to ensure that they can manually calculate bolus doses in the event that they need to discontinue pump therapy. In addition, it is important that the programming of the bolus calculator software is adjusted to individual needs and not left automatically at the manufacturer's default settings. These bolus calculators have an important role in minimizing the risk for hypoglycemia from multiple boluses that result in cumulative dose stacking, which are a common practical problem for some pump users. When calculating an insulin dose, the pump software will consider the amount of active insulin-on-board resulting from earlier boluses (commonly referred to as IOB) and subtract this IOB from the recommended dose. This IOB calculation is based on insulin action plots that predict the amount of insulin remaining as a function of time; the assumed insulin duration of action used by the software in this calculation is individually programmed by the person with diabetes or healthcare professional, and can be varied depending on the pump type [72]. In practice, the major consideration in setting the insulin duration of action in the bolus calculator software is usually a best guess based on a clinical assessment of the hypoglycemia risk of the individual and the imperative for achieving tight glycemic control (in particular, preconception and pregnancy) [73]. For those with frequent hypoglycemia, hypoglycemia unawareness, or a history of severe hypoglycemic reactions, the duration of action may be set longer, whereas for the woman who is pregnant or trying to conceive, a shorter duration of action is often set. The glucose records of the individual can be assessed to determine if the duration of action settings are appropriate. If the duration of action time programmed into the software is less than the true duration of action,

the pump will indicate that there is less IOB than is actually the case, and the pump user will mistakenly take more insulin than required; the glucose records will show evidence of hypoglycemia from "stacking" of doses. Conversely, if the setting programmed into the pump is longer than the true duration of insulin action, this can lead to underdosing of insulin and hinder attempts to optimize glycemic control.

Patch pumps

Although insulin pumps have become significantly smaller since they were first introduced, they are still relatively bulky and, owing to their electronic sophistication, relatively expensive. Several companies are now working on various types of "patch pumps," devices that have a low, flat profile that fit snugly against the body. They generally do not have the ability to deliver multiple basal rates or preprogrammed boluses. Primarily intended for use in T2DM, various configurations of patch pumps may deliver only basal insulin at a prefixed rate, insulin boluses in fixed increments when manually activated by the user, or both basal and bolus insulin. Their simpler structure allows for a less expensive device. Clinical studies are ongoing to determine the clinical benefits of such systems.

Closed-loop insulin delivery: the artificial pancreas

Insulin pump therapy as it is currently used is considered to be an "open-loop system," in which the person with diabetes must make decisions about when to check the glucose level and what to do with the information. Clearly, there is inherent human error in this system and overdosing or underdosing of insulin based on a small miscalculation could result in subsequent hypoglycemic or hyperglycemic episodes, respectively. In a "closed-loop system" that integrates a continuous glucose monitor and insulin pump, together with an automated algorithm to control insulin delivery, the person with diabetes would be removed from the decision loop, and the system would essentially function as an artificial pancreas.

At present, one of the major challenges for the fully automated closed-loop system may be in the development of a fail-safe algorithm that is capable of "interpreting" a person's metabolic state based on data obtained from the continuous glucose monitor and then relaying this information to the pump for automatic insulin delivery of the appropriate dose of insulin. Several algorithms, including model predictive control and proportional integral derivative control, are already being evaluated in both *in vivo* and *in silico* settings [74]. There are also several technical obstacles to developing a closed-loop system, including having glucose sensors that are both accurate and reliable (e.g. minimal calibration drift, limited potential mechanisms for sensor failure), and also physiological lag, which can be particularly problematic during times of rapid rates of change in blood glucose levels (e.g. during meals or exercise) [75]. Hence the development of a sensor with a short lag time would also be important.

Because of the amount of research that must be done to establish the effectiveness, and especially the safety, of a fully closed-loop system, intermediate steps have been suggested [76]. An initial approach is a system that will automatically discontinue insulin administration if the glucose sensor detects a level below a preset value, or if the glucose trend predicts that a low glucose is likely. Such a type of sensor-augmented pump therapy with low glucose threshold suspend has been shown to lead to a 38% reduction in nocturnal hypoglycemic events without increasing glycated hemoglobin values [77]. The first closed-loop product with any automatic control of insulin is the Medtronic (Northridge, CA, USA) low glucose suspend sensor augmented pump, known as 530G with Enlite in the United States and Veo in Europe. Predictive algorithms have also been shown to reduce the incidence of hypoglycemia during exercise in preliminary studies [78]

A second step in the development of an artificial pancreas is the control to range (CTR) approach. A CTR system reduces the likelihood of a hypoglycemic event or a hyperglycemic event (when blood glucose is dangerously high) by adjusting insulin dosing only if a person's glucose level approaches the low or high glucose thresholds. People using this system will still need to check blood glucose levels and give themselves insulin to maintain control of glucose levels. The final stage would be a control to target (CTT) system. A CTT system sets target glucose levels and tries to achieve these levels at all times. This system is fully automated and requires no interaction from the user except for calibration of the continuous glucose monitoring system [76]. A CTT system could be based on an insulin-only approach, a bihormonal approach (using one hormone to lower glucose and another to raise it), or a hybrid approach that allows the individual to supplement insulin automatically before a meal [76].

A small study of a CTR system using a fully automated closed-loop single-hormone system demonstrated that during the study period, which included unannounced meals and exercise, 80% of values could be maintained between 70 and 180 mg/dL and there were no values below 60 mg/dL [79]. Weinzimer et al. compared a fully closed-loop (FCL) insulin-only system with a hybrid closed-loop (HCL) system in which the individual could manually give a premeal priming bolus. Mean glucose levels were 135 ± 45 mg/dL in the HCL group versus 141 ± 55 mg/dL in the FCL group ($p = 0.09$), and daytime glucose levels averaged 149 ± 47 mg/dL in the HCL group versus 159 ± 59 mg/dL in the FCL group ($p = 0.03$). Peak postprandial glucose levels averaged 194 ± 47 mg/dL in the HCL group versus 226 ± 51 mg/dL in the FCL group ($p = 0.04$). Nighttime control was similar in both groups (111 ± 27 vs. 112 ± 28 mg/dL) [80]. A multicenter study using a CTR algorithm demonstrated that the mean percentage of values in the 71–180 mg/dL range was 66%. The system fared better overnight than during the day and had difficulty preventing postprandial excursions above the target range. Performance was variable between participants even after individualization [81].

Haidar et al. studied a bihormonal artificial pancreas, using insulin and glucagon, and compared it with an insulin-only artificial pancreas and with conventional insulin pump therapy (CSII) in a randomized crossover study [82]. They found that both single and dual hormonal therapy provided better glycemic control than conventional CSII. The mean proportional time in the glucose target range was 62% with single hormonal therapy, 63% with dual hormone therapy, and 51% for CSII. Both closed-loop systems were statistically improved over CSII. There were 52 hypoglycemic events with conventional insulin pump therapy (12 of which were symptomatic), 13 with the single-hormone artificial pancreas (five of which were symptomatic), and nine with the dual-hormone artificial pancreas (none of which were symptomatic); the number of nocturnal hypoglycemic events was 13 (0 symptomatic), 0, and 0, respectively. A bihormonal fully automatic closed-loop system was also studied by Russell et al. [83]. Their "bionic" pancreas consisted of a glucose sensor and two infusion pumps, with an algorithm on a mobile phone wirelessly controlling the pumps. Over a 5-day unrestricted outpatient period, the "bionic" pancreas improved mean glucose levels, with less frequent hypoglycemic episodes, compared with conventional insulin pump therapy.

Insulin pens

The insulin pump frees people with diabetes from the need to draw up insulin accurately from an insulin vial prior to each injection. This eliminates a potential source of patient error in insulin therapy, but adds a new level of complexity in filling and priming the pump. For those who do not require the flexibility of basal-bolus therapy that a pump offers, the insulin pen offers a way to inject insulin conveniently and accurately without the need to carry an insulin vial and individually draw up each dose. A pen may be a prefilled disposable device or may use a replaceable insulin cartridge, and includes a mechanism for delivering a specified number of units. Compared with a syringe and insulin vial, pens have been shown to be more accurate, particularly at doses less than 5 units [84], and to lead to increased patient satisfaction [85]. Studies in hospitalized patients have also shown that nurses felt that pens were easier to use and led to increased dosing confidence [86] and greater patient and provider satisfaction, improved safety, and reduced costs. [87] Newer pens, such as the NovoPen Echo®, HumaPen®, LUXURA® HD, and JuniorSTAR® can deliver in half-unit increments. Some pens also have a memory to review dosing.

Inhaled insulin

Survey studies have indicated that fear of needles and discomfort and inconvenience from injecting insulin are barriers to the use of insulin by many. The lung is an attractive mode for administration of a systemic drug because of its large available area for drug absorption and accessibility. A number of approaches to inhaled insulin have been tried. In January 2006, the FDA approved the use of Exubera® (Pfizer), the first inhalable insulin, but this was later withdrawn from the market for commercial reasons.

Afrezza® (insulin human) Inhalation Powder, developed by MannKind Corporation, was approved by the FDA in 2014. It is based on Technosphere® technology in which insulin particles are optimized for inhalation (2.5 μm in diameter) and dissolve rapidly after inhalation (pH-sensitive carrier particles). Pharmacokinetic studies have demonstrated that this formulation has very rapid systemic insulin uptake (insulin T_{max} ≈12–14 min), a fast onset of action (maximum activity ~20–30 min), and a short duration of action (~2–3 h) [88], which could potentially provide better postprandial control than subcutaneously injected insulin [89].

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31 Oral Glucose-Lowering Agents

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Key points

- Glycemic control is a fundamental part of the management of type 2 diabetes mellitus. Adequate glycemic control is necessary to address acute symptoms and to prevent, defer, or reduce the severity of chronic microvascular and macrovascular complications.
- Treating type 2 diabetes is complicated by the multivariable and progressive natural history of the disease. Insulin resistance, a progressive decline in β-cell function, defects of other gluco-regulatory hormones, and nutrient metabolism, give rise to a continually changing presentation of the disease that requires therapy to be adjusted accordingly. People with diabetes are often overweight or obese, exhibit substantial comorbidity and elevated cardiovascular risk, and receive many other medications that further complicate treatment.
- Care plans and treatment programs should be tailored to fit the prevailing circumstances of the individual. Lifestyle management (diet and exercise) should be emphasized from the time of diagnosis and reinforced thereafter. Drug treatment should be undertaken promptly if lifestyle intervention does not achieve adequate glycemic control.
- Choice of drug therapy should ideally address underlying pathophysiology, but any safe means of restraining the escalating hyperglycemia may be appropriate. Combinations of differently acting agents are frequently required to provide additive efficacy, and single-tablet, fixed-dose combinations are available to facilitate combination therapy. Contraindications and precautions associated with each component must be respected.
- The biguanide metformin is often selected as initial oral glucose-lowering therapy. It counters insulin resistance and lowers blood glucose through several insulin-dependent and -independent mechanisms, notably reducing hepatic glucose production and also increasing glucose uptake by skeletal muscle. It does not stimulate insulin secretion, carries a low risk of frank hypoglycemia, and does not cause weight gain. Metformin also exerts several potentially beneficial effects on cardiovascular risk factors independently of glycemic control, with evidence of improved long-term cardiovascular outcomes. Metformin may be conveniently combined with other classes of glucose-lowering drugs. Gastrointestinal side effects including diarrhea limit the use of metformin. The rare but serious adverse effect of lactic acidosis precludes the use of the drug in people with significant renal insufficiency, significant liver disease, or any condition predisposing to hypoxia or hypoperfusion including cardiac or respiratory failure.
- Sulfonylureas (e.g. gliclazide, glimepiride, glibenclamide/glyburide, glipizide) act on the pancreatic β cells to stimulate insulin secretion. They bind to the transmembranal complex of sulfonylurea receptors SUR1 with ATP-sensitive Kir6.2 potassium efflux channels. This closes the channels, depolarizes the membrane, opens voltage-dependent calcium channels, and raises intracellular free calcium concentrations. This in turn activates proteins that regulate insulin secretion. The efficacy of sulfonylureas depends on adequate remaining function of the β cells. Hypoglycemia is the most serious adverse effect, particularly with longer acting sulfonylureas and in the elderly. Caution with hepatic and/or renal insufficiency is warranted in accordance with the metabolism and elimination of individual preparations, and interactions with other protein-bound drugs can occur.
- Meglitinides (repaglinide and nateglinide), also known as prandial insulin releasers, are rapid and short-acting insulin secretagogues taken before meals to boost insulin levels during digestion, thereby reducing prandial hyperglycemia and decreasing the risk of interprandial hypoglycemia. They act in a similar manner to sulfonylureas by binding to a "benzamido" site on the SUR1–Kir6.2 complex. They are conveniently used in combination with an agent that reduces insulin resistance.
- Thiazolidinediones (pioglitazone and rosiglitazone) produce a slow-onset glucose-lowering effect, attributed mainly to increased insulin sensitivity. They alter the expression of certain insulin-sensitive genes by stimulating the peroxisome proliferator-activated receptor γ, increasing adipogenesis, and rebalancing the glucose–fatty acid (Randle) cycle. Thiazolidinediones can be used as monotherapy or in combination with other classes of glucose-lowering agents. They have a low risk of hypoglycemia but often cause weight gain. The potential for fluid retention and an attendant risk of congestive heart failure should be borne in mind, especially in

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combination with insulin. Thiazolidinediones are not recommended for individuals at high risk for cardiac disease or women with reduced bone density, and one or other agent in this class has been discontinued in some countries.

- Dipeptidyl peptidase 4 (DPP-4) inhibitors (sitagliptin, vildagliptin , saxagliptin, linagliptin and alogliptin), also termed gliptins, act predominantly as prandial insulin secretagogues by raising the circulating concentrations of endogenous incretin hormones, notably glucagon-like peptide 1 (GLP-1). This enhances the "incretin" effect of endogenous GLP-1 to potentiate nutrient-stimulated insulin secretion. DPP-4 inhibitors are weight neutral and, as monotherapy, they carry a low risk of interprandial hypoglycemia. They are often used in combination with metformin or a thiazolidinedione.
- Sodium–glucose co-transporter-2 (SGLT-2) inhibitors (canagliflozin, dapagliflozin, empagliflozin) increase the elimination of excess glucose in the urine (glucosuria) by reducing glucose reabsorption from the renal filtrate. They carry a low risk of hypoglycemia and the glucosuria facilitates weight loss. Their action is independent of insulin, enabling use with other glucose-lowering agents irrespective of the extent of insulin resistance or β-cell dysfunction, but their efficacy requires adequate renal function. The glucosuria may increase the risk of genital and urinary tract infection, although an associated osmotic diuresis may assist blood pressure control.
- α-Glucosidase inhibitors (acarbose, miglitol, voglibose) slow the digestion of carbohydrates by competitive inhibition of intestinal α-glucosidase enzymes. This delays glucose absorption and reduces postprandial glucose excursions without stimulating insulin secretion. These agents must be used in conjunction with meals rich in digestible complex carbohydrate. They do not cause weight gain or hypoglycemia as monotherapy and can be used alongside any other glucose-lowering agents.
- The dopamine D2 receptor agonist bromocriptine and the bile sequestrant colesevelam have an indication for the treatment of type 2 diabetes in some countries. Their glucose-lowering mechanisms are unclear but they do not cause weight gain and carry a low risk of hypoglycemia.
- As type 2 diabetes advances, combinations of glucose-lowering agents with different modes of action are often required. Eventually β-cell function can become too severely compromised to support the continued use of oral agents alone and/or other non-insulin treatments. Insulin therapy should then be initiated, continuing one or more other agents where appropriate.

Introduction

Appropriate glycemic control is fundamental to the management of type 2 diabetes mellitus (T2DM). It is required to prevent and relieve acute symptoms and complications of hyperglycemia, prevent, defer, and reduce the severity of microvascular complications, and afford some benefits against macrovascular complications (Table 31.1) [1]. Treatment of the hyperglycemia is an integral part of individualized care that takes account of coexisting diseases and personal circumstances, offers suitable advice on lifestyle and diet, includes other measures to address modifiable cardiovascular risk, selects realistic targets, and facilitates patient education and empowerment, as considered in detail in Part 5. This chapter focuses on the role of oral blood glucose-lowering agents (other glucose-lowering therapies are addressed in Chapters 29 and 32) in the treatment of T2DM [2–5].

Table 31.1 Aims of appropriate glycemic control in T2DM.

Purpose	Complications
Prevent acute symptoms of hyperglycemia	Dehydration, thirst, polyuria, blurred vision, increased infections
Prevent acute complications	Hyperosmolar non-ketotic state
Prevent, defer or reduce severity of chronic vascular complications	Microvascular: retinopathy, nephropathy, neuropathy
	Macrovascular: coronary, cerebrovascular, peripheral vascular

Pathophysiological considerations

The interdependent multiplicity of genetic and environmental factors underlying T2DM gives rise to a highly heterogeneous and progressive natural history [1, 6, 7]. The pathophysiology typically involves defects of insulin secretion *and* insulin action. Obesity, especially visceral adiposity, and abnormalities of glucagon secretion, incretin hormone action, the microbiome, inflammation and neurotransmitters contribute to the disease process, while cellular disturbances of nutrient metabolism participate as both causes and consequences of glucotoxicity and lipotoxicity [8–10]. An ideal approach to therapy might therefore address the basic endocrine defects, but any other safe means of ameliorating the hyperglycemia and attendant biochemical disruptions should provide clinical benefits.

The progressive nature of T2DM was well illustrated by the UK Prospective Diabetes Study (UKPDS), a randomized trial of 5102 individuals with newly diagnosed T2DM followed for a median of 10 years while receiving either "conventional" (diet) therapy or "intensive" therapy with various oral glucose-lowering agents or insulin (Figure 31.1). Note that insulin was introduced earlier than is usual in clinical practice, and insulin was also used as necessary when oral agents were deemed inadequate. Although glycemic control (illustrated by the glycated hemoglobin [HbA_{1c}] level) deteriorated with time irrespective of the treatment, the improvement in glycemic control afforded by intensive therapy (median HbA_{1c} reduced by 0.9% [10 mmol/mol]) was associated with a 12% reduction in overall diabetes-related endpoints and a 25% reduction in microvascular endpoints [11]. An

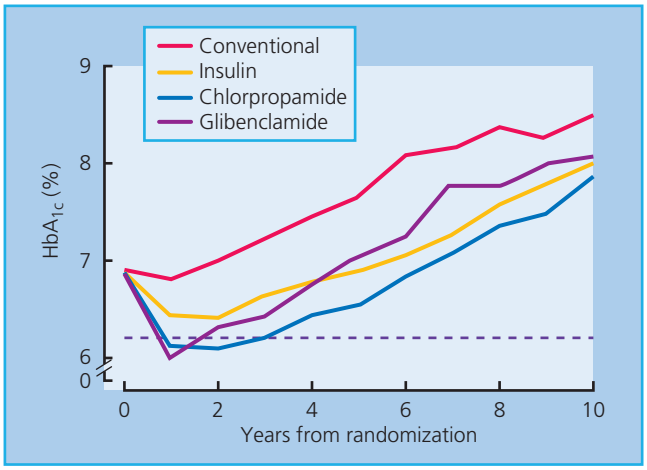

Figure 31.1 The UK Prospective Diabetes Study (UKPDS) shows the progressive rise in HbA_{1c} occurring with time in groups receiving "conventional" (diet) therapy and "intensive" therapy with various glucose-lowering drugs (two sulfonylureas—chlorpropamide and glibenclamide—and insulin). Source: Data from UK Prospective Study (UKPDS) Group [11].

epidemiological analysis showed that benefits of intensive therapy continued to accrue until glucose levels were returned to the normal range [12]. Moreover, the benefits of earlier "intensive" control were continued during an unrandomized post-trial follow-up (median 8.5 years) during which glycemic differences between the former groups were not maintained [13]. This illustrates the glycemic "legacy" effect in which early intensive glycemic control confers an extended reduction in complications, even when control deteriorates at later stages in the disease process.

Other large randomized trials [14–16] have confirmed fewer microvascular complications amongst those receiving more intensive glycemic management (Table 31.2). One such study, the Action to Control Cardiovascular Risk in Diabetes (ACCORD) study, noted increased mortality during highly intensified (5% mortality, 257/5128) versus standard (4% mortality, 205/5123) glycemic management. Although the cause the increased mortality associated with highly intensified management remains uncertain, deaths were more common among those individuals who continued to have poor glycemic control [17]. In this context, it is noteworthy that an acceptable HbA_{1c} value does not exclude excessive daily fluctuations in glycemia with hyperglycemic excursions and hypoglycemic troughs, the latter often unrecognized nocturnally. Survival of a myocardial event appears to be reduced by both hypo- and hyperglycemia [18].

Guidelines and algorithms

Factors to consider when selecting a glycemic target for a particular individual are deliberated in detail in Chapter 33, but it is pertinent to reiterate here that the general principle is to return glycemia safely as close to normal as practicable, while avoiding hypoglycemia, minimizing adverse effects on body weight and potential drug interactions, and observing other necessary cautions and contraindications. An individualized approach is recommended. Current treatment algorithms [3, 4] provide a framework for initiating and intensifying therapy, but clinical judgment should be applied to harmonize this with patient circumstances. Thus, a younger, newly diagnosed individual without comorbidity who is responsive to therapy might be expected to meet a more rigorous target, whereas an elderly, infirm individual with comorbidity or a long history of problems with diabetes control

Table 31.2 Trials comparing intensive with standard (conventional) glycemic control in type 2 diabetes.

Trial	No.	Duration of follow-up (years)	Age (years)	Duration of diabetes (years)	Baseline HbA_{1c} (%)	Intensive HbA_{1c} (%)		Conventional HbA_{1c}%	Relative risk reduction			
									Microvascular		Macrovascular	
									%	*p*	%	*p*
UKPDS	3867[a]	10	53	New	7.1[b]	7.0	vs.	7.9	↓ 25	0.009	↓ 16[c]	0.052[d]
UKPDS (post-trial follow-up)	2998	8.5	63	10	–		–		↓ 24	0.001	↓ 15[c]	0.014
ADVANCE	11140	5	66	8	7.5	6.5	vs.	7.3	↓ 14	0.01	↓ 6	0.32[b]
ACCORD[e]	10251	3.5[e]	62	10	8.3	6.4[e]	vs.	7.5	↓ 33	0.005[f]	↓ 10	0.16[b]
VADT	1791	5.6	60	11.5	9.4	6.9	vs.	8.4	↓ 2.5[g]	0.05	↓ 12	0.14[b]

[a] Non-obese participants.
[b] After a 3-month dietary run-in.
[c] Myocardial infarction.
[d] Non-significant.
[e] Intensive therapy discontinued at median 3.5 years because of increased deaths in the intensive (257/5128; 5%) versus conventional (203/5123; 4%) group.
[f] Reduction in new or worsening nephropathy. No effect on incidence of progression of retinopathy.
[g] Any increase in albuminuria.
ACCORD, Action to Control Cardiovascular Risk in Diabetes; ADVANCE, Action in Diabetes and Vascular Disease: Preterax and Diamicron-MR Controlled Evaluation; UKPDS, UK Prospective Diabetes Study; VADT, Veterans Affairs Diabetes Trial.

may require a less rigorous target. Management of hyperglycemia should always be part of a comprehensive management program to address coexisting disease and modifiable cardiovascular risk factors.

It is emphasized that diet, exercise, and other lifestyle measures should be introduced at diagnosis and reinforced at every appropriate opportunity thereafter. These measures can provide valuable blood glucose-lowering efficacy and may initially enable the desired glycemic target to be achieved. However, even when lifestyle advice is successfully implemented, the progressive natural history of the disease dictates that the majority of people with T2DM will later require pharmacological therapy, and this should be introduced promptly if the glycemic target is not met or not maintained.

The main classes of oral glucose-lowering drugs and their principal modes of action are listed in Table 31.3. Not all agents are available in all countries and prescribing information may vary between countries. The main tissues through which agents exert their glucose-lowering effects are illustrated in Figure 31.2, and the main cautions and contraindications are listed in Table 31.4. Although there are several different classes from which to choose, many dilemmas continue to impinge on both strategy and individualization of treatment. For example, an increase in fasting glycemia usually accounts for the majority of the total burden of hyperglycemia in T2DM; ideally, therefore, this should be adequately addressed using appropriate therapy [19]. It is also pertinent to note the link between postprandial hyperglycemic excursions and cardiovascular risk, which mandates the need also to address this component of the hyperglycemic day profile [20]. Additionally, consideration should be given to the improvements in glycemic control that can be achieved through the treatment of obesity [21]. By the time of diagnosis, insulin resistance is usually well established and usually shows only a modest further increase with extended duration of the disease [6, 7]. Nevertheless, the association between insulin resistance and cardiovascular risk warrants the amelioration of insulin resistance as a valued

Table 31.3 Classes of oral glucose-lowering drugs and their main modes of action.

Class with examples	Main mode of glucose-lowering action	Main cellular mechanism of action
Biguanide		
Metformin	Counter insulin resistance (especially decrease hepatic glucose output)	Enhance various insulin-dependent and -independent actions including effects on AMPK, mitochondrial respiratory chain, and insulin receptor signaling
Sulfonylureas		
Glimepiride, gliclazide, glipizide glyburide (= glibenclamide)[a]	Stimulate insulin secretion (typically 6–24 h)	Bind to SUR1 sulfonylurea receptors on pancreatic β cells, which closes ATP-sensitive Kir6.2 potassium channels
Meglitinides		
Repaglinide, nateglinide	Stimulate insulin secretion (faster onset and shorter duration of action than sulfonylureas)	Bind to benzamido site on SUR1 receptors on pancreatic β cells, which closes ATP-sensitive Kir6.2 potassium channels
DPP-4 inhibitors (gliptins)		
Sitagliptin, vildagliptin, saxagliptin, linogliptin, alogliptin	Increase prandial insulin secretion	Inhibit DPP-4 enzyme, which increases plasma half-life of incretin hormones, notably GLP-1
Thiazolidinediones (PPAR-γ agonists)		
Pioglitazone, rosiglitazone[b]	Increase insulin sensitivity (especially increase peripheral glucose utilization)	Activate nuclear receptor PPAR-γ mainly in adipose tissue, which affects insulin action and glucose–fatty acid cycle
Sodium—glucose co-transporter-2 (SGLT-2) inhibitors		
Canagliflozin, dapagliflozin, empagliflozin	Increase elimination of glucose in the urine	Inhibit SGLT-2 transporters in renal proximal tubules
α-Glucosidase inhibitors		
Acarbose, miglitol, voglibose	Slow rate of carbohydrate digestion	Competitive inhibition of intestinal α-glucosidase enzymes
Dopamine agonist		
Bromocriptine[b]	Reduce hepatic glucose production	Central dopaminergic effect
Bile acid sequestrant		
Colesevelam[b]	Not established	Not established

[a] Glyburide is the same active compound as glibenclamide.
[b] Rosiglitazone has been withdrawn in some countries, and bromocriptine and colesevelam are not widely used for the treatment of T2DM.
AMPK, adenosine 5′-monophosphate-activated protein kinase; ATP, adenosine triphosphate; DPP-4, dipeptidyl peptidase 4; GLP-1, glucagon-like peptide-1: PPAR-γ, peroxisome proliferator-activated receptor γ; SGLT-2, sodium–glucose co-transporter-2.

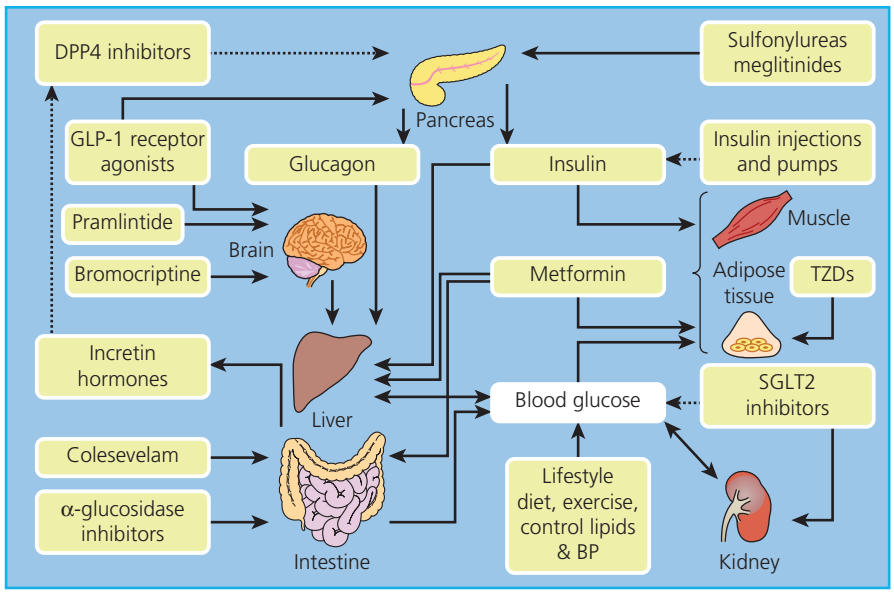

Figure 31.2 Main tissues through which oral glucose-lowering agents exert their glucose-lowering effects TZD: thiazolidinedione.

Table 31.4 General features of the more widely used oral blood glucose-lowering treatments for T2DM including the main cautions and contraindications.

Feature	Metformin	Sulfonylureas	Meglitinides	Thiazolidinediones	SGLT-2 inhibitors	DPP-4 inhibitors	α-Glucosidase inhibitors
HbA_{1c} (%)	↓ 1–2	↓ 1–2	↓ 0.5–1.5[f]	↓ 1–1.5	↓ 0.5–1.5	↓ 0.5–1.5	↓ 0.5–1
Body weight	–/↓	↑	↑/–	↑	↓	–	–
Lipids	–/+	–	–	+/–/×	–/+	–	–/+
Blood pressure	–	–	–	↓/–	↓	–	–
Tolerability	GI[a]	Hypo[d]	Hypo[g]	Fluid	Mycotic infection	–	GI[a]
Safety	Lactic acidosis[b]	Hypo[d]	Hypo[g]	Edema[h] Anemia Heart failure[i] Fractures	Dehydration[j]	–	–
Cautions	Renal Liver Hypoxemia[c]	Liver Renal[e]	Liver Renal[e]	CV[i]	Renal[k]	Liver[l]	–

[a] Gastrointestinal side effects.
[b] Lactic acidosis is rare.
[c] Check for adequate renal and hepatic function, avoid in conditions with heightened risk of hypoxemia.
[d] Risk of hypoglycemia, occasionally severe.
[e] Check liver and/or renal function relevant to mode of metabolism/elimination.
[f] Mostly act to lower postprandial hyperglycemia; lesser impact on fasting glycemia and on HbA_{1c}.
[g] Lesser risk of severe hypoglycemia than sulfonylurea.
[h] Fluid retention, anemia, increased risk of heart failure in susceptible individuals.
[i] Check for pre-existing cardiovascular disease or developing signs of heart disease: controversy regarding possible early increase in myocardial infarction with rosiglitazone not confirmed in long-term prospective studies.
[j] Rare reports of ketoacidosis.
[k] Ensure adequate renal function.
[l] Monitoring of liver function with vildagliptin.
↑, Increased; ↓, decreased; –, neutral; +, benefit; ×, impair.
CV, cardiovascular; GI, gastrointestinal; HbA_{1c}, glycated hemoglobin (1% ≈ 11 mmol/mol); Hypo, hypoglycemia.

therapeutic strategy. The ongoing deterioration in glycemic control after diagnosis is considered to be largely attributable to a further progressive decline in β-cell function [6, 7]. Thus, preserving β-cell function and mass are important considerations in the quest to maintain long-term glycemic control. If β-cell function deteriorates beyond the capacity of oral agents and non-insulin injectable agents (such as glucagon-like peptide-1 receptor agonists) to provide adequate glycemic control, then the introduction of insulin should not be delayed [22]. Incorporating some or all of the above into the treatment process is inevitably a challenge, and the need to explore suitable combinations of therapies to accommodate the changing status of the disease is common practice [3, 4].

The increasing prevalence of T2DM among younger adults and youth adds an extra long-term dimension to risk–benefit considerations. Although initial adequate intervention remains paramount, there is limited experience with oral glucose-lowering agents in children and adolescents; metformin has been used safely in pediatric practice from 10 years of age, and sulfonylureas have been used in pediatric presentations of certain monogenic forms of diabetes, e.g. maturity-onset diabetes of the young (MODY). Treating T2DM in women who are of childbearing age carries the risk of unplanned pregnancy while receiving oral glucose-lowering agents. Treatment with metformin or a sulfonylurea at the time of conception and during the first trimester has not been shown to have any adverse effects on mother or fetus, and judicious use of metformin has been shown to reduce miscarriage and gestational diabetes. Insulin remains the preferred glucose-lowering medication in pregnancy as there is a substantial evidence base for the safety and flexibility of insulin in gestational diabetes. A paucity of evidence, allied with animal toxicity data or theoretical considerations for some classes, contraindicates thiazolidinediones, gliptins, and sodium–glucose co-transporter-2 (SGLT-2) inhibitors during pregnancy and lactation.

Older people are more vulnerable to most of the cautions and contraindications for glucose-lowering drugs, and a deterioration in pathophysiological status can occur rapidly, necessitating more frequent monitoring. Hypoglycemia is a particular concern in this age group. Although safety must be judged on an individual drug–patient basis, it is noteworthy that several commonly used concomitant medications can impair glycemic control (e.g. glucocorticoids, certain antipsychotics, diuretics and β-blockers), whereas others may have their own minor glucose-lowering effect (e.g. aspirin, some angiotensin-converting enzyme [ACE] inhibitors and mineral supplements) (see Chapter 28). The most frequent interactions with glucose-lowering drugs are summarized in Table 31.5.

Descriptive terminology applied to glucose-lowering drugs may simplify the use of the different agents. Hypoglycemic agents have the capacity to lower blood glucose below normal to the extent of frank hypoglycemia (e.g. sulfonylureas, meglinitides, and insulin). Antihyperglycemic agents can reduce hyperglycemia, but when acting alone they do not usually have the capability to lower blood glucose below normoglycemia to the extent of frank hypoglycemia (e.g. metformin, dipeptidyl peptidase-4 [DPP-4] inhibitors, thiazolidinediones, SGLT-2 inhibitors, glucagon-like

Table 31.5 Drug interactions with oral antidiabetes agents that may affect their glucose-lowering effects.

Agent	Increase glucose-lowering effect	Decrease glucose-lowering effect
Any	Combination with other antidiabetes drugs Minor insulin releasers (e.g. aspirin) Minor insulin sensitivity enhancers (e.g. ACE inhibitors, magnesium or chromium supplements)	Agents that impair insulin action (e.g. glucocorticoids, some antipsychotics, minor effects of diuretics, β-blockers, some β_2-agonists) Impair insulin secretion (e.g. octreotide, some calcium channel blockers)
Metformin	Renal cation secretion competition by cimetidine Minor PK interaction with furosemide and nifedipine	–
Sulfonylureas	Reduce hepatic metabolism (e.g. some antifungals and MAOIs) Displace plasma protein binding (e.g. coumarins, NSAIDs, sulfonamides) Decrease excretion (e.g. probenecid)	K^+–ATP channel openers (e.g. diazoxide) Metabolism secondary to enzyme induction (e.g. rifampicin)
Meglitinides	Reduce hepatic metabolism, gemfibrozil Potentially displace plasma protein binding	Metabolism secondary to enzyme induction (e.g. rifampicin, barbiturates, carbamazepine)
Thiazolidinediones	Reduce hepatic metabolism, gemfibrozil Potentially displace plasma protein binding	Metabolism secondary to enzyme induction (e.g. rifampicin)
SGLT-2 inhibitors	–	Impaired renal function
DPP-4 inhibitors	Potential interactions with liver and renal metabolism and plasma protein binding	–
α-Glucosidase inhibitors	Slow gut motility (e.g. cholestyramine)	Potentially with agents that increase gut motility

ACE, angiotensin-converting enzyme; MAOI, monooxidase inhibitor; NSAID, non-steroidal anti-inflammatory drug; PK, pharmacokinetic.

peptide-1 (GLP-1) receptor agonists, α-glucosidase inhibitors, bromocriptine, and colesevelam).

Biguanides

Metformin (dimethylbiguanide) is the only biguanide currently used in most countries (Figure 31.3). The history of biguanides stems from a guanidine-rich herb, *Galega officinalis* (goat's rue or French lilac), that was used as a traditional treatment in Europe [23]. Guanidine has a glucose-lowering effect, and several guanidine derivatives were adopted for the treatment of diabetes in the 1920s [24]. These agents all but disappeared as insulin became available, but three biguanides—metformin, phenformin, and buformin—were introduced in the late 1950s. Phenformin and buformin were withdrawn in many countries in the late 1970s because of a high incidence of lactic acidosis. Metformin remained and was introduced into the United States in 1995 [25], and it has since become the most prescribed glucose-lowering agent worldwide [26].

Mode of action

Metformin exerts a range of actions that counter insulin resistance and lower blood glucose; the drug also offers some protection against vascular complications independently of its antihyperglycemic effect (Table 31.6) [27, 28]. At the cellular level, metformin exerts insulin-dependent and -independent effects on glucose metabolism that vary with the concentration of metformin to which the tissue is exposed and the prevailing gluco-regulatory mechanisms in that tissue (Figure 31.4). For example, high concentrations of metformin in the intestinal wall can suppress the mitochondrial respiratory chain at complex 1 independently of insulin and promote anaerobic glycolysis to lactate. The conversion of lactate to glucose in other tissues (increased glucose turnover as part of the Cori cycle) may help to prevent weight gain. Lower concentrations of metformin modestly improve insulin sensitivity in liver and muscle in part by enhancing post-receptor signaling pathways for insulin,

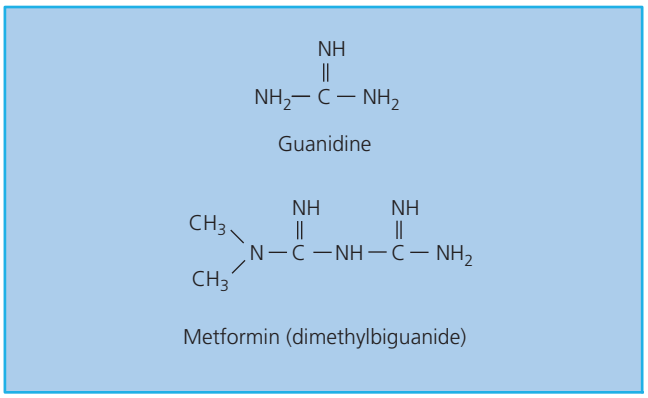

Figure 31.3 Chemical structures of guanidine and metformin.

Table 31.6 Diverse metabolic and vascular effects of metformin.

Features associated with diabetes		Effects of metformin
Hyperglycemia	↓	↓ HGP, ↑ peripheral glucose uptake, ↑ glucose turnover
Insulin resistance	↓	↑ Receptor–postreceptor insulin signals
Hyperinsulinemia	↓	↓ Fasting and often postprandial insulin
Obesity	↓/–	↓ or stabilizes body weight
IGT	↓	↓ Progression to T2DM
Dyslipidemia	↓/–	Modest benefits if abnormal ↓ VLDL-TG, ↓ LDL, ↑ HDL May decrease FA oxidation
Blood pressure	–	No significant effect
Pro-coagulant state	↓	Antithrombotic (↓ fibrinogen, ↓PAI-1, ↓ platelet aggregation)
Endothelial function	↑	↓ Vascular adhesion molecules
Atherosclerosis	↓	↓ MI, ↓ stroke, ↑ vascular reactivity, ↓ cIMT, ↑ life expectancy, antiatherogenic in animals

↑, Increase; ↓, decrease; –, no significant effect.
cIMT, carotid intima-media thickness; FA, fatty acid; HDL, high-density lipoprotein cholesterol; HGP, hepatic glucose production; IGT, impaired glucose tolerance; LDL, low-density lipoprotein cholesterol; MI, myocardial infarction; PAI-1, plasminogen-activator inhibitor-1; VLDL-TG, very low-density lipoprotein cholesterol triglyceride.

and also by effects on nutrient metabolism and energy production independently of insulin via activation of adenosine 5′-monophosphate-activated protein kinase (AMPK) [29].

The glucose-lowering efficacy of metformin requires a presence of at least some insulin because metformin does not mimic or activate the genomic effects of insulin. Also, metformin does not stimulate insulin release; its main glucose-lowering effect appears to be a reduction of hepatic glucose production by suppressing gluconeogenesis and glycogenolysis, but not sufficiently to cause frank hypoglycemia when used as monotherapy. Metformin reduces gluconeogenesis by increasing hepatic insulin sensitivity, reducing hepatic glucagon receptor signaling, and decreasing hepatic extraction of some gluconeogenic substrates such as lactate (Figure 31.5). Metformin can enhance insulin-stimulated glucose uptake in skeletal muscle by increasing the translocation of insulin-sensitive glucose transporters (GLUT-4) into the cell membrane and increasing the activity of glycogen synthase, which promotes glycogen synthesis.

Pharmacokinetics

Metformin is rapidly but incompletely absorbed, shows little binding to plasma proteins and is not metabolized, and so it does not interfere with co-administered drugs. Metformin is widely distributed at concentrations similar to plasma (about 10^{-5} mol/L), but much higher concentrations are retained in the walls of the gastrointestinal tract. The plasma half-life ($t_{1/2}$) is about 6 h with elimination of unchanged drug in the urine, mostly within

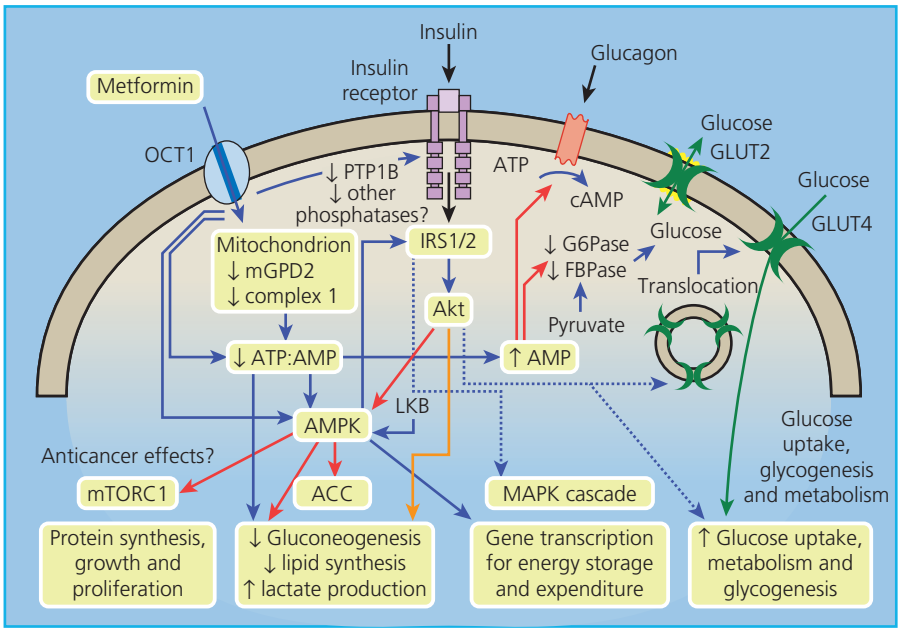

Figure 31.4 Multiple cellular actions of metformin involve insulin-dependent and -independent effects and vary according to the tissue and the level of exposure to metformin. For example, very high exposure to metformin in the intestine can reduce oxidative phosphorylation and promote anaerobic metabolism. Lower concentrations of metformin can improve insulin sensitivity in liver and muscle via effects on insulin receptor signaling and post-receptor signaling pathways of insulin action. Metformin can influence cellular nutrient metabolism and energy production independently of insulin via activation of adenosine 5′-monophosphate (AMP)-activated protein kinase (AMPK). Oct1, organic cation transporter 1; LKB1, protein kinase; Akt, protein kinase B (PKB); AMPK, adenosine monophosphate-activated protein kinase; GLUT, glucose transporter isoform; IRS, insulin receptor substrate; MAPK, mitogen-activated protein kinase; mTOR, mammalian target of rapamycin; PTP, protein tyrosine phosphatase;. Solid lines indicate direct effects; dashed lines indicate multistep pathways; up arrows indicate positive effect; down arrows indicate negative effect. Source: Adapted from Bailey CJ. *Nat Rev Endocrinol* 2012; **8**:449–450.

12 h [30]. Although renal clearance is achieved more by tubular secretion than glomerular filtration, metformin is contraindicated for people with significant impairment of glomerular filtration. Cimetidine is the only drug known to compete for clearance sufficiently to cause a clinically significant increase in plasma metformin concentrations.

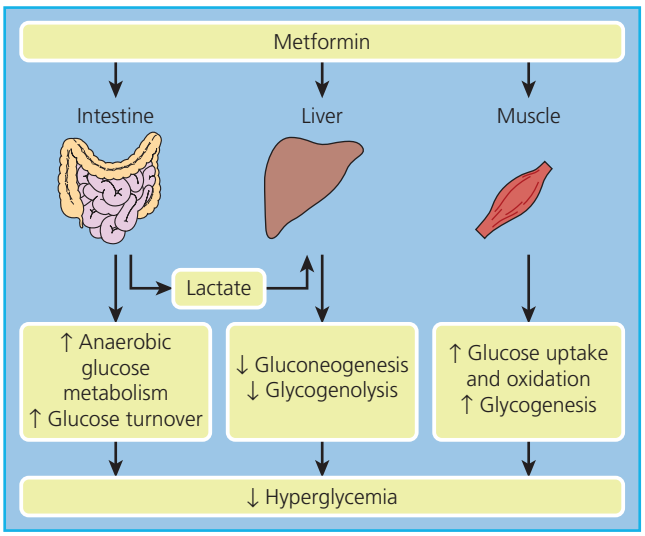

Figure 31.5 Main sites of action of metformin contributing to glucose-lowering effect.

Indications and contraindications

Because metformin does not cause weight gain, it is often preferred for overweight and obese people with T2DM, although it shows similar antihyperglycemic efficacy in normal-weight individuals [31]. To preclude drug accumulation, patient suitability should be considered very carefully if there is any evidence of impaired renal function (e.g. if serum creatinine is >130 μmol/L or creatinine clearance is <60 mL/min), although reduced doses of the drug are permitted in some countries down to an estimated glomerular filtration rate (eGFR) of 30 mL/min/1.73 m^2. Further contraindications include significant cardiac or respiratory insufficiency, or any other condition predisposing to hypoxia or reduced tissue perfusion (e.g. hypotension, septicemia), and also significant liver disease, alcohol abuse, or a history of metabolic acidosis. Because the potential for acute deterioration in renal, cardiopulmonary, and hepatic function should be taken into account, it is difficult to identify precise cutoffs for starting or stopping metformin therapy. With this in mind, metformin can be used in the elderly provided that renal insufficiency and other exclusions are not present. Ovulation can resume in women with anovulatory polycystic ovary syndrome (PCOS), which is an unlicensed

application of the drug in the absence of diabetes [32]. Metformin is also under investigation for a possible inhibitory effect on tumor formation and progression in some tissues.

A standard (so-called immediate release [IR]) tablet, sachet, or liquid formulation of metformin should be taken with meals or immediately before meals to minimize possible gastrointestinal side effects. Treatment should start with 500 or 850 mg once daily, or 500 mg twice daily (divided between the morning and evening meals). The dosage is increased slowly—one tablet at a time—at intervals of about 1–2 weeks until the target level of blood glucose control is attained. If the target is not attained and an additional dose produces no further improvement, the previous dose should be resumed. In the case of monotherapy, combination therapy can be considered by adding a differently acting agent (e.g. an insulin-releasing drug, SGLT-2 inhibitor or thiazolidinedione). The maximal effective dosage of metformin is about 2000 mg/day, taken in divided doses with meals, and the maximum is 2550 or 3000 mg/day in different countries [33].

Slow-release formulations (XR/SR/ER) of metformin are available in most countries; they can be taken once daily in the morning, or if necessary morning and evening. Metformin can also be used in combination with any other class of antidiabetes agent, including insulin, and several fixed-dose combination tablets are available in which metformin is combined with either a sulfonylurea, SGLT-2 inhibitor, DPP-4 inhibitor, or thiazolidinedione (see below). It should be noted that although metformin alone is unlikely to cause serious hypoglycemia, it can occur when metformin is used in combination with an insulin-releasing agent or insulin.

During long-term use of metformin, it is advisable to check at least annually for the emergence of contraindications, particularly renal (as a minimum, serum creatinine). Metformin can reduce gastrointestinal absorption of vitamin B_{12}, and although this is rarely a cause of frank anemia, an annual hemoglobin measurement is recommended, especially for individuals with known or suspected nutritional deficiencies. Metformin should be stopped temporarily when using intravenous radiographic contrast media, or during surgery with general anesthesia or other intercurrent situations in which the exclusion criteria could be invoked. Substitution with insulin may be appropriate at such times [33].

Efficacy

As monotherapy in people whose diabetes is not adequately controlled by lifestyle management, optimally titrated metformin typically reduces fasting plasma glucose by 2–4 mmol/L, corresponding to a decrease in HbA_{1c} by ~1–2% (11–22 mmol/mol) [25, 31, 33, 34]. This is largely independent of body weight, age, and duration of diabetes provided that some β-cell function is still present. To accommodate the progressive nature of T2DM, it is likely that uptitration of dosage and addition of a second agent will be required to maintain glycemic control in the long term.

Metformin carries minimal risk of significant hypoglycemia or weight gain when used as monotherapy. It may lead to a decrease in basal insulin concentrations, notably in people with hyperinsulinemia, which should help to improve insulin sensitivity. Minor improvements in the blood lipid profile have been observed during metformin therapy, mostly in those with hyperlipidemia: plasma concentrations of triglycerides, fatty acids, and low-density lipoprotein (LDL) cholesterol tend to fall, whereas that of high-density lipoprotein (HDL) cholesterol tends to rise [31, 33]. These effects appear to be independent of the antihyperglycemic effect, although a lowering of triglyceride and free fatty acids is likely to help improve insulin sensitivity and benefit the glucose–fatty acid (Randle) cycle.

In the UKPDS, overweight individuals who started oral antidiabetes therapy with metformin showed a 39% reduced risk of myocardial infarction (MI) compared with conventional treatment ($p = 0.01$) [35]. There was no obvious relationship with metformin dosage, suggesting that people who can tolerate only a low dosage of metformin may benefit from continuing the drug, even when other agents are required to achieve adequate glycemic control. The decrease in MI was not related to the extent of the glucose-lowering effect of metformin, or effects on classic cardiovascular risk factors such as blood pressure or plasma lipids. Reported benefits of metformin on various atherothrombotic risk markers and factors have been reported, including reduced carotid intima-media thickness (cIMT), increased fibrinolysis, and reduced concentrations of the antithrombolytic factor plasminogen activator inhibitor-1 (PAI-1) (Table 31.6) [28].

When metformin is added to the regimens of people receiving insulin therapy, a reduction of insulin dosage is often required, consistent with the ability of metformin to improve insulin sensitivity. Similarly, addition of insulin in people already receiving metformin usually requires lesser dosages of insulin and results in less weight gain. Lesser amounts of insulin are also associated with fewer and less severe episodes of hypoglycemia [36, 37]. Although metformin is not indicated for the prevention of diabetes, it is noteworthy that the US Diabetes Prevention Program found metformin to reduce the incidence of new cases of diabetes in overweight and obese participants with impaired glucose tolerance by 33%, compared with a reduced risk of 58% using an intensive regimen of diet and exercise [38]. The preventive effect of metformin was most evident amongst younger, more obese individuals.

Adverse effects

The main tolerability issue with metformin is abdominal discomfort and other gastrointestinal adverse effects, including diarrhea. These are often transient and can be ameliorated by taking the drug with meals and titrating the dose slowly. Symptoms may remit if the dose is reduced, but around 10% of people cannot tolerate the drug at any dose. The most serious adverse event associated with metformin is lactic acidosis; it is rare (probably about 0.03–0.06 cases per 1000 patient-years), but about half of cases are fatal [39]. Because the background incidence of lactic acidosis among people with T2DM has not been established, it is possible that some cases previously attributed to metformin were caused by other factors.

Most reported cases of lactic acidosis in people receiving metformin have been caused by inappropriate prescription, particularly overlooking renal insufficiency. The resulting accumulation of metformin is likely to increase lactate production, and increasing lactate will be aggravated by any hypoxic condition or impaired liver function. Hyperlactatemia occurs in cardiogenic shock and other illnesses that decrease tissue perfusion, so metformin may be only an incidental factor in some cases. Nevertheless, metformin should be stopped immediately in all cases of suspected or proven lactic acidosis, regardless of cause.

Lactic acidosis is typically characterized by a raised blood lactate concentration (e.g. >5 mmol/L), decreased arterial pH and/or bicarbonate concentration with an increased anion gap ($[Na^+] - [Cl^- + HCO_3^-]$ >15 mmol/L). Presenting symptoms are generally non-specific, but often include hyperventilation, malaise, and abdominal discomfort. Treatment should be commenced promptly without waiting to determine whether metformin is a cause; bicarbonate remains the usual therapy, but evidence of its efficacy is limited. Hemodialysis to remove excess metformin can be helpful, and may assist restoration of fluid and electrolyte balance during treatment with high-dose intravenous bicarbonate.

Sulfonylureas

Since their introduction in the 1950s, sulfonylureas have been used extensively as insulin secretagogues for the treatment of T2DM. Sulfonylureas were developed as structural variants of sulfonamides after the latter were reported to cause hypoglycemia [40]. Early sulfonylureas such as carbutamide, tolbutamide, acetohexamide, tolazamide, and chlorpropamide are often referred to as "first generation" compounds. These have been largely superseded by more potent "second-generation" sulfonylureas, notably glibenclamide (= glyburide), gliclazide, glipizide, and glimepiride (Figure 31.6).

Mode of action

Sulfonylureas act directly on the β cells of the islets of Langerhans to stimulate insulin secretion (Figure 31.7). They enter the β cell and bind to the cytosolic surface of the sulfonylurea receptor 1 (SUR1), which forms part of the transmembrane complex of ATP-sensitive Kir6.2 potassium channels (K^+ATP channels) (Figure 31.8) [41, 42]. Binding of a sulfonylurea closes the K^+ATP channel, reducing the efflux of potassium and enabling membrane depolarization. Localized membrane depolarization opens adjacent voltage-dependent L-type calcium channels, increasing calcium influx and raising the cytosolic free calcium concentration. This activates calcium-dependent signaling proteins that control the contractility of microtubules and microfilaments that mediate the exocytotic release of insulin granules. Preformed insulin granules adjacent to the plasma membrane are promptly released ("first-phase" insulin release), followed by a protracted ("second-phase") period of insulin release that begins about 10 min later [43]. The "second phase" of insulin release involves translocation of preformed and newly formed insulin granules to the plasma membrane for secretion. Sulfonylureas continue to stimulate insulin release while they are bound to the SUR1 provided that the β cells are functionally competent. Some desensitization, however, occurs during repeated and protracted stimulation

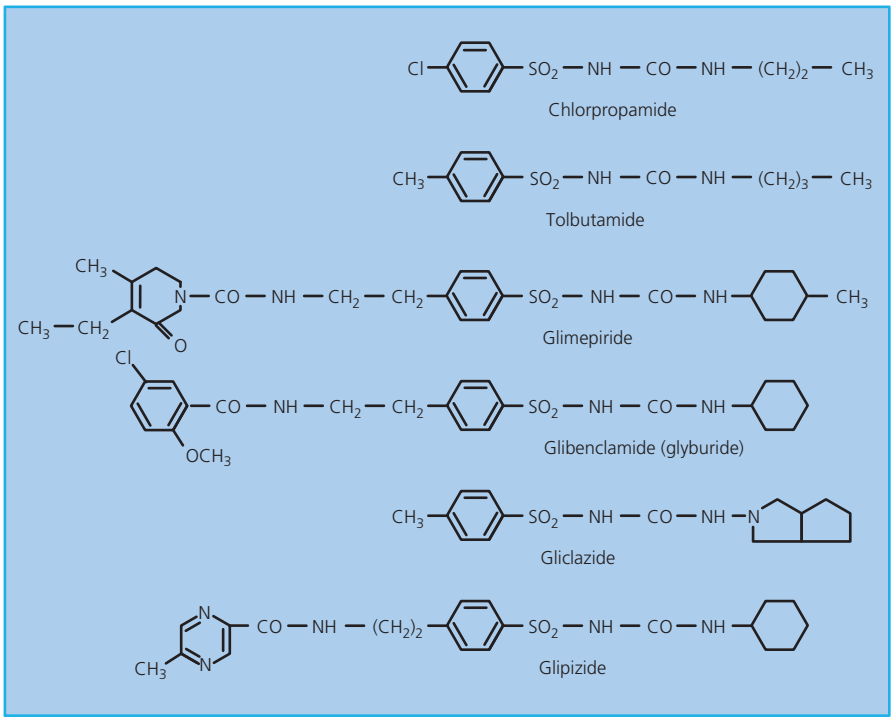

Figure 31.6 Chemical structures of sulfonylureas.

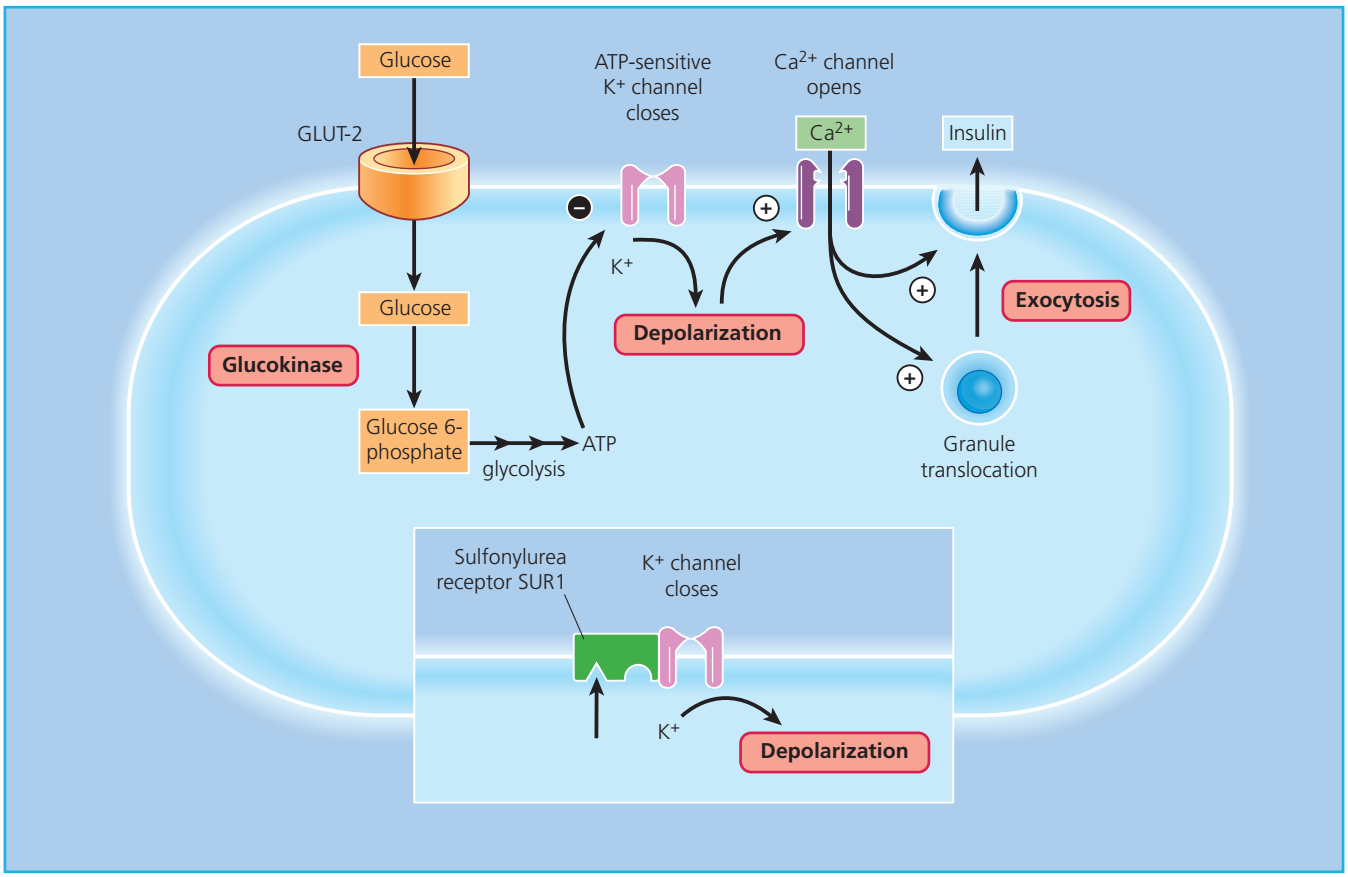

Figure 31.7 Sulfonylureas act on the pancreatic β cell to stimulate insulin secretion. They bind to the cytosolic surface of the sulfonylurea receptor 1 (SUR1), causing closure of ATP-sensitive Kir6.2 potassium channels, depolarizing the plasma membrane, opening calcium channels, and activating calcium-dependent signaling proteins that control insulin exocytosis.

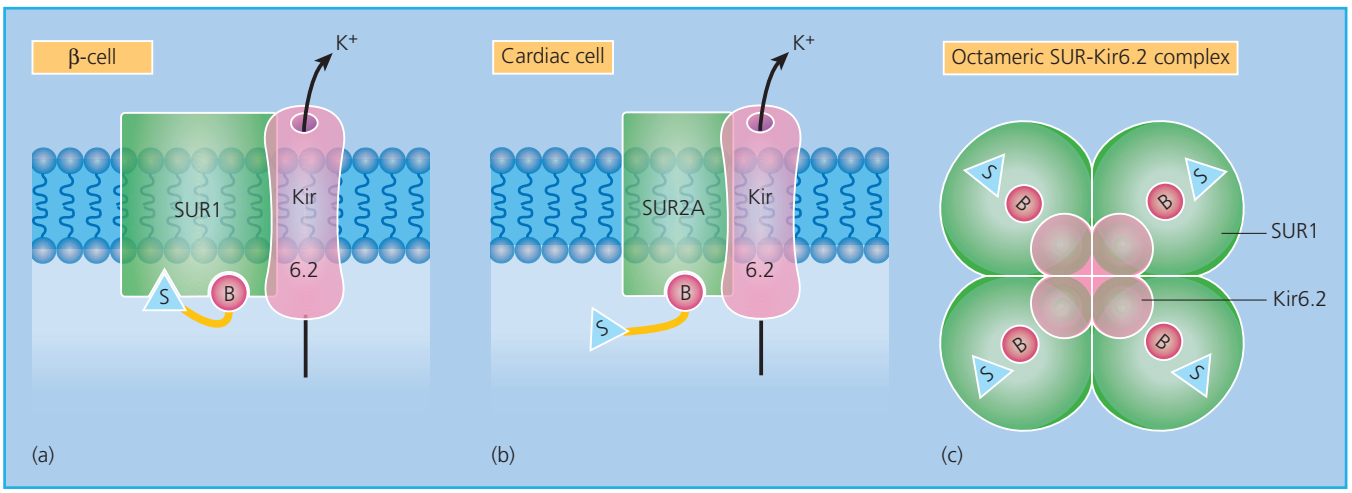

Figure 31.8 This illustrates the transmembrane complex of the SUR1 sulfonylurea receptor and the ATP-sensitive Kir6.2 potassium efflux channel on the pancreatic β cells (a). Each SUR1 has a cytosolic sulfonylurea (S) binding site and a benzamido (B) binding site. SUR2A on cardiac muscle cells (and SUR2B on vascular smooth muscle cells) does not have a sulfonylurea binding site (b). The SUR1–Kir6.2 complex is a non-covalently bonded octamer comprising 4 × SUR1 and 4 × Kir6.2, illustrated from the cytosolic surface to show the sulfonylurea and benzamido binding sites (c). The Kir6.2 molecules are located at the center and form the K^+ efflux pore. The Kir6.2 channel has a cytosolic binding region for ADP/ATP.

Table 31.7 Sulfonylureas.

Agent[a]	Dose range (mg/day)	Duration of action (h)	Metabolites	Elimination
Tolbutamide	500–2000	6–10	Inactive	Urine 100%
Glipizide	2.5–20	6–16	Inactive	Urine ~70%
Gliclazide	40–320	12–20	Inactive	Urine ~65%
Gliclazide MR	30–120	18–24	Inactive	Urine ~65%
Glimepiride	1.0–6.0	12–>24	Active	Urine ~60%
Glibenclamide[b]	1.25–15	12–>24	Active	Bile >50%
Chlorpropamide	100–500	24–50	Active	Urine >90%

[a] New patients are not usually started on first-generation sulfonylureas (tolbutamide, chlorpropamide).
[b] Glibenclamide is also known as glyburide in some countries.
MR, modified release.

[44]. Because sulfonylureas can stimulate insulin release when glucose concentrations are below the normal threshold for glucose-stimulated insulin release (~5 mmol/L), they are capable of causing hypoglycemia, mainly through insulin-induced suppression of hepatic glucose production.

There is some evidence that sulfonylureas exert minor glucose-lowering effects independently of increased insulin secretion [45, 46]. A small reduction in glucagon concentrations, increased peripheral glucose transport and increased hepatic glucose deposition have been reported, but these effects are not considered to be of sufficient magnitude to be clinically relevant.

Pharmacokinetics

Sulfonylureas vary considerably in their pharmacokinetic properties (Table 31.7), which in turn affects their clinical suitability for different individuals [45–47]. They are generally well absorbed, and reach peak plasma concentration in 2–4 h. Sulfonylureas are highly bound to plasma proteins, which can lead to interactions with other protein-bound drugs such as salicylates, sulfonamides, and warfarin. Also, displacement of protein-bound sulfonylurea can increase the risk of hypoglycemia (Table 31.5). Sulfonylureas are metabolized in the liver to varying extents to a range of active and inactive metabolites that are eliminated along with unchanged drug via the bile and urine. Longer acting sulfonylureas can be given once daily but carry a greater risk of hypoglycemia, especially with active metabolites. Sites and rates of metabolism and elimination are also important considerations, especially in older people and individuals with coexisting liver or kidney disease or taking several other medications.

The formulation of some sulfonylureas has been altered to modify the duration of action. For example, a micronized formulation of glibenclamide (termed glyburide) in the USA increases the rate of gastrointestinal absorption for earlier onset of action. A longer acting ("extended-release") formulation of glipizide and a "modified-release" (MR) formulation of gliclazide have been introduced for once-daily dosing. Interestingly, the 30 mg preparation of gliclazide MR gives similar efficacy to 80 mg of unmodified gliclazide and reduces the risk of severe hypoglycemia [48].

Indications and contraindications

Sulfonylureas are widely used as monotherapy and in combination with metformin or a thiazolidinedione. They can also be used with an α-glucosidase inhibitor, and there are individuals who can benefit from a combination of a sulfonylurea with an incretin agent or insulin. Combination of a sulfonylurea with a different type of antidiabetes agent usually affords approximately additive glucose-lowering efficacy, at least initially, but there is increased risk of hypoglycemia. The additive efficacy of a sulfonylurea with another type of insulin secretagogue is dependent on different modes of action on the β cell.

The pharmacological theory of adding a sulfonylurea (or other insulin secretagogue) to insulin therapy for people with T2DM is that subcutaneous insulin injections do not mimic the normal endogenous delivery of more insulin to the liver than to the periphery. Thus, where there is residual endogenous β-cell function, a stimulus to increase delivery of endogenous insulin to the liver should assist in reducing hepatic glucose production, particularly during digestion of a meal. Hence daytime sulfonylurea is sometimes given with bedtime insulin, and this can substantially, if only temporarily, reduce the required insulin dose [46, 47]. Guidelines generally include sulfonylureas as alternative first-line oral therapy where metformin is not appropriate or not tolerated. Because sulfonylurea therapy is associated with weight gain, these agents have customarily been preferred for people who are not overweight.

Sulfonylurea therapy is begun with a low dose, preferably with self-monitoring of blood glucose by the individual at least once daily during the first few weeks. This is especially recommended where there are strong concerns about the potential consequences of hypoglycemia (e.g. in elderly individuals and those living alone, operating machinery, or driving). In general, people who have responded to some extent (but still inadequately) with lifestyle measures and have less marked fasting hyperglycemia are more likely to incur hypoglycemia with a sulfonylurea. The dosage is uptitrated at 2–4-week intervals as required. Hypoglycemia or early hypoglycemic symptoms are the main limitation to dose escalation of sulfonylureas. If evidence of hypoglycemia occurs

before the glycemic target is achieved, or if a dosage increment produces no further glycemic benefit, it is advisable to return to the previous dose. Adjustment of the administration regimen may assist or an alternative class of insulin secretagogue may be more suitable. Where the sulfonylurea is taken as monotherapy and the glycemic target is not achieved, then addition of an agent to reduce insulin resistance or an SGLT-2 inhibitor or an α-glucosidase inhibitor is the usual recourse. Note that the maximal blood glucose-lowering effect of a sulfonylurea is usually achieved at a dose that is well below the recommended maximum, indicating that maximal stimulation of insulin secretion has already been achieved.

Efficacy

As monotherapy in people whose diabetes is inadequately controlled by lifestyle measures, sulfonylureas can be expected to reduce fasting plasma glucose by about 2–4 mmol/L, equating to a decrease in HbA_{1c} of 1–2% (11–22 mmol/mol) [3, 4, 46, 47]. The glucose-lowering effect of sulfonylureas is immediate, and sulfonylureas are particularly effective in the short term. Efficacy is dependent, however, on sufficient reserve of β-cell function, and this is set against the inevitable decline in β-cell function as the natural history of T2DM proceeds. Hence it is expected that the dose will need to be escalated to counter the progressive loss of β-cell function, which can reduce the durability of the glucose-lowering efficacy. A rapid deterioration of glycemic control during sulfonylurea therapy (sometimes termed "secondary sulfonylurea failure") occurs in ~5–10% of people per annum [55]. Although this may possibly vary between compounds, it largely reflects the progression of β-cell failure [3, 4, 46, 47]. Early intervention in people with a greater reserve of β-cell function usually produces a better and longer response to sulfonylureas, although not without risk of hypoglycemia, whereas late intervention in those with severely compromised β-cell function is less effective.

Sulfonylureas generally have little effect on blood lipids. Occasionally, their use will cause a small decrease in plasma triglyceride or increase in HDL cholesterol.

Adverse effects

Weight gain, typically in the range 1–4 kg, is common after initiation of sulfonylurea therapy; it stabilizes by about 6 months [11, 46, 47]. The weight gain probably reflects the anabolic effects of increased plasma insulin concentrations together with reduced loss of glucose in the urine.

Hypoglycemia is a common and potentially the most serious adverse effect of sulfonylurea therapy. Although it is only rarely life threatening in people with T2DM, even mild impairment of neural or motor function can endanger the individual and others, and may predispose to a poor prognosis after a MI [49, 50]. People treated with sulfonylureas should be given instruction on the prevention and recognition of hypoglycemia and the prompt actions required. In the UKPDS, ~20% of sulfonylurea-treated participants reported one or more episodes of hypoglycemic symptoms annually. Other studies have suggested similar rates [11, 46, 47]. Severe hypoglycemia (requiring third-party assistance) during sulfonylurea therapy occurred in ~1% of participants annually in the UKPDS, and lower rates (~0.2–2.5 episodes per 1000 patient-years) have been reported elsewhere. The mortality risk from sulfonylurea-induced hypoglycemia is reported to be 0.014–0.033 per 1000 patient-years [49]. Longer acting sulfonylureas, irregular meals, other antidiabetes drugs, especially insulin, excessive alcohol consumption, already near-normal fasting glycemia, old age, and interacting drugs can predispose to increased risk of hypoglycemia.

Sulfonylurea-induced hypoglycemia requires prompt admission to hospital. Treatment with glucose by continuous intravenous infusion, probably for more than 1 day, is applied to guard against the tendency for a recurrence of hypoglycemia where long-acting sulfonylureas are concerned. If accumulation of chlorpropamide is suspected, renal elimination may be enhanced by forced alkaline diuresis. The vasodilator diazoxide and the somatostatin analog octreotide have been used successfully (but with extreme caution) to inhibit insulin secretion in severe sulfonylurea-induced hypoglycemia. Use of glucagon in people with T2DM should be avoided as this is itself an insulin secretagogue.

Very occasionally, sulfonylureas produce sensitivity reactions, usually transient cutaneous rashes. Erythema multiforme is rare. Fever, jaundice, acute porphyria, photosensitivity, and blood dyscrasias are also rare. Chlorpropamide (no longer in common use) was known for its propensity to cause facial flushing with alcohol and increasing renal sensitivity to antidiuretic hormones, occasionally causing water retention and hyponatremia. Glibenclamide is claimed to have a mild diuretic action.

Although the efficacy of sulfonylureas depends on the stimulation of insulin secretion, this seldom raises plasma insulin concentrations beyond the range of normal individuals without diabetes and those with impaired glucose tolerance (IGT). The suggestion emanating from the University Group Diabetes Program study in the 1960s that tolbutamide-induced hyperinsulinemia might have a detrimental effect on the cardiovascular system remains unsubstantiated.

Further studies on the cardiovascular safety of sulfonylureas were prompted by the finding that two isoforms of the sulfonylurea receptor, SUR2A and SUR2B, are expressed in cardiac muscle and vascular smooth muscle, respectively. These isoforms lack the sulfonylurea binding site but they retain the benzamido binding site (Figure 31.8). Therefore, SUR2A/B can only bind those sulfonylureas that contain a benzamido group (glibenclamide, glipizide, glimepiride) [42]. Sulfonylureas without a benzamido group (e.g. tolbutamide, chlorpropamide, gliclazide) show very little interaction with the cardiac and vascular SUR receptors. The effects of the K^+ATP channel opener nicorandil (an antianginal drug with cardioprotective properties) are blocked by sulfonylureas that have a benzamido group. Compounds with a benzamido group could theoretically interfere with ischemic preconditioning and increase vascular contractility at a time when this might be undesirable (e.g. severe myocardial ischemia).

However, there is no clear evidence that therapeutic concentrations of sulfonylureas exert such an effect. Indeed, hyperglycemic states appear to obviate ischemic preconditioning; but some authorities continue to advocate that the use of sulfonylureas is kept to a minimum in people with overt coronary artery disease [50].

Meglitinides (short-acting prandial insulin releasers)

Meglinide analogs (sometimes termed glinides) were evaluated as potential antidiabetes agents after an observation in the 1980s that meglitinide—the non-sulfonylurea moiety of glibenclamide which contains the benzamido group—could stimulate insulin secretion similarly to a sulfonylurea [51]. The pharmacokinetic properties of these compounds favored a rapid but short-lived insulin secretory effect that suited administration with meals to promote prandial insulin release. By generating a prompt increase of insulin to coincide with meal digestion, these agents help to restore partially the first-phase glucose-induced insulin response that is lost in T2DM. Specifically targeting postprandial hyperglycemia might also address the vascular risk attributed to prandial glucose excursions and reduce the risk of interprandial hypoglycemia [52–54]. Two agents, the meglitinide derivative repaglinide and the structurally related phenylalanine derivative nateglinide, were introduced in 1998 and 2001, respectively, as "prandial insulin releasers" (Figure 31.9). Although acting mainly during the prandial and early postprandial period, their effects extend sufficiently to produce some reduction of fasting hyperglycemia, particularly with repaglinide.

Mode of action

Prandial insulin releasers bind to the benzamido site on the sulfonylurea receptor SUR1 in the plasma membrane of the islet β cells (Figure 31.8). This site is distinct from the sulfonylurea site, but the response to binding is the same as for sulfonylureas, causing closure of the K^+ATP channel. Thus, there is usually no therapeutically additive advantage of using the two types of agents together.

Pharmacokinetics

Repaglinide is almost completely and rapidly absorbed with peak plasma concentrations after about 1 h. It is quickly metabolized in the liver to inactive metabolites, which are mostly excreted in the bile (Table 31.8). Taken about 15 min before a meal, repaglinide produces a prompt insulin response which lasts about 3 h, coinciding with the duration of meal digestion. Nateglinide has a slightly faster onset and shorter duration of action [52–54].

Indications and contraindications

Prandial insulin releasers can be used as monotherapy in people whose diabetes is inadequately controlled by non-pharmacological measures. They are perhaps most suited for individuals who exhibit postprandial glycemic excursions while retaining near-normal fasting glycemia. As rapid-acting insulin releasers, they can be helpful to individuals with irregular lifestyles with unpredictable or missed meals. The lower risk of hypoglycemia also provides a useful option for some older individuals, particularly if other agents are contraindicated, although the need for multiple daily dosages may be a disincentive.

Repaglinide is ideally taken 15–30 min before a meal. Therapy is introduced with a low dose (e.g. 0.5 mg) and glycemic control

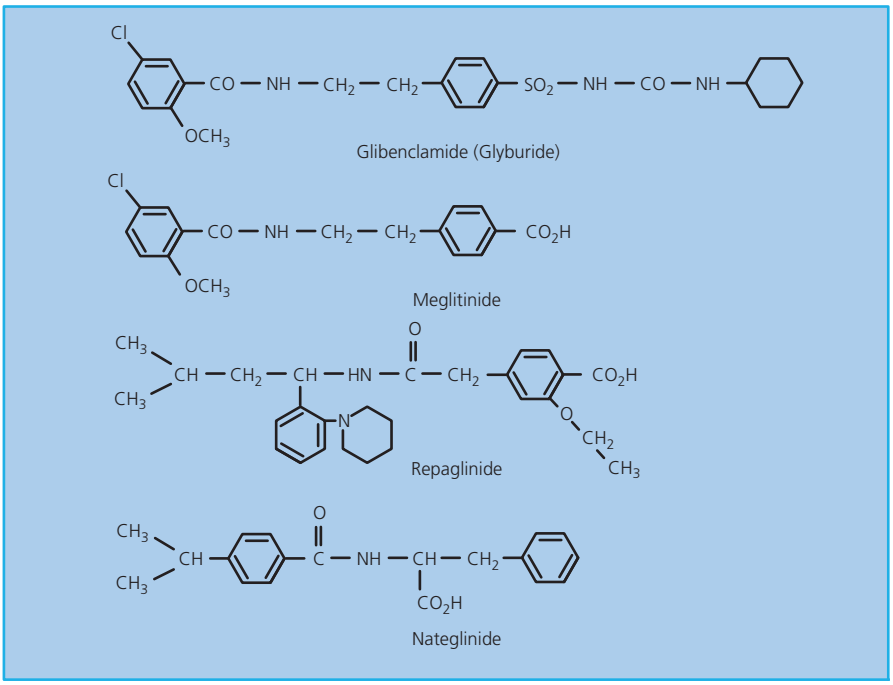

Figure 31.9 Chemical structures of meglitinide and the prandial insulin releasers repaglinide and nateglinide compared with glibenclamide (glyburide).

Table 31.8 The meglitinides: repaglinide and nateglinide.

Agent	Dose range (mg/meal)	Maximum daily dose (mg)	Duration of action (h)	Metabolites	Elimination
Repaglinide	0.5–4.0	16	4–6	Inactive	Bile ~90%
Nateglinide	60–180	540	3–5	One slightly active	Urine ~80%

is monitored during titration every 2 weeks up to a maximum of 4 mg before each main meal. When a meal is not consumed, the corresponding dose of repaglinide should be omitted. With appropriate caution and monitoring, repaglinide can be given to those with moderate renal impairment where some sulfonylureas and metformin are contraindicated.

Nateglinide can be used as monotherapy in much the same way as repaglinide, although nateglinide tends to be faster and shorter acting and requires caution in people with hepatic disease. Note that in some countries, such as the United Kingdom, nateglinide is not licensed for use as monotherapy, only for combination therapy.

If the desired glycemic target is not met with a prandial insulin releaser, early introduction of combination therapy (e.g. with an agent to reduce insulin resistance) can be considered. Prandial insulin releasers can also be useful add-ons to monotherapy with metformin or a thiazolidinedione.

Efficacy

Consistent with their use to boost prandial insulin secretion, repaglinide (0.5–4 mg) and nateglinide (60–180 mg) taken before meals produce dose-dependent increases in insulin concentrations and reduce postprandial hyperglycemia. There is usually a small reduction in fasting hyperglycemia. Reductions in HbA_{1c} are similar to or smaller than with sulfonylureas, as predicted by their shorter duration of action. As add-on to metformin, they can reduce HbA_{1c} by an additional 0.5–1.5% (6–17 mmol/mol).

Adverse effects

Hypoglycemic episodes are fewer and less severe with prandial insulin releasers than with sulfonylureas. Sensitivity reactions, usually transient, are uncommon. Plasma levels of repaglinide may be increased during co-administration with gemfibrozil. Prandial insulin releasers may cause a small increase in body weight when started as initial monotherapy, but body weight is little affected among people switched from a sulfonylurea or when a prandial insulin releaser is combined with metformin.

Thiazolidinediones

The glucose-lowering activity of a thiazolidinedione (ciglitazone) was reported in the early 1980s. In the early 1990s, the peroxisome proliferator-activated receptor (PPAR) family was identified as part of the nuclear receptor superfamily 1, and it became evident that thiazolidinediones were potent agonists of PPAR-γ [55]. The PPAR-γ-mediated transcriptional effects of thiazolidinediones were shown to improve whole-body insulin sensitivity, and troglitazone became the first thiazolidinedione to enter routine clinical use, introduced in the USA in 1997. The drug, however, was associated with fatal cases of idiosyncratic hepatotoxicity and was withdrawn in 2000. Troglitazone was available for only a few weeks in 1997 in the UK. Two other thiazolidinediones, rosiglitazone and pioglitazone (Figure 31.10), which did not show hepatotoxicity, were introduced in the USA in 1999 and in Europe in 2000. Fixed-dose combinations of each agent with metformin are also available.

By 2007, meta-analyses of safety data for rosiglitazone were indicating increased risk of heart failure, MI and cardiovascular deaths, resulting in withdrawal of rosiglitazone in Europe in 2010 and restricted use in the USA (placement on Risk Evaluation and Mitigation Strategy [REMS]) [56]. However, evaluation of a large prospective cardiovascular outcome study with rosiglitazone (Rosiglitazone Evaluated for Cardiac Outcomes and Regulation of Glycemia in Diabetes [RECORD]) did not confirm the increased risk of MI and cardiovascular death, and the REMS restriction in the USA was lifted in 2013. An earlier (2007) study with pioglitazone (Prospective Pioglitazone Clinical Trial in Macrovascular Events [PROactive]) had not shown increased risk of MI or cardiovascular death, and pioglitazone is the only thiazolidinedione available in many countries [57, 58].

Mode of action

Most of the glucose-lowering efficacy of thiazolidinediones appears to be achieved through stimulation of PPAR-γ, leading to increased insulin sensitivity [55, 59]. PPAR-γ is highly expressed in adipose tissue, and to a lesser extent in muscle and liver. When activated it forms a heterodimeric complex with the retinoid X receptor and binds to a nucleotide sequence (AGGTCAXAGGTCA) termed the peroxisome proliferator

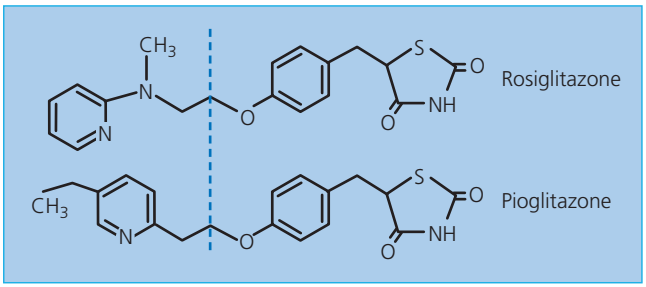

Figure 31.10 Chemical structures of thiazolidinediones rosiglitazone and pioglitazone.

Table 31.9 Examples of key genes activated by thiazolidinediones via stimulation of the peroxisome proliferator-activated receptor γ (PPAR-γ). Not all genes appear to be activated in all tissues. The main effects are in adipose tissue.

↑ Lipoprotein lipase
↑ Fatty acid transporter protein (FATP/CD36)
↑ Adipocyte fatty acid-binding protein (aP2)
↑ Acyl-CoA synthetase
↑ Malic enzyme
↑ Glycerol kinase (in adipocytes?)
↑ PEPCK (adipocytes), ↑ perilipin
↑ GLUT-4 (by derepression), ↑ GLUT-2 (islet β cells)
↓ 11β-Hydroxysteroid dehydrogenase-1
↓ Resistin, ↓ RBP 4
↑ Adiponectin (↑ leptin?)
↓ TNF-α, ↓ IL-6
↓ CRP and some proinflammatory cytokines, ↓ NFκB
↓ PAI-1, ↓ MMP-9
↑ UCP-1 (?)

↑, Increase expression; ↓, decrease expression; ?, unconfirmed.
CRP, C-reactive protein; GLUT, glucose transporter; IL-6, interleukin 6; NFκB, nuclear factor κB; PAI-1, plasminogen activator inhibitor 1; MMP-9, matrix metalloproteinase 9; PEPCK, phosphoenolpyruvate carboxy kinase; RBP, retinol-binding protein; TNF-α, tumor necrosis factor α; UCP-1, uncoupling protein 1.

response element (PPRE) located in the promoter regions of PPAR-responsive genes. In conjunction with co-activators such as PGC-1, this alters the transcriptional activity of a range of insulin-sensitive and other genes (Table 31.9). Many of these genes participate in lipid and carbohydrate metabolism (Figure 31.11). Stimulation of PPAR-γ by a thiazolidinedione promotes differentiation of pre-adipocytes into mature adipocytes; these new small adipocytes are particularly sensitive to insulin, and show increased uptake of fatty acids with increased lipogenesis. This in turn reduces circulating non-esterified (free) fatty acids, which rebalances the glucose–fatty acid (Randle) cycle, facilitating glucose utilization and restricting fatty acid availability as an energy source for hepatic gluconeogenesis. By reducing circulating fatty acids, ectopic lipid deposition in muscle and liver is reduced, which further contributes to improvements of glucose metabolism. Thiazolidinediones also increase mitochondrial biogenesis but may act directly on mitochondria to reduce respiratory function.

Thiazolidinediones increase glucose uptake into adipose tissue and skeletal muscle via increased availability of GLUT-4 glucose transporters. Improvements in insulin sensitivity are likely to be assisted by reduced production of several adipocyte-derived pro-inflammatory cytokines, notably tumor necrosis factor α (TNF-α), which is implicated in muscle insulin resistance. Thiazolidinediones also increase the production of adiponectin, which enhances insulin action and exerts potentially beneficial effects on vascular reactivity. Because PPAR-γ is expressed to a small extent in many tissues, thiazolidinediones can therefore affect responsive genes at these locations, and this has given rise to the tag "pleotropic effects" [59, 60].

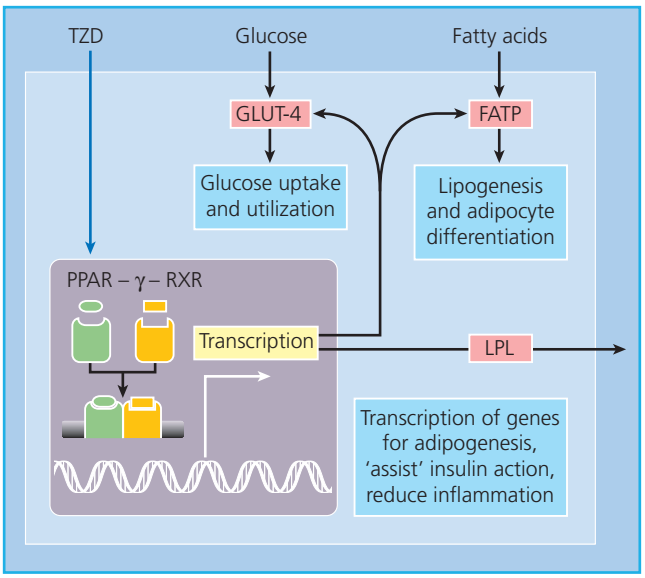

Figure 31.11 Mechanism of action of thiazolidinediones. Most actions of a thiazolidinedione (TZD) are mediated via stimulation of the nuclear peroxisome proliferator-activated receptor γ (PPAR-γ), which is highly expressed in adipose tissue. When stimulated, PPAR-γ forms a heterodimeric complex with the retinoid X receptor (RXR). The complex binds to the peroxisome proliferator response element (PPRE) nucleotide sequence (AGGTCAXAGGTCA) in the promoter regions of certain genes, recruits co-activators, and alters the transcriptional activity of these genes. This modifies nutrient uptake and metabolism, and also the other functions of the cell.

Thiazolidinediones, like metformin, are antihyperglycemic agents and require the presence of sufficient insulin to generate their blood glucose-lowering effect. Plasma insulin concentrations are typically lowered by thiazolidinediones, and there is evidence that long-term viability of islet β cells might be improved [61].

Pharmacokinetics

Absorption of rosiglitazone and pioglitazone is rapid and almost complete, with peak concentrations at 1–2 h, but slightly delayed when taken with food. Both drugs are metabolized extensively by the liver. Rosiglitazone is metabolized mainly by cytochrome P450 isoform CYP2C8 to inactive or only very weakly active metabolites with a plasma $t_{1/2}$ of 100–160 h; these are mostly eliminated in the urine. Pioglitazone is metabolized predominantly by CYP2C8 and CYP3A4 to active metabolites that are eliminated in the bile (Table 31.10). Rosiglitazone can interact with gemfibrozil.

Table 31.10 The thiazolidinediones: pioglitazone and rosiglitazone.

Agent	Dose range (mg/day)	Duration of action (h)	Metabolites	Elimination
Pioglitazone	15–45	~24	Active	Bile >60%
Rosiglitazone	4–8	~24	Inactive	Urine ~64%

Pioglitazone does not appear to cause any clinically significant reductions in plasma concentrations of other drugs metabolized by CYP3A4, such as oral contraceptives. Both thiazolidinediones are almost completely bound to plasma proteins, but their concentrations are not sufficient to interfere with other protein-bound drugs.

Indications and contraindications

Thiazolidinediones can be used as monotherapy in non-obese and obese individuals with T2DM in whom lifestyle does not afford adequate glycemic control. Various treatment algorithms ascribe different positions for thiazolidinediones, but in general they can be used as monotherapy if metformin is inappropriate or not tolerated, and for those in whom an insulin secretagogue is less favored. They are often used to gain additive efficacy in combination with other antidiabetes drugs, particularly metformin [62]. Because of their slow onset of action, it is not straightforward to substitute a thiazolidinedione for either a sulfonylurea or metformin without a temporary deterioration in glycemic control. Combination of a thiazolidinedione with insulin can improve glycemic control while reducing insulin dosages, especially in obese individuals, but requires extra caution as peripheral edema is more common [63].

A particular issue with thiazolidinediones is their propensity for fluid retention with an increased plasma volume of up to 500 mL, a reduced hematocrit, and a decrease in hemoglobin concentration of up to 1 g/dL. Hence the use of thiazolidinediones is contraindicated in people with evidence of heart failure. The exclusion criteria, based on cardiac status, vary between countries; for example, New York Heart Association classes I–IV are exclusions in Europe, whereas classes III and IV are exclusions in the USA [63]. Appropriate clinical monitoring is important, especially for people considered at higher risk for cardiac failure and those showing marked initial weight gain. Despite an increased fluid volume, thiazolidinediones do not increase, and usually slightly decrease, blood pressure.

Although hepatotoxicity has not been a concern with either rosiglitazone or pioglitazone, the troglitazone experience prompted vigilance concerning liver function by measuring serum alanine aminotransferase (ALT) before starting therapy and periodically thereafter. Pre-existing liver disease, development of clinical hepatic dysfunction, or elevated ALT levels >2.5 times the upper limit of normal are contraindications to thiazolidinediones. Interestingly, because of the effects of thiazolidinediones on hepatic fat metabolism, recent studies have suggested that this class of drug might even be useful for the treatment of non-alcoholic steatohepatitis.

If there are no contraindications, a thiazolidinedione can be used in the elderly. A thiazolidinedione can also be considered for individuals with mild renal impairment, but appreciating the potential for edema. Use of a thiazolidinedione in women with anovulatory PCOS can cause ovulation to resume, but thiazolidinediones should not be continued in pregnancy.

Efficacy

Thiazolidinediones produce a slowly generated antihyperglycemic effect, which usually requires 2–3 months to reach maximum effect [55, 61]. This tends to prolong the dose titration process, and because the therapeutic response can vary considerably between individuals, it is appropriate to consider the patient as a non-responder and to switch to another treatment if there is no clinically meaningful effect after 3 months. The two thiazolidinediones have similar blood glucose-lowering effects, reducing HbA_{1c} by around 0.5–1.5% (6–17 mmol/mol). In a long-term monotherapy comparison with metformin or a sulfonylurea (the ADOPT study), rosiglitazone showed a slower onset but a more durable glucose-lowering effect over more than 3 years [61]. Data from clinical trials suggest that the effect of thiazolidinediones may be better in people with greater β-cell reserve and in more overweight individuals, but a clear indicator of the best responders has not been established. Thiazolidinediones do not cause hypoglycemia as monotherapy.

Both thiazolidinediones substantially reduce circulating nonesterified (free) fatty acids, but effects on other components of the plasma lipid profile have been the subject of debate. Rosiglitazone tends to cause a small rise in the total cholesterol concentration, which stabilizes by about 3 months, although this may be mitigated by adequate statin therapy. The effect appears to reflect a rise in both LDL and HDL cholesterol, leaving the LDL : HDL cholesterol ratio and the total : HDL cholesterol ratio little changed or slightly improved. Pioglitazone generally appears to have little effect on total cholesterol, and has frequently reduced triglyceride concentrations in clinical trials. Both thiazolidinediones reduce the proportion of the smaller, more dense (more atherogenic) LDL particles [64].

Weight gain, similar in magnitude to sulfonylurea therapy (typically 1–4 kg) and stabilizing over 6–12 months, is usually observed after initiation of thiazolidinedione therapy. Several studies indicate that the distribution of body fat is altered. The visceral adipose depot is little changed or reduced, while the subcutaneous depot is increased as new small, insulin-sensitive adipocytes are formed [65].

Thiazolidinediones have been reported to exert beneficial effects on a selection of atherothrombotic risk markers, indices of vascular reactivity, and components of the "metabolic syndrome" [63, 65]. For example, thiazolidinediones downregulate PAI-1 expression, decrease urinary albumin excretion to a greater extent than expected for the improvement in glycemic control, reduce cIMT and coronary restenosis, and reduce circulating markers of chronic low-grade inflammation. Thiazolidinediones also reduce the occurrence of new-onset diabetes in individuals with IGT or those with a history of gestational diabetes [66, 67].

Adverse effects

Despite improvements in several atherothrombotic risk factors, the main concerns over thiazolidinediones have focused on the cardiovascular impact of edema, reduced hemoglobin levels, and congestive heart disease. Although long-term cardiovascular

events were reduced during a large prospective study with pioglitazone (PROactive), the cardiovascular safety issues raised over rosiglitazone have reduced confidence in the class [57, 58, 63].

Recent studies have noted an approximate doubling of the risk of a bone fracture—notably at distal sites—amongst postmenopausal women receiving a thiazolidinedione, and possibly a slightly increased risk amongst men [68]. This has been attributed at least in part to a reduction in bone mineral density. Stimulation of PPAR-γ in colonic cells has been reported both to increase and to decrease the risk of tumors in animals and cell models; thus, familial polyposis coli is a contraindication to thiazolidinediones on theoretical grounds. There has been debate concerning a possible increased risk of bladder cancer with pioglitazone, and the drug is not recommended for people with active bladder disease or a history of bladder disease. However, long-term safety analyses have not confirmed a significant increase in risk of bladder cancer with pioglitazone [58, 69].

Hypoglycemia may occur several weeks after adding a thiazolidinedione to a sulfonylurea; self-monitoring of blood glucose can be helpful to identify when the dosage of the sulfonylurea should be reduced. It has been suggested that rosiglitazone is initiated at half maximal dosage with a sulfonylurea.

DPP-4 inhibitors

Dipeptidyl peptidase 4 (DPP-4) inhibitors (often termed gliptins) inhibit the enzyme DPP-4, which is responsible for the rapid degradation of two key incretin hormones, glucose-dependent insulinotropic polypeptide (GIP) and glucagon-like peptide 1 (GLP-1). Thus DPP-4 inhibitors enhance endogenous incretin activity by preventing the rapid degradation of these incretin hormones. The history, structure, and function of incretin hormones, and the therapeutic role of subcutaneously injected GLP-1 receptor agonists such as exenatide, liraglutide, lixisenatide, dulaglutide, and albiglutide, are covered in Chapter 32. Briefly, incretin hormones are secreted from the intestine in response to meal digestion; one of their main actions is to increase glucose-induced insulin secretion by the pancreatic islet β cells, thereby reducing prandial glucose excursions [70–72]. GLP-1 also suppresses glucagon secretion from the islet α cells, exerts a satiety effect, and delays gastric emptying.

It was noted in the 1980s that the incretin effect is reduced in T2DM, and subsequent studies have shown that this is largely due to reduced activity of GLP-1 [73], suggesting that administration of extra GLP-1 might be therapeutically useful. Because GLP-1 is rapidly degraded ($t_{1/2}$ <2 min) by DPP-4, the potential of DPP-4 inhibitors was investigated in the 1990s, giving rise to the introduction of several specific inhibitors [74], notably sitagliptin (2007), vildagliptin (2008), saxagliptin (2008), linagliptin (2011), and alogliptin (2013) (Figure 31.12).

Mode of action

DPP-4 inhibitors act to prevent the aminopeptidase activity of DPP-4; the enzyme is found free in the circulation and tethered to endothelia and other epithelial cells in most tissues, especially in the intestinal mucosa [75]. DPP-4 cleaves the N-terminal dipeptide from peptides that have either an alanine or a proline residue penultimate to the N-terminus. The incretins GLP-1 and GIP are prime targets for DPP-4, and DPP-4 inhibitors more than double their circulating concentrations (but this is not as high as the concentrations of subcutaneously administered GLP-1 receptor agonists) [75, 76]. Raised endogenous incretin concentrations enhance nutrient-induced insulin secretion. Increased insulin biosynthesis and increased β-cell mass have also been noted in some animal studies, but these effects have not been confirmed in clinical studies (Table 31.11). Increased GLP-1 concentrations also suppress excessive glucagon secretion.

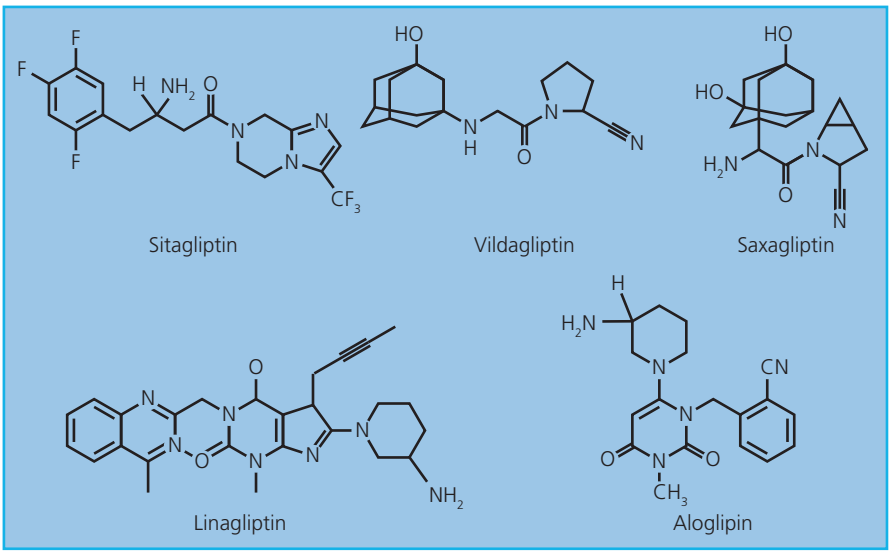

Figure 31.12 Chemical structures of the gliptins (DPP-4 inhibitors) sitagliptin, vildagliptin, saxagliptin, linogliptin, and alogliptin.

Table 31.11 Effects of the incretin hormones glucagon-like peptide 1 (GLP-1) and glucose-dependent insulinotropic polypeptide (GIP) on glucose homeostasis.

	GLP-1	GIP
Effects on pancreatic islets		
Increase nutrient-induced insulin secretion	✓	✓
Increase insulin biosynthesis[a]	✓	✓
Increase β-cell mass[a]	✓	✓
Suppress glucagon secretion	✓	–
Increase somatostatin secretion	✓	–
Extrapancreatic effects		
Slow gastric emptying	✓	–
Decrease gastric acid secretion	–	✓
Promote satiety and weight reduction	✓	–
Promote lipogenesis	–	✓

[a] Effect observed in animal studies but not confirmed by clinical studies inT2DM.
✓, Yes; –, no effect.

Because these effects are glucose dependent, there is low risk of inducing significant hypoglycemia. The elevation of GLP-1 levels produced by DPP-4 inhibitors is not generally sufficient to create a measurable satiety effect or sufficient slowing of gastric emptying to cause any nausea, and body weight is usually little changed or slightly reduced (Figure 31.13).

Because the incretin-mediated effect of DPP-4 inhibitors potentiates glucose-dependent insulin secretion, the activity period of these agents is mostly prandial. Although they are particularly effective in lowering postprandial hyperglycemia, there is a substantial carryover effect to benefit the control of interprandial glycemia [74, 76]. By contrast, DPP-4 inhibitors do not initiate insulin secretion and so they do not increase basal insulin secretion. Also, they only suppress glucagon secretion in the hyperglycemic state, and so there is a low risk of interprandial "overshoot" into hypoglycemia.

Pharmacokinetics

The pharmacokinetic properties of DPP-4 inhibitors are summarized in Table 31.12. DPP-4 inhibitors are selective, competitive and reversible inhibitors of DPP-4 (IC_{50} in the lower nmol/L range). They mimic the N-terminal dipeptide structure of the incretins, which enables them to block the catalytic site of DPP-4 through either covalent (vildagliptin and saxagliptin) or non-covalent (sitagliptin, linagliptin, and alogliptin) interactions. DPP-4 inhibitors are absorbed rapidly with onset of activity in <10 min of administration and t_{max} achieved mostly within 2 h. They produce >90% inhibition of DPP-4 activity for most of a 24-h period, although the shorter elimination half-life of vildagliptin requires twice-daily administration compared with once daily for other agents in the class. Two DPP-4 inhibitors are substantially metabolized (vildagliptin to inactive metabolites and saxagliptin to active metabolites), whereas the others undergo little metabolism. Linagliptin is eliminated mostly via the bile into the feces and can be used without dose adjustment in people with moderate to severe renal impairment. Other members of the class are eliminated in the urine, necessitating dose reduction in people

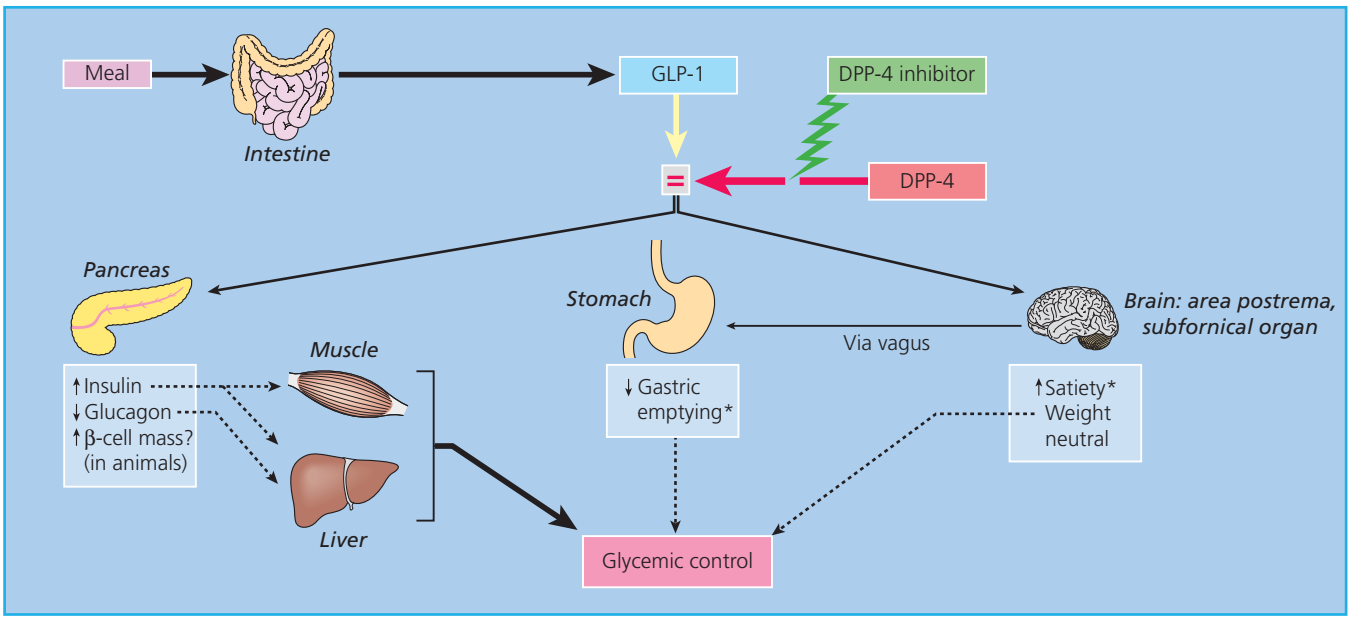

Figure 31.13 Sites of action of DPP-4 inhibitors (gliptins). Incretin hormones such as GLP-1 are released in response to a meal. These hormones are normally degraded rapidly by the enzyme DPP-4. Gliptins act as inhibitors of DPP-4, allowing the normal effects of the incretin hormones to be enhanced. The main site of the enhanced incretin effect is on the pancreas to increase nutrient-induced insulin secretion. GLP-1 also reduces glucagon secretion. *Potential effects to slow gastric emptying and increase satiety probably contribute little to the therapeutic efficacy of DPP-4 inhibitors.

Table 31.12 Dipeptidylpeptidase-4 (DPP-4) inhibitors (gliptins): sitagliptin, vildagliptin, saxagliptin, linagliptin and alogliptin.

Agent	od/bd[a]	Dose (mg/day)	$t_{1/2}$ (h)	IC_{50} (nM)[b]	Selectivity for DPP4[c]	Metabolism	Excretion
Sitagliptin	od	100	8–24	19	>2500	Unchanged	Urine ~80%
Vildagliptin	bd	50	1.5–4.5	62	32–270	Inactive metabolites	Urine ~80%[d]
Saxagliptin	od	5	2–7[e]	50	77–390	Active metabolites	Urine ~60%[d]
Linagliptin	od	5	10–40	1	>10000	Mostly unchanged	Bile ~80%
Alogliptin	od	25	12–21	24	>14000	Mostly unchanged	Urine >70%

[a] od, once daily; bd, twice daily.
[b] Concentration causing 50% inhibition of DPP-4 activity.
[c] Fold selectivity for inhibition of DPP-4 versus inhibition of DPP-8 and DPP-9.
[d] Unchanged drug.
[e] Includes metabolites.

with moderate renal impairment (typically a GFR <50 mL/min) [74, 76].

Indications and contraindications

DPP-4 inhibitors can be used as monotherapy in people with T2DM who have responded inadequately to lifestyle measures, and as "add-on" therapy in people whose diabetes is inadequately controlled by metformin or a thiazolidinedione. Theoretically, they could be used with any other class of oral agent or insulin, as their mode of action on the β cell is different from that of sulfonylureas and meglitinides, and their ability to reduce glucagon levels might be useful as add-on therapy to insulin even without β-cell function. In practice, however, full efficacy in T2DM requires adequate β-cell reserve. Lack of weight gain makes DPP-4 inhibitors suitable for overweight and obese individuals, and the low risk of hypoglycemia when used as monotherapy (and when used with non-insulin-releasing agents) favors their use in people who have only slightly raised basal glycemia, are close to glycemic target, or have unpredictable meal times [74, 76].

Efficacy

The antihyperglycemic effect of DPP-4 inhibitors is quickly generated, with HbA_{1c} values typically reduced by ~0.7–1.0% (8–11 mmol/mol). Postprandial glucose excursions are reduced by ~3 mmol/L and basal glycemia by ~1–1.5 mmol/L. The glucose-dependent mode of action (i.e. DPP-4 inhibitors only potentiate insulin secretion when glucose concentrations are raised) reduces the risk of any significant hypoglycemia, lowering concern over missed meals. Thus, there is no dose titration, but it is recommended that fasting and postprandial glycemia are reviewed after about 2 weeks of therapy, especially when added as a second agent. The incretin-raising effects of DPP-4 inhibitors do not appear to be sufficient to reduce gastric emptying or produce a measurable satiety effect. Accordingly, DPP-4 inhibitors do not cause weight gain and may assist slight weight loss [74, 76–78].

Adverse effects

Substantial clinical experience with DPP-4 inhibitors has indicated a good safety profile to date. In clinical trials (typically 6–12 months), measures of tolerability and adverse events were generally similar to those with placebo or comparator. Owing to their glucose-dependent action on the pancreas, DPP-4 inhibitors carry a low risk of serious hypoglycemia unless administered along with an agent that itself carries significant risk of hypoglycemia. Thus, when a DPP-4 inhibitor is used in combination with a sulfonylurea or with insulin, it may be appropriate initially to lower the dose of the sulfonylurea or insulin, especially for those who are only modestly hyperglycemic and more vulnerable to hypoglycemia. DPP-4 inhibition has been associated with some hyperplasia of the exocrine pancreas, and there is evidence from several prospective and retrospective clinical studies that DPP-4 inhibition can increase the risk of acute pancreatitis in T2DM. Although this has not been consistently observed, or numerical data have not been statistically significant, appropriate caution is recommended and a DPP-4 inhibitor should be stopped if pancreatitis is suspected, and alternative therapy sought for people with a history of pancreatitis. Long-term cardiovascular safety studies have raised the possibility of an increased risk of hospitalization for angina during use of some DPP-4 inhibitors, but the evidence is equivocal [58, 74, 76].

In addition to GLP-1 and GIP, there are many natural substrates for DPP-4, including bradykinin, enkephalins, neuropeptide Y, peptide YY1-36, gastrin-releasing polypeptide, substance P, insulin-like growth factor I, the α chains of thyrotropin, luteinizing hormone, and chorionic gonadotropin, and several chemokines such as monocyte chemotactic protein 1 (MCP-1). Hence DPP-4 inhibitors have the potential to influence the hunger–satiety system, gastrointestinal motility, growth, vascular reactivity, and immune mechanisms, but there is little evidence of any clinically significant changes in these physiological processes [74, 75]. DPP-4 is also the CD26 T-cell activation antigen, but neither CD26 knockout mice nor the DPP-4-specific inhibitors used in animals or humans have shown any significant untoward immune-related effects. The importance of selective DPP-4

inhibition is also noted because inhibition of related enzymes such as DPP-8 and DPP-9 has produced blood dyscrasias and skin lesions in some species, but not in clinical use. No significant drug interactions have been noted with DPP-4 inhibitors, but evidence of reproductive toxicity in animals warrants discontinuation in pregnancy.

SGLT-2 inhibitors

SGLT-2 is highly expressed in the first segment of the proximal tubules of the kidneys, where it is responsible for the reabsorption of ~90% of glucose in the glomerular filtrate. Partial inhibition of SGLT-2 provides a non-insulin-dependent mechanism to reduce glucose reabsorption, eliminate excess glucose in the urine, and so reduce hyperglycemia [79, 80]. Studies in the 1980s showed that phlorizin, a naturally occurring inhibitor of sodium–glucose transporters found in apple tree bark, could reduce hyperglycemia in partially pancreatectomized rodents with diabetes. However, phlorizin was degraded too rapidly in the intestine to be used therapeutically, but chemical modifications to minimize intestinal breakdown and increase selectivity against SGLT-2 have given rise to a class of selective SGLT-2 inhibitors represented by canagliflozin, dapagliflozin, and empagliflozin (Figure 31.14).

Mode of action

SGLT-2 is a high-capacity secondary active co-transporter that transfers one sodium ion with one glucose molecule down an electrochemical gradient for sodium, generated by, for example, the activity of an Na^+–K^+ ATPase pump [81]. SGLT-2 inhibitors interact with SGLT-2 transporters located at the luminal surface of the epithelium lining the initial region of the renal proximal tubules (Figure 31.15). They competitively inhibit the transporter, reducing glucose reabsorption and thereby lowering the renal threshold for glucosuria. In this way, SGLT-2 inhibitors enable ~20–30% of filtered glucose (about 50–100 g glucose/day) to be eliminated in the urine of people with T2DM [82]. As the blood glucose concentration declines, the amount of filtered glucose declines and the glucosuria declines, minimizing the effect of SGLT-2 inhibition in the euglycemic range and avoiding frank hypoglycemia. Because the mechanism is independent of insulin, it will continue to operate under conditions of insulin resistance and β-cell failure, but requires adequate kidney function to filter sufficient glucose for partial SGLT-2 inhibition to create enough glucosuria to impact the hyperglycemia. The glucosuria induced by SGLT-2 inhibition can assist weight loss and generate a mild osmotic diuresis that may contribute to a small reduction in blood pressure [79, 80].

SGLT-2 inhibitors can weakly suppress the activity of SGLT-1 transporters (transfer two sodium ions with one glucose or galactose). SGLT-1 is abundant in the intestine and accounts for the absorption of glucose; it is also expressed in the third (straight descending) segment of the proximal tubules, where it is responsible for ~10% of glucose reabsorption. Canagliflozin may interact with SGLT-1 to defer intestinal glucose absorption slightly more distally along the intestinal tract and possibly reduce SGLT-1 activity in the kidney.

Pharmacokinetics

The pharmacokinetic properties of SGLT-2 inhibitors are summarized in Table 31.13. They reversibly inhibit SGLT-2 at low nmol/L concentrations by blocking the glucose site for several minutes. SGLT-2 inhibitors are taken as once-daily tablets; they are rapidly absorbed with high bioavailability. In plasma they are mostly protein bound and are degraded mainly through glucuronidation by uridine diphosphoglucuronosyltransferases to inactive metabolites. They show little or no inhibition by or induction of P450 isoforms that metabolize other common medications, and no clinically significant drug interactions have been noted [80].

Indications and contraindications

SGLT-2 inhibitors can be used as monotherapy in people with T2DM who have not responded adequately to lifestyle measures, although they are more often used as "add-on" therapy in those whose diabetes is inadequately controlled by metformin or another glucose-lowering agent. In principle, an SGLT-2 inhibitor can be used with any other class of oral agent or insulin, as the mode of action is different from those of all other classes of glucose-lowering agents. Body weight reduction makes an SGLT-2 inhibitor suitable for overweight and obese individuals, and

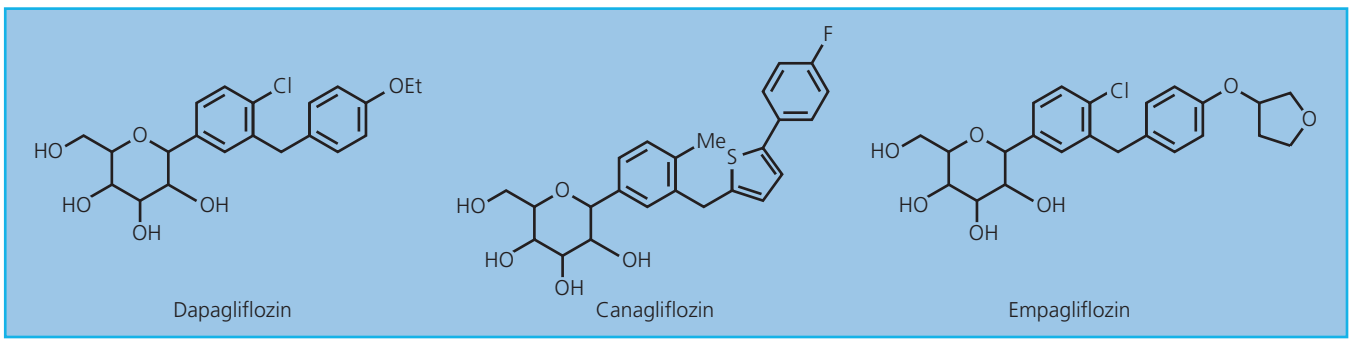

Figure 31.14 Structures of the sodium–glucose co-transporter-2 (SGLT-2) inhibitors dapagliflozin, canagliflozin, and empagliflozin.

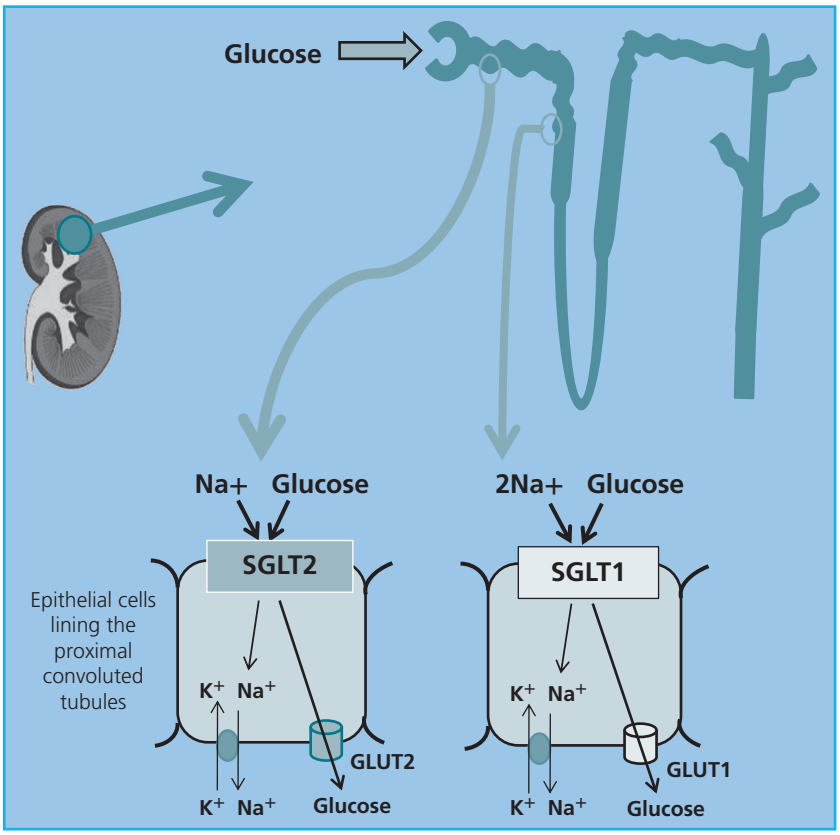

Figure 31.15 Renal sodium–glucose transporters reabsorb glucose from the renal proximal tubules. Glucose is filtered at the glomerulus into the proximal tubule and mostly reabsorbed from the initial region of the proximal tubule via the high-capacity transporter SGLT-2. Remaining glucose is reabsorbed more distally along the proximal tubule via the low-capacity transporter SGLT-1. Source: Bailey, CJ. New drugs for the treatment of diabetes mellitus. In: *International Textbook of Diabetes Mellitus*, 4th edn. John Wiley & Sons, 2015.

the low risk of hypoglycemia renders this class of agent suitable for people with glucose values close to target. Modest reductions of blood pressure in individuals with hypertension may also be expected [80].

Adequate renal function is an important consideration for use of an SGLT-2 inhibitor to enable glucosuric efficacy. Although recommendations may vary slightly between countries, an SGLT-2 inhibitor can be used at full daily dosage for eGFR >60 mL/min. For people with an eGFR value of 45–60 mL/min, a reduced dose (canagliflozin and empagliflozin) or discontinuation (dapagliflozin) is generally suggested. Patients should be informed about the need to remain hydrated and the risk of initial nocturia and genital and urinary tract infections. People with insulin-treated T2DM should ensure that they maintain an adequate insulin dose since insulin is required for many more physiological purposes than glycemic control. At the time of writing, SGLT-2 inhibitors are not approved for use in T1DM and should be discontinued in pregnancy.

Efficacy

The glucose-lowering efficacy of SGLT-2 inhibitors in T2DM has been confirmed in prospective randomized clinical trials during use as monotherapy and in combination with other glucose-lowering therapies including insulin. There is a rapid onset of action to reduce postprandial and basal hyperglycemia. HbA_{1c} is typically reduced by ~0.6–1.2% (7–13 mmol/mol), although larger reductions may be seen in people with severe hyperglycemia and those with good renal function [83, 84]. Efficacy during trials has extended over several years and risk of hypoglycemia has been low unless used in combination with an agent that can itself cause hypoglycemia (such as a sulfonylurea or insulin). Most people achieve a weight loss of ~2–4 kg, which levels out by 6–12 months, possibly reflecting an increase in metabolic efficiency or some increase in food intake as the glucose level declines. The weight loss is predominantly a decrease in fat mass, notably from the visceral adipose depot. In clinical trials involving participants with insulin-treated T2DM, glycemic control is often improved

Table 31.13 Sodium–glucose co-transporter-2 (SGLT-2) inhibitors: dapagliflozin, canagliflozin, and empagliflozin.

Agent	Dose (mg/day)	IC_{50} SGLT2 vs. SGLT1(nM)	t_{max} (h)	C_{max}	$t_{1/2}$ (h)
Dapagliflozin	5–10	1.1 vs. 1390	1–2	~160 ng/mL	~13
Canagliflozin	100–300	2.2 vs. 910	1–2	~1–5 μg/mL	~13
Empagliflozin	10–25	3.1 vs. 8300	~1.5	~250–700 nmol/L	~13

while the insulin dose is slightly lowered, and control is maintained over time without insulin dose escalation. Combination of an SGLT-2 inhibitor with insulin can also reduce the weight gain normally associated with insulin therapy. SGLT-2 inhibitors have also consistently reduced systolic blood pressure by 3–5 mmHg in hypertensive and normotensive individuals with diabetes, with smaller reductions in diastolic blood pressure and without dipping into hypotension.

Adverse effects

The glucosuric effect of SGLT-2 inhibitors increases the risk of genital infections, particularly vulvovaginal mycotic infections in women during the initial months of therapy, and there is also a small increase in the risk of urinary tract infections. The occurrence and severity of these infections can be reduced by appropriate advice when starting therapy and most of these infections respond to standard treatments, often by patient self-management. The osmotic diuresis generated by the glucosuria (usually <500 mL/day) requires patient attention to adequate hydration, especially in hot climates, and should be emphasized when initiating therapy. The GFR may temporarily decline after introduction of an SGLT-2 inhibitor, and extra caution is recommended for people receiving diuretic therapy, although electrolyte imbalances have not been seen in clinical trials [80].

Accounts of atypical ketoacidosis in individuals treated with an SGLT-2 inhibitor have described a hyperosmolar metabolic acidosis with only modest hyperglycemia. Many of these people had T1DM (currently contraindicated) or were insulin-treated patients of unclear diagnosis in whom the insulin dose may have been over-reduced because the hyperglycemia was well controlled with the SGLT-2 inhibitor. Basal insulin should be maintained in insulinopenic individuals, as this reduces lipolysis (thereby reducing the supply of fatty acids for ketogenesis) and is required for other physiological purposes beyond glycemic control. Indeed, people with a history of ketotic episodes are unlikely to be appropriate for SGLT-2 inhibitor therapy; SGLT-2 inhibition may cause a compensatory increase in glucagon release [85], especially at low glucose levels, and this can assist ketogenesis [86].

Because SGLT-2 inhibitors do not interfere with P450 isoenzymes, they do not appear to have any clinically meaningful drug interactions. Minor changes in the circulating lipid profile have been reported with SGLT-2 inhibitors, notably some increases in LDL and HDL cholesterol, but without altering the LDL : HDL ratio. During clinical trials, the numbers of cardiovascular events have generally been similar to or fewer than with comparator therapies. A large prospective long-term (3.1 years) safety study with empagliflozin in participants with T2DM at high cardiovascular risk reported a 14% reduction in a composite endpoint of cardiovascular death and non-fatal MI and stroke, and also a 32% reduction in overall mortality and a 36% reduction in death from cardiovascular causes [87]. The effects became evident during the first few months of treatment and could not be directly attributed to improved glycemic and/or weight control. The results of additional studies are awaited to confirm these findings, assess the extent to which improved blood pressure control may be involved, and determine cardiovascular outcomes with other SGLT-2 inhibitors.

α-Glucosidase inhibitors

Studies conducted in the late 1970s noted that inhibitors of intestinal α-glucosidase enzymes could retard the final steps of carbohydrate digestion with a consequent delay in the absorption of sugars. By the early 1980s, it was demonstrated that this approach could reduce postprandial hyperglycemia in diabetes [88]. Acarbose, the first α-glucosidase inhibitor, was introduced in the early 1990s. Subsequently, two further agents, miglitol and voglibose, were introduced in some countries (Figure 31.16). In people who consume meals containing complex carbohydrate, α-glucosidase inhibitors can effectively reduce postprandial glucose excursions. These agents also have a good safety record but their application has been limited by gastrointestinal side effects and modest efficacy.

Mode of action

α-Glucosidase inhibitors competitively inhibit the activity of α-glucosidase enzymes in the brush border of enterocytes lining the intestinal villi (Figure 31.17). They bind to the enzymes with high affinity, preventing the enzymes from cleaving disaccharides and oligosaccharides into monosaccharides. This delays completion of carbohydrate digestion and can defer the process distally along the intestinal tract, leading to a delay in glucose absorption [88]. Different α-glucosidase inhibitors have different affinities for the various α-glucosidase enzymes. This gives slightly different activity profiles (e.g. acarbose has greatest affinity for glycoamylase > sucrase > maltase > dextrinases, whereas miglitol is a stronger inhibitor of sucrase). It is emphasized that α-glucosidase inhibitors can only be effective if the person is consuming complex digestible carbohydrate. These agents do not significantly affect the absorption of glucose per se. By moving glucose absorption more distally along the intestinal tract, α-glucosidase inhibitors may alter the release of glucose-dependent incretin hormones such as GIP and GLP-1, which enhance nutrient-induced insulin secretion. Hence release of GIP, which occurs mainly from the jejunal mucosa, may be reduced by α-glucosidase inhibitors, whereas secretion of GLP-1 (mostly from the ileal mucosa) is increased. α-Glucosidase inhibitors probably reduce postprandial insulin concentrations through the attenuated rise in postprandial glucose levels [88].

Pharmacokinetics

Acarbose is degraded by amylases in the small intestine and by intestinal bacteria; <2% of the unchanged drug is absorbed along with some of the intestinal degradation products. Absorbed material is mostly eliminated in the urine within 24 h [88]. Miglitol is almost completely absorbed and eliminated unchanged in the urine.

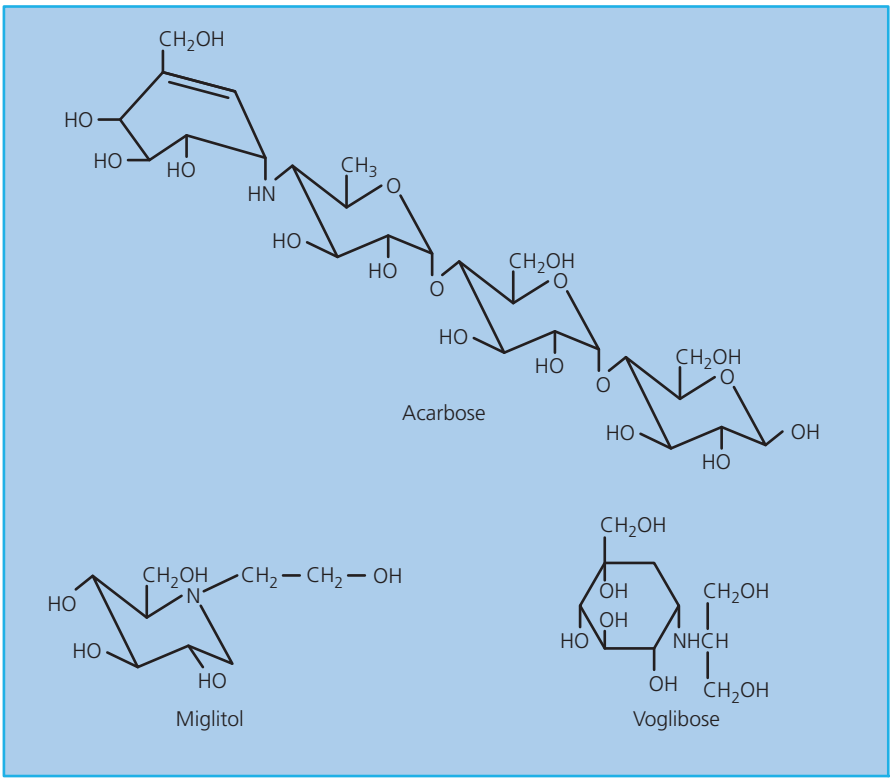

Figure 31.16 Chemical structures of the α-glucosidase inhibitors acarbose, miglitol, and volglibose.

Indications and contraindications

α-Glucosidase inhibitors can be used as monotherapy, usually for people with T2DM with postprandial hyperglycemia but only slightly raised fasting glycemia; however, they are more commonly used as add-on to other therapies, again to target postprandial hyperglycemia [88]. α-Glucosidase inhibitors can also be used to extend the postprandial period to reduce interprandial glycemic troughs or hypoglycemia in individuals receiving a sulfonylurea and/or insulin. Acarbose has also been shown to prevent progression of IGT to T2DM [89], although this is not a licensed use.

When starting an α-glucosidase inhibitor, the person should be advised that a diet containing complex digestible carbohydrate is important. α-Glucosidase inhibitors should be taken with meals, starting with a low dose (e.g. 50 mg/day acarbose) and slowly uptitrated over several weeks. Monitoring of postprandial glycemia is often helpful. Hypoglycemia is unlikely when used as monotherapy, but gastrointestinal symptoms commonly limit

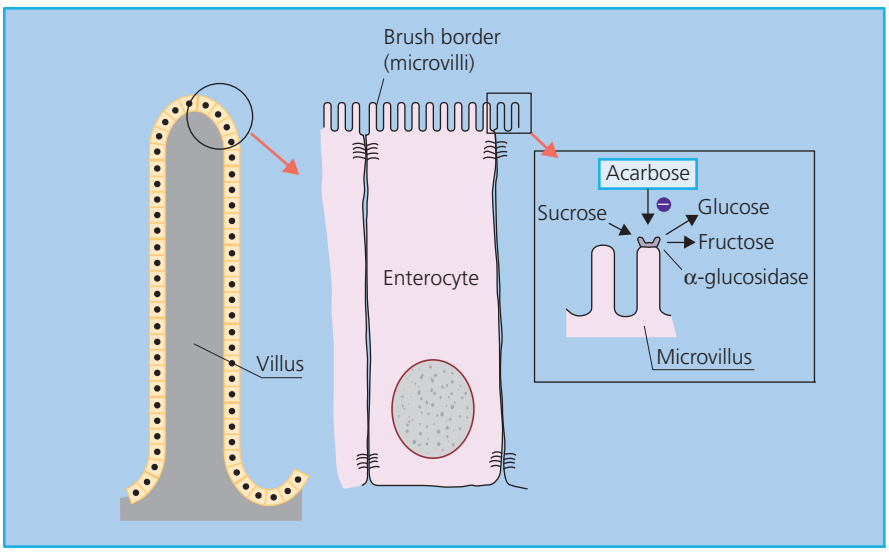

Figure 31.17 Mode of action of α-glucosidase inhibitors. α-Glucosidase inhibitors competitively inhibit the activity of α-glucosidase enzymes in the brush border of enterocytes lining the intestinal villi, preventing these enzymes from cleaving disaccharides and oligosaccharides into monosaccharides. This delays carbohydrate digestion.

initial tolerability and dose titration. Symptoms tend to be reduced by slow titration and usually subside with time, possibly reflecting some adaptation of the intestinal tract, but tolerability is poor.

α-Glucosidase inhibitors are contraindicated for people with a history of chronic intestinal disease, and as high dosages of acarbose can occasionally increase liver enzyme concentrations, it is recommended to measure transaminase concentrations periodically in those receiving a maximum dosage (200 mg acarbose three times daily). Raised liver enzymes should remit as the dosage is reduced, otherwise alternative causes of hepatic dysfunction should be considered.

Efficacy

Because α-glucosidase inhibitors target postprandial glucose excursions during meals that contain complex carbohydrate, their effectiveness is entirely dependent on dietary adherence. As monotherapy, these agents can reduce peak postprandial glucose concentrations by 1–4 mmol/L. The incremental area under the postprandial plasma glucose curve can be more than halved in some individuals, and there is usually some extended duration of effect to modestly lower basal glycemia up to ~1 mmol/L. The decrease in HbA_{1c} can be 0.5–1.0% (6–11 mmol/mol), provided that a high dose of the drug is tolerated and dietary adherence is maintained [90].

Although overall reductions in HbA_{1c} are usually modest, α-glucosidase inhibitors offer several useful features: they do not cause weight gain or frank hypoglycemia and they may reduce interprandial episodes of hypoglycemia. When combined with other antidiabetes agents, α-glucosidase inhibitors can reduce postprandial hyperinsulinemia, and they often lower plasma triglyceride concentrations. Use of an α-glucosidase inhibitor can produce minor alterations to the intestinal absorption of other oral glucose-lowering agents when used in combination therapy, but α-glucosidase inhibitors usually provide additive efficacy gains when used in combination with any other class of antidiabetes agent [88]. There is preliminary evidence that acarbose might reduce major cardiac events, including MI, and prospective studies are ongoing, but it is unclear if this could be caused by the targeting of postprandial hyperglycemia or an independent effect of the drug [91].

Adverse effects

Gastrointestinal side effects represent the main problem with α-glucosidase inhibitors. For example, in the STOP-NIDDM trial, 31% of acarbose-treated participants compared with 19% on placebo discontinued treatment early [89]. If the dosage is too high (relative to the amount of complex carbohydrate in the meal), undigested oligosaccharides pass into the large bowel. These are fermented, causing flatulence, abdominal discomfort, and sometimes diarrhea, but usually ameliorating with slower titration and time. Hypoglycemia is uncommon and there are no clinically significant drug interactions, although use in conjunction with agents affecting gut motility or cholestyramine is not recommended.

Bromocriptine

The dopamine D2 receptor agonist bromocriptine (Figure 31.18), which has long been used to treat pituitary tumors and Parkinson disease (albeit in a different formulation), has an indication for use in the treatment of T2DM in some countries [92, 93].

Mode of action

Studies in animals have noted that the interruption of dopaminergic pathways in the hypothalamus is associated with the development of insulin resistance, and this can be reversed by localized dopamine infusion. Studies in individuals with T2DM suggest that a low dose of a rapid acting formulation of bromocriptine administered early in the morning soon after waking can temporarily boost hypothalamic dopamine. This appears to rebalance several features of the circadian periodicity of glucose homeostasis by reducing sympathetic tone and enhancing the neural suppression of hepatic glucose production. Additionally, there is a reduction of adipose tissue lipolysis and an improvement in peripheral glucose disposal without elevation of plasma insulin, indicating improved peripheral insulin sensitivity [92, 93].

Pharmacokinetics

The low-dose formulation of bromocriptine used for blood glucose lowering is rapidly absorbed (t_{max} by 1 h), highly protein bound, rapidly removed by the liver (mostly metabolized by CYP3A4) and eliminated via the bile; the half-life is ~6 h. Prolactin levels are reduced consistent with increased dopaminergic activity.

Indications and contraindications

Based on considerable experience with the use of bromocriptine for other purposes, use to treat T2DM requires caution if patients are prone to low blood pressure, various psychotic disorders, or somnolence, and exclusion for those who experience migraine or take dopaminergic antagonists. Potential interactions with other medications that influence or may be influenced by changes in

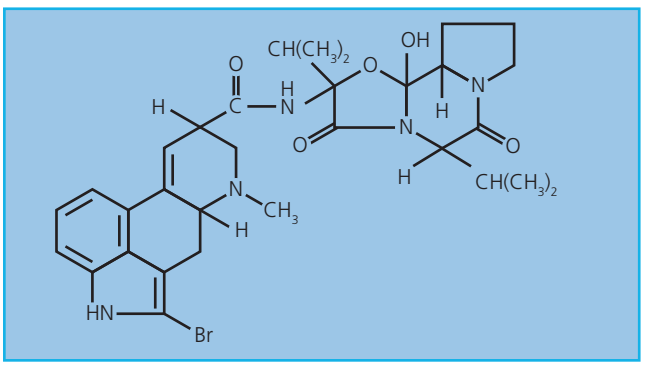

Figure 31.18 Chemical structure of bromocriptine.

CYP3A4 should be appreciated, and evidence regarding use during pregnancy is limited.

Efficacy

In clinical trials, participants with T2DM receiving a low dose (0.8–4.8 mg) of quickly acting bromocriptine early in the morning showed HbA_{1c} reductions of ~0.5–0.7% (5–8 mmol/mol) when taken as monotherapy or in combination with other oral glucose-lowering agents. Fasting and postprandial glucose, fatty acid, and triglyceride concentrations were reduced, insulin was not raised, risk of hypoglycemia was low, and there was no weight gain [92, 93].

Adverse effects

Although high doses of bromocriptine carry some long-term risk for pulmonary and pericardial fibrosis, hypotension, and aggravation of psychotic disorders, these were not seen with low doses during clinical trials for T2DM.

Colesevelam

In addition to its use as a bile acid sequestrant, colesevelam (a polyallylamine derivative) also has an indication for glucose lowering in some countries.

Mode of action

The glucose-lowering mechanism of colesevelam is not clear. By interrupting the enterohepatic circulation of bile acids, colesevelam appears to reduce the availability of bile acids to activate the bile acid receptor-1 (TGR5) and the farnesoid X receptor (FXR), which results in increased hepatic glucose metabolism [94]. A further possibility is that the bile acids are carried more distally along the intestine owing to their entrapment by colesevelam. This could bring more bile acids into contact with TGR5 receptors on L -cells, which could enhance the secretion of GLP-1.

Pharmacokinetics

Up to three 625-mg tablets of colesevelam can be taken with each of two main meals daily; the colesevelam is not absorbed.

Indications and contraindications

Colesevelam requires caution if any intestinal disorders, especially obstruction, are known or suspected. Colesevelam can alter the absorption of other oral medications, including oral glucose-lowering therapies, and dose adjustments may be required.

Efficacy

Clinical trials with colesevelam in T2DM have noted modest reductions of HbA_{1c} of ~0.5% (5 mmol/mol) when used as an add-on to metformin, sulfonylurea, or insulin. There is no effect on body weight, low risk of hypoglycemia, and, consistent with its use in the treatment of hypercholesterolemia, there is usually a reduction in LDL cholesterol [94].

Adverse effects

Colesevelam may increase circulating triglycerides and cause abdominal symptoms, especially constipation.

Antiobesity therapies

Obesity, especially excess visceral adiposity, predisposes to diabetes, complicates glycemic control, and substantially increases the risk of vascular disease [95]. The blood glucose-lowering efficacy of lifestyle measures to reduce adiposity in obese individuals with T2DM is well appreciated, although it is often very difficult to achieve and maintain significant weight loss in these persons. Several studies have noted the reductions in blood glucose that accompany the use of pharmacological antiobesity therapies in T2DM. Whether this is entirely explained by greater weight loss and improved dietary adherence is unclear, because it has been mooted that some antiobesity therapies could have some modest independent glucose-lowering effects [21].

In conjunction with a mildly hypocaloric and reduced-fat diet, the intestinal lipase inhibitor orlistat (120 mg three times daily with meals) can reduce dietary fat absorption by up to 30%. In overweight and obese individuals with T2DM, this typically increases weight reduction by an extra 2–3 kg, and additional reductions in HbA_{1c} of 0.28–1.1% (3–12 mmol/mol) have been reported [21]. Potential improvements in the glucose–fatty acid cycle might be envisaged.

The satiety-inducing serotonin–norepinephrine reuptake inhibitor sibutramine, which is no longer available in most countries owing to cardiovascular side effects, has permitted greater reductions of body weight in overweight and obese people with T2DM, with extra reductions in HbA_{1c} of ~0.6% (7 mmol/mol). The cannabinoid CB1 receptor antagonist rimonabant, now withdrawn owing to psychiatric effects, also improved glycemic control in association with weight loss in individuals with T2DM [21].

Recently emerging antiobesity agents, notably the 5HT2c receptor agonist lorcaserin, a phentermine–topiramate combination (Qsymia), and a bupropion–naltrexone combination (Contrave), have been shown in clinical trials to improve glycemic control in people with T2DM in association with weight loss [21]. It is noted that antiobesity therapies carry their own contraindications, cautions, and side effects and may interfere with the absorption or actions of other therapies, including glucose-lowering agents.

Fixed-dose combinations

As early and intensified interventional approaches to the management of hyperglycemia in individuals with T2DM gain acceptance, the use of combinations of two or more oral agents with different mechanisms of action has become commonplace [96]. To facilitate combination therapy, several fixed-dose, single-tablet combinations have been made available (Table 31.14). These are

Table 31.14 Fixed-dose single-tablet combinations of antidiabetes agents.

Tablet[a]	Components	Strengths (mg)
Glucovance	Metformin + libenclamide	250:1.25, 500:2.5, 500:5
Metaglip	Metformin + glipizide	250:2.5, 500:2.5, 500:5
Avandamet	Metformin + rosiglitazone	500:1, 500:4, 500:2, 1000:2, 1000:4
Competact (Actoplusmet)	Metformin + pioglitazone	500:15, 850:15
Eucreas	Metformin + vildagliptin	850:50, 1000:50
Janumet	Metformin + sitagliptin	500:50, 1000:50
Prandimet	Metformin + repaglinide	500:1, 500:2
Kombiglyze	Metformin + saxagliptin	500:5, 1000:2.5, 1000:5
Jentadueto	Metformin + linagliptin	500:2.5, 850:2.5, 1000:2.5
Kazano (Vipdomet)	Metformin + alogliptin	500:12.5, 1000:12.5
Avaglim (Avandaryl)	Rosiglitazone + glimepiride	4:1, 4:2, 4:4, 8:2, 8:4
Tandemact (Duetact)	Pioglitazone + glimepiride	30:, 45:4
Xigduo	Metformin + dapagliflozin	850:5, 1000:5
Vokanamet	Metformin + canagliflozin	1000:50
Incresync	Pioglitazone + alogliptin	30:12.5
Glyxambi	Empagliflozin + linagliptin	10:5, 25:5
Synjardy	Metformin + empagliflozin	850:5, 850:12.5, 1000:5, 1000:12.5

[a]The availability of tablets and component strengths differ between countries. Names vary between Europe and the USA. Alternative names are given in parentheses.

designed to provide bioequivalence and thereby similar efficacy, although minor adjustments to the formulation may also allow some extra blood glucose-lowering efficacy. Fixed-dose combinations can offer convenience, reduce the "pill burden," and simplify administration regimens, and they may increase adherence compared with equivalent combinations of separate tablets. Lower doses of two different types of agents rather than a high dose of one agent may also provide a way to achieve efficacy while circumventing dose-related side effects. Although single tablets could reduce titration flexibility, most of the commonly used dosage combinations have been accommodated. It is reiterated that any form of combination therapy necessitates the same cautions and contraindications as apply to each active component.

Conclusions

A minimalistic archetypal algorithm to treat hyperglycemia in T2DM is shown in Figure 31.19. This illustrates the typical sequence of pharmacological interventions advocated in most

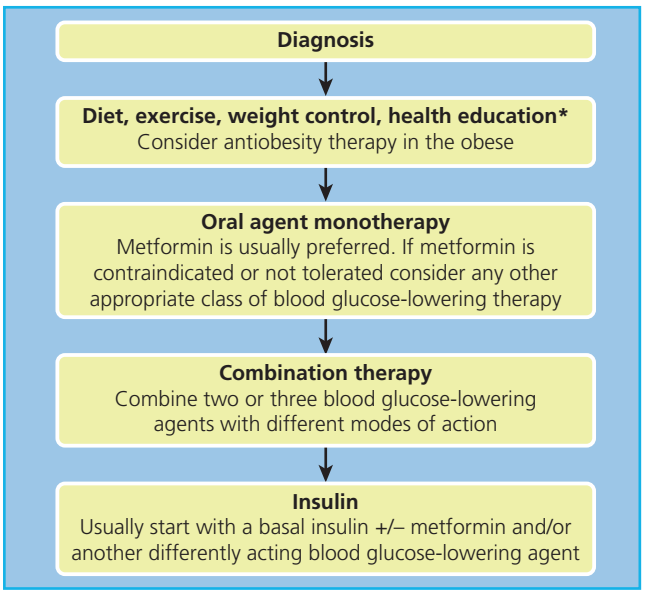

Figure 31.19 Archetypal algorithm used in the treatment of hyperglycemia in type 2 diabetes (except for those presenting with severe hyperglycemia who may require immediate insulin therapy). Start with lifestyle measures (diet and exercise). If the individualized glycemic target is not achieved quickly using lifestyle measures, then add pharmacological therapy without delay. The selected monotherapy is uptitrated to achieve the desired glycemic effect. If an uptitration step does not add benefit or is not tolerated, revert back a step. When the desired glycemic effect is not achieved or adequate titration is not tolerated, move promptly to the addition of a second agent with a different mode of action and uptitrate. If the desired glycemic control is not achieved or maintained, consider triple therapy or introduce insulin while maintaining one or two of the existing therapies where appropriate. Respect drug cautions and contraindications at all times, monitor as required, and try to select glycemic targets that are realistic, safely achievable, and avoid hypoglycemia. Various guidelines (e.g. see [3, 4]) offer more detail with suggested glycemic targets and suggested sequence orders for the introduction of the pharmacotherapies. *Lifestyle advice reinforced throughout.

current guidelines. Guidelines should be interpreted with flexibility, however, to ensure that the care plan, treatment targets, and selection of therapies are individualized to suit the circumstances of the patient. The value of lifestyle intervention as initial and ongoing therapy in conjunction with pharmacological agents should not be underestimated. In view of the progressive natural history of T2DM, the introduction of drug therapy, the need for periodic uptitration of dosage, and the use of combination therapy can be expected for most people with T2DM.

A range of differently acting oral agents is available: metformin and thiazolidinediones counter insulin resistance; sulfonylureas, meglitinides, and DPP-4 inhibitors increase insulin secretion; SGLT-2 inhibitors increase renal glucose elimination; and α-glucosidase inhibitors slow carbohydrate digestion. Additionally, injected GLP-1 receptor agonists increase insulin secretion and reduce glucagon. When adequate control is not achieved or not maintained, it is important to proceed to the next therapeutic stage without delay to avoid periods of excessive hyperglycemia.

Insulin should be considered when other therapies do not provide adequate glycemic control or are unsuitable. Integrated management to address cardiovascular risk and comorbid conditions is essential. Glucose monitoring, making therapeutic adjustments for efficacy, safety, avoidance of hypoglycemia, and contraindications, requires constant vigilance and forms an integral part of the treatment process. Early, effective, and sustained glycemic control is essential to minimize the risk for vascular complications later in life.

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32 Non-Insulin Parenteral Therapies

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Key points

- Glucagon-like peptide-1 (GLP-1) is a blood glucose-lowering (via insulinotropic and glucagonostatic effects) and satiety-promoting hormone secreted from enteroendocrine L-cells found in the intestinal epithelium.
- The most robust physiological stimulus for GLP-1 secretion is meal ingestion and within 5–15 min after food ingestion, plasma concentrations of GLP-1 start to rise.
- Glucose-lowering drugs based on the physiological effects of GLP-1 are part of the treatment algorithms and guidelines for type 2 diabetes.
- GLP-1 receptor agonists target a broad spectrum of the pathophysiology of type 2 diabetes and improve glucose homeostasis with low risk of hypoglycemia combined with body weight loss.
- Differences in structure, pharmacokinetics, and size of the different GLP-1 receptor agonists are important, as the dosing schedule (convenience), efficacy, and tolerability depend on these differences.
- Adverse events to GLP-1 receptor agonists are typically of gastrointestinal character (mainly nausea, vomiting, and diarrhea) and seem to diminish over time.
- Two outcome studies involving the GLP-1 receptor agonists have been finalized; 1) the LEADER trial demonstrating that fewer participants died from cardiovascular causes during treatment with liraglutide (long-acting GLP-1 receptor agonist) treatment than with placebo, and 2) ELIXA evaluating lixisenatide (short-acting GLP-1 receptor agonist) showing non-inferiority compared to placebo in terms of cardiovascular outcomes. Several other cardiovascular outcome trials are underway.
- Amylin is co-secreted with insulin from the pancreatic beta cells and has been shown to reduce gastric emptying appetite and glucagon secretion.
- Amylin analogs are used to obtain clinically beneficial glycemic control and body weight loss in individuals with diabetes.
- Preclinical data suggest that a single-molecule dual or triple agonist approach, e.g. involving amylin and GLP-1 dual receptor agonism, may be as efficient as co-administration of the individual peptides.

Introduction

During recent decades, the globally increasing prevalence of obesity and associated type 2 diabetes has promoted extensive research with the aim of clarifying the physiological and pharmacological role of pancreas- and gut-derived peptide hormones in the regulation of glucose homeostasis and feeding behavior.

Glucagon-like peptide-1 (GLP-1) and GLP-1 receptor agonists (GLP-1RAs)

Introduction

Over the last decade, glucose-lowering drugs based on the physiological effects of the gut incretin hormone glucagon-like peptide-1 (GLP-1) have been introduced into the international type 2 diabetes treatment algorithms and guidelines [1, 2]. The inclusion of GLP-1-based treatment modalities (i.e. the orally available dipeptidyl peptidase 4 [DPP-4] inhibitors (Chapter 31) and the parenteral GLP-1 receptor agonists [GLP-1RAs]) in the armamentarium of glucose-lowering drugs has increased treatment options and helped clinicians tailor individualized treatments for their patients with type 2 diabetes (as recommended in modern treatment guidelines). In particular, the introduction of the injectable GLP-1RAs with their glucose-dependent glucose-lowering action (active only when plasma glucose levels are high) and the consequent low risk of hypoglycemia, combined with their body weight-reducing effect, has been welcomed by healthcare providers and people with diabetes. Owing to the increased requirements of regulatory agencies (particularly the US Food and Drug Administration [FDA] and European Medicines Agency [EMA]) for extensive safety data on new glucose-lowering drugs coinciding with the course of development of most incretin-based drugs, this drug class represents one of the most thoroughly investigated and monitored. Thus, despite the relatively young age of incretin-based drugs a considerable amount of data on safety and efficacy on this drug class exists. Owing to the body weight-reducing effect of GLP-1 receptor (GLP-1R) activation, one GLP-1RA has also been approved for the treatment of

Textbook of Diabetes, Fifth Edition. Edited by R. Holt, C. Cockram, A. Flyvbjerg and B. Goldstein.

overweight/obesity and currently several studies are evaluating the applicability of GLP-1RA treatment in other disease states and high-risk conditions. In the first part of the chapter, a historical overview of the investigations leading to the discovery of the gut incretin hormone GLP-1 and its potential as a glucose-lowering drug is presented, the physiology of native GLP-1 is outlined, and the pharmacology, safety, and efficacy of the individual GLP-1RAs currently available for the treatment of type 2 diabetes are considered. Finally, perspectives for GLP-1RA treatment within other disease areas and their potential position in future treatment algorithms are highlighted.

Historical overview

The introduction of GLP-1-based treatment modalities in the beginning of the third millennium was the result of a century of investigations. In 1906, extracts of mucosa from porcine small intestine were tested by Moore et al. as a treatment for diabetes in the hope that "the pancreas secretion might be stimulated by the substance of the nature of a hormone yielded by the duodenal mucosa membrane" [3]. In 1928, Zunz and LaBarre described a hypoglycemic effect following injection of extracts from small intestinal mucosa and, using cross-circulation experiments, they were able to show that the effect was mediated through the pancreas [4]. Four years later, LaBarre named the unidentified substance thought to exert this effect "incretin" in order to dissociate it from secretin (which stimulates exocrine pancreatic secretion) discovered by Bayliss and Starling at the beginning of the century [5]. Then, in 1964, McIntyre et al. and Elrick et al. demonstrated that orally administered glucose evokes a greater insulin response than does intravenously administered glucose, and both groups hypothesized that gut-derived factors could have potentiating effects on insulin secretion after oral ingestion of glucose [6, 7]. A few years later, in 1967, this finding was confirmed by Perley and Kipnis, who administered oral glucose and, on a separate day, copied the oral glucose curve with an isoglycemic intravenous (i.v.) glucose infusion in obese and normal-weight people with diabetes and in healthy people without diabetes [8]. They concluded that the insulin response to isoglycemic i.v. glucose administration only amounted to 30–40% of that seen after oral administration of glucose; they had come across the "the incretin effect" (i.e. the phenomenon of oral glucose eliciting a higher insulin response than i.v. glucose at identical plasma glucose profiles). However, at that time, the insulinotropic substance eliciting this effect was unknown.

In 1970, gastric inhibitory polypeptide, secreted from small intestinal endocrine K cells in response to ingestion of nutrients, was discovered [9] and, eventually, the 42 amino acid polypeptide was shown to be insulinotropic at elevated glucose concentrations and was renamed glucose-dependent insulinotropic polypeptide (GIP) [10]. Later, experimental and clinical studies suggested that the gut produces more than a single insulinotropic hormone of importance for glucose homeostasis [11]. In 1983, the gene encoding the human pancreatic hormone, glucagon, was cloned, and the structure of its precursor, proglucagon, was surprisingly shown to include the sequence of two glucagon-like peptides (including GLP-1 [Figure 32.1]) in addition to glucagon itself [12]. The gene was found to be expressed in both pancreatic α cells and enteroendocrine L cells in the small intestine [13]. The primary transcripts and translational products of the gene in the two types of cells are identical but, as illustrated in Figure 32.2, the post-translational processing was shown to differ in the two tissues [13–15]. In the pancreas, proglucagon is cleaved by prohormone convertase 2 to glucagon, glicentin-related pancreatic peptide (GRPP) and a major proglucagon fragment. Apart from glucagon, these fragments seem to be biologically inactive. In contrast, in the intestinal L cells, proglucagon is processed by prohormone convertase 1/3 to GLP-1, glucagon-like peptide-2 (GLP-2), and glicentin. The 30 amino acid peptide GLP-1 was found to be secreted in response to ingestion of nutrients and to be strongly insulinotropic, an incretin hormone [16, 17]. GLP-2 is also secreted in response to ingestion of nutrients and is a key regulator of small intestinal growth. The bioactive forms of GLP-1,

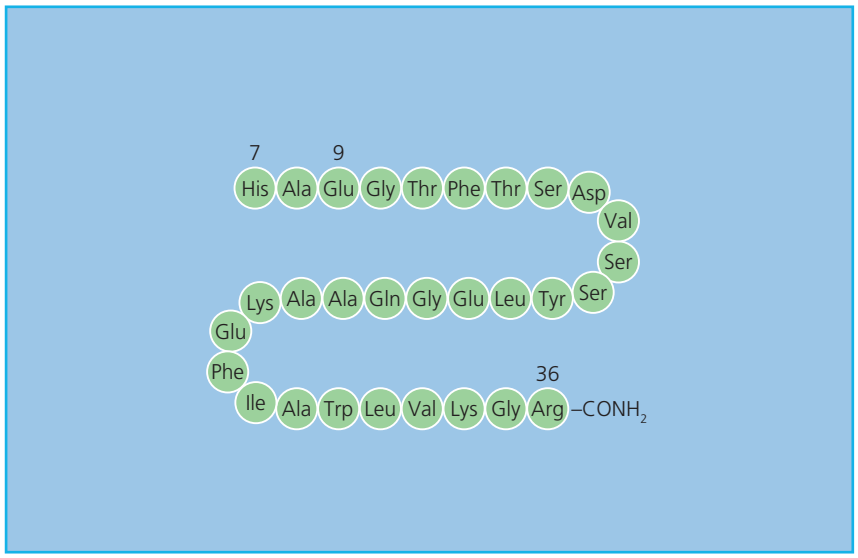

Figure 32.1 Native human GLP-1 circulates as GLP-1(7–36) amide (illustrated here) or glycine extended GLP-1(7–37). The enzyme dipeptidyl peptidase 4 (DPP-4) inactivates the hormone by cleaving off the two N-terminal amino acids (His and Ala).

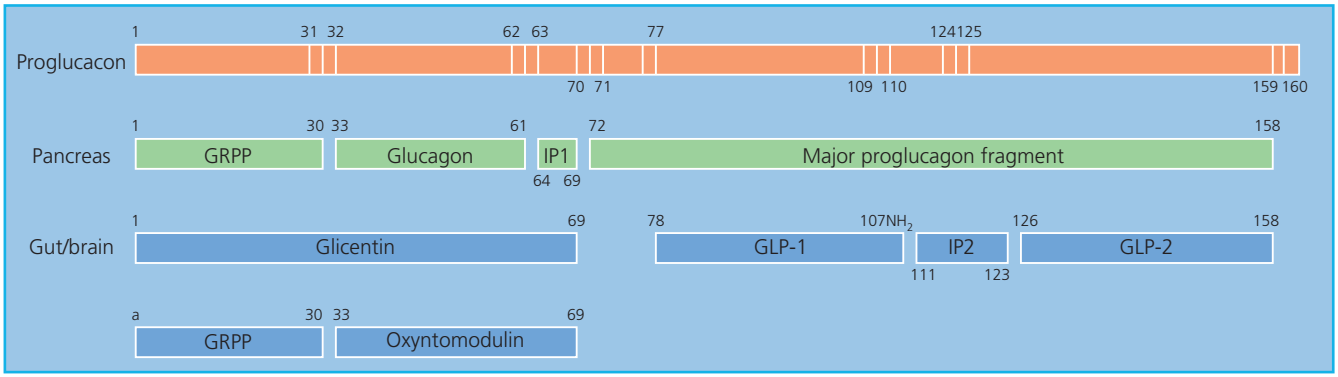

Figure 32.2 Proglucagon processing in human pancreatic α cells (by prohormone convertase 2) and in enteroendocrine L cells in the small intestine (by prohormone convertase 1/3). In proglucagon producing neurons in the nucleus tractus solitarii (brain), proglucagon is most likely processed by prohormone convertase 1/3 as in the gut.

amidated and glycine extended GLP-1, respectively, are designated GLP-$1_{7–36\ amide}$ and GLP-$1_{7–37}$ (Figure 32.1).

Many hormones have been suspected to contribute to the incretin effect, but today there is ample evidence to suggest that the incretin effect is mainly conveyed by the two incretin hormones GIP and GLP-1. In 1983, Nauck et al. showed that the incretin effect is reduced in persons with type 2 diabetes [18]. The precise mechanisms behind this pathophysiological characteristic remain somewhat controversial. In the 2000s, publications reported reduced secretion of GLP-1 in individuals with type 2 diabetes [19, 20], but recent meta-analyses suggest that the secretion of GLP-1 among persons with type 2 diabetes, in general, is normal [21, 22]. In contrast to the severely reduced insulinotropic effect of GIP in type 2 diabetes [23], the insulinotropic effect of GLP-1 has consistently been shown to be sustained in these individuals, albeit with reduced potency.

The reduced incretin effect in type 2 diabetes, the early reports on reduced postprandial GLP-1 responses, and the preserved glucose-dependent insulinotropic and glucagonostatic (see below) effects of GLP-1 constituted important incentives to pursue GLP-1 as a target for the treatment of type 2 diabetes. In contrast, the other incretin hormone, GIP, was not pursued as an antidiabetes target owing to its severely diminished insulinotropic effect in type 2 diabetes combined with reports suggesting glucagonotropic effects of GIP. Also, studies have suggested that GIP may act as a fat storage hormone promoting lipogenesis, adipokine secretion, and weight gain. Nevertheless, as GIP, like GLP-1, is a substrate of DPP-4, it may contribute to the glucose-lowering effect of DPP-4 inhibitors (see Chapter 31) and dual or even triple hormonal receptor agonists involving GIP receptor stimulation are currently being given new scientific and pharmaceutical attention.

GLP-1 physiology and antidiabetes actions

Proglucagon distribution, GLP-1 release, and metabolism

The glucagon gene is expressed in pancreatic α cells as well as in the enteroendocrine L cells and a subset of central nervous system [CNS] neurons in the nucleus tractus solitarii. The processing of proglucagon into "pancreatic" glucagon or "intestinal" GLP-1 (and GLP-2) depends on tissue-specific prohormone convertases (Figure 32.2). In the pancreas, prohormone convertase 2 represents the predominant prohormone convertase and, therefore, glucagon production is favored. Conversely, in the gut, prohormone convertase 1/3 is abundant and processing of proglucagon predominantly yields the hormones GLP-1 and GLP-2 (and oxyntomodulin) (Figure 32.2). Nevertheless, the distribution of the two prohormone convertases may not be as stringent as previously considered and small amounts of GLP-1/GLP-2 may be formed in the pancreas, and similarly, gut-derived glucagon secretion can also occur.

The most robust physiological stimulus for GLP-1 secretion is meal ingestion. Within 5–15 min after ingestion of a meal, plasma concentrations of GLP-1 start to rise and peak levels are typically reached after 45–60 min (Figure 32.3). Fat, carbohydrates, and protein all stimulate GLP-1 secretion. The interaction of nutrients with luminal microvilli of the L cell apical parts results in secretion of GLP-1 from the baso-lateral parts into the intestinal bloodstream. In this process, associations between glucose absorption and metabolism within the L cell and GLP-1 secretion has been observed. Furthermore, L cells express several G protein-coupled

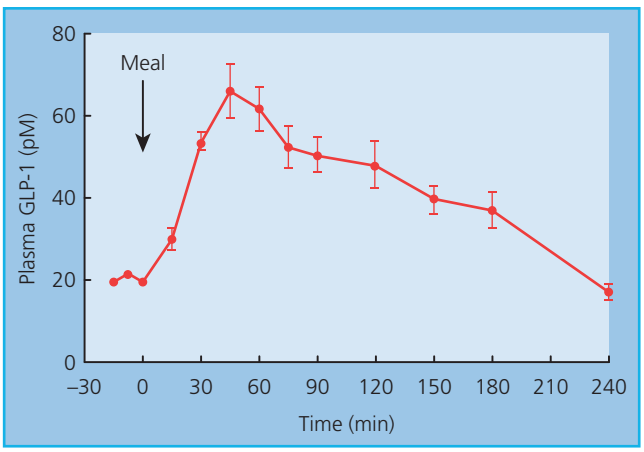

Figure 32.3 Mean postprandial plasma concentrations (± standard error of the mean) of glucagon-like peptide-1 (GLP-1) in healthy individuals. Source: Unpublished data, Filip K. Knop.

receptors, which can be activated by short- and long-chain fatty acids, bile acids, and possibly other factors that thereby stimulate GLP-1 secretion. In addition, paracrine (e.g. via somatostatin and GIP) and neurohormonal mechanisms (via vagus and sympathetic neural activation) have been suggested to contribute to postprandial GLP-1 secretion.

After secretion, GLP-1 is degraded by the enzyme DPP-4. This enzyme is widely expressed and is highly active in the liver, the intestinal and renal brush border membranes, and the lungs. It is also found on capillary surfaces and in a soluble form in plasma. DPP-4 cleaves off the two N-terminal amino acids of peptides with a penultimate proline or alanine residue, and for GLP-1 this abolishes its insulinotropic activity completely. Thus, after secretion of GLP-1, the active hormone is rapidly degraded to an inactive metabolite in the circulation, resulting in a clearance, which exceeds cardiac output, and an apparent half-life of 1–1.5 min. The truncated metabolite is eliminated more slowly through the kidneys and endogenous protease activity, with a half-life of 4–5 min.

GLP-1 receptor distribution and physiological effects of GLP-1

The GLP-1R is found within the pancreas, lung, adipose tissue, kidney, heart, vascular smooth muscle, the peripheral nervous system, and a number of specific nuclei in the CNS [24]. The exact effect of receptor activation in a number of these tissues remains to be established, and here emphasis will be put on receptor activation that relates to the clinical effects observed with GLP-1RA treatment. These include glucose-dependent insulin secretion, inhibition of glucagon secretion, delayed gastric emptying, and decreased appetite/increased satiety. Other potential beneficial effects on the cardiovascular system and CNS, for example, have been suggested from mainly *in vitro* or animal studies, and the translation to human (patho)physiology and their potential as pharmacological targets are currently being investigated.

Effects on pancreatic insulin and glucagon secretion

Specific receptors for GLP-1 are found in the pancreatic β-cell plasma membrane. The receptor belongs to the glucagon subfamily of G protein-coupled receptors. Following binding and subsequent activation of the receptor, several intracellular pathways are initiated [24], which ultimately results in intracellular accumulation of cyclic adenosine monophosphate, closure of ATP-sensitive K^+ channels, elevation of cytosolic Ca^{2+} concentrations, and mobilization and exocytosis of insulin-containing granules. Importantly, GLP-1R activation in β cells leads only to insulin secretion when glucose concentrations are elevated above 4–5 mmol/L [25]. Thus, GLP-1 can be perceived to act as a β-cell sensitizer potentiating glucose-induced insulin secretion. In addition to its glucose-dependent insulinotropic effect, GLP-1 enhances all steps of insulin biosynthesis and also insulin gene transcription. Furthermore, GLP-1 has been shown to be involved in β-cell growth and differentiation and may protect β cells from apoptosis [24]. However, the role of these cell cycle regulatory mechanisms in relation to human physiology and pathophysiology, and also GLP-1RA treatment, remains to be established.

In pancreatic α cells, GLP-1 exerts glucagon suppressive effects. As for its insulinotropic effect in β cells, this glucagonostatic effect is glucose dependent and is likewise only active when plasma glucose levels are elevated above 4–5 mmol/L. The mechanisms by which GLP-1 reduces α-cell secretion of glucagon remain incompletely understood. Thus, it is controversial whether GLP-1-induced glucagon suppression is mediated via GLP-1Rs on pancreatic α cells (which have been shown to exist in small amounts in some studies whereas other studies have failed to detect them) or whether indirect mechanisms (e.g. via glucagon-suppressive effects of β-cell secretory products and/or somatostatin from pancreatic δ cells) are at play.

Effects on the gastrointestinal tract

GLP-1 reduces gastrointestinal motility and intermittent GLP-1R activation has a pronounced effect on gastric emptying of both liquid and solid meals [26]. This phenomenon has been referred to as the "ileal brake" (i.e. GLP-1 secreted from enteroendocrine cells in the distal small intestine slows further delivery of nutrients to the small intestines from the stomach) [27]. GLP-1-induced deceleration of gastric emptying translates into dramatically reduced postprandial plasma glucose excursions [28]. Of note, prolonged GLP-1R activation leads to tachyphylaxis of this effect [29], which most likely explains the sustained effect of short-acting GLP-1RA on postprandial blood glucose excursions and the lesser effects seen with long-acting GLP-1RA (see below) [30].

Effects on appetite and food intake

GLP-1Rs are found in both the peripheral nervous system and in the CNS with GLP-1R positive neurons in hypothalamus and the brain stem. Activation of GLP-1Rs in the brain is believed to be responsible for the reduced appetite and food intake observed after administration of GLP-1. The pathways controlling modulation of food intake by GLP-1 may, nevertheless, involve GLP-1R activation in neurons of both the peripheral nervous system and the CNS [24]. Importantly, infusion of GLP-1 in lean and obese individuals with and without diabetes causes dose-dependent reductions in satiety measures and *ad libitum* food intake. Furthermore, studies using the specific GLP-1R antagonist exendin 9-39 suggest that GLP-1R activation is important for these effects. On the other hand, GLP-1R knockout mice are not obese [31], indicating that GLP-1R activation is not a prerequisite for body weight regulation. Nevertheless, there seems little doubt that GLP-1R activation and its related effects on appetite and food intake constitute an important part of the body weight-lowering effect of pharmaceutical GLP-1RAs.

Other effects

In line with the widespread distribution of the GLP-1R, it has been suggested that GLP-1 exerts multiple effects in addition to those mentioned above. A few of these, with potential clinical relevance, are highlighted below.

The effects of GLP-1 on the heart in animal models have attracted much attention. Mice lacking the GLP-1R exhibit impaired left ventricular contractility and diastolic function, and also impaired responses to exogenous epinephrine [32]. Furthermore, some studies have indicated that GLP-1 protects the ischemic and reperfused myocardium in rats [33], improves the ejection fraction in people treated with angioplasty after acute myocardial infarction [34], and improves left ventricular function and systemic hemodynamics in dogs with induced dilated cardiomyopathy [35]. In addition, GLP-1 has been found to reduce the postprandial rise in triglycerides and lower the concentration of free fatty acids in healthy people [36], and improve endothelial dysfunction in individuals with type 2 diabetes and coronary heart disease [37]. These promising findings from preclinical and small-scale clinical studies and the effect of GLP-1RAs on cardiovascular endpoints in larger clinical studies, including a recent cardiovascular outcome study [38] have convincingly demonstrated cardiovascular benefits. Furthermore, the small, but significant, increase in heart rate during treatment with GLP-1RAs, most likely mediated by GLP-1Rs in the sinoatrial node ([39]; see below), did not appear to confer any cardiovascular safety risk.

GLP-1 increases natriuresis through inhibition of the Na^+/H^+ exchanger in the proximal tubules. This may in part explain why GLP-1RAs have subtle antihypertensive effects [39, 40]. Although preclinical studies suggest that atrial natriuretic peptide or the renin–angiotensin system may be involved in GLP-1's natriuretic and proposed diuretic effects [41], in human studies this does not seem to be the case. Likewise, results from rodent studies suggesting renoprotection of GLP-1 (beyond what can be expected from GLP-1-induced metabolic improvements) in models of diabetic nephropathy and acute kidney injury have not yet been confirmed in human studies.

Finally, GLP-1 has been associated with improved learning in rats and has also displayed neuroprotective effects but, again, human studies have so far not been able to establish GLP-1 as a neuroprotective hormone or provided convincing evidence for significant effects of GLP-1R agonism on neurodegenerative diseases [42].

As alluded to above, most of what is known about GLP-1's pleiotropic physiological effects stems from studies in pancreatic islet function particularly β-cell function. It is well acknowledged that GLP-1-induced insulinotropic and glucagonostatic effects represent the main mediators of the normalization of fasting plasma glucose and diurnal plasma glucose excursions and also improved glycemic control observed in studies utilizing native GLP-1 in people with type 2 diabetes [43–46]. Such studies have been of great importance to the development of GLP-1RAs.

GLP-1 receptor agonists for the treatment of diabetes

In 2005, the GLP-1RAs were introduced into clinical practice, and since 2009 they have been part of the joint position statements on treatment of type 2 diabetes by the European Association for the Study of Diabetes (EASD) and the American Diabetes Association (ADA) [1, 2]. The GLP-1RAs are based on the pleiotropic effects

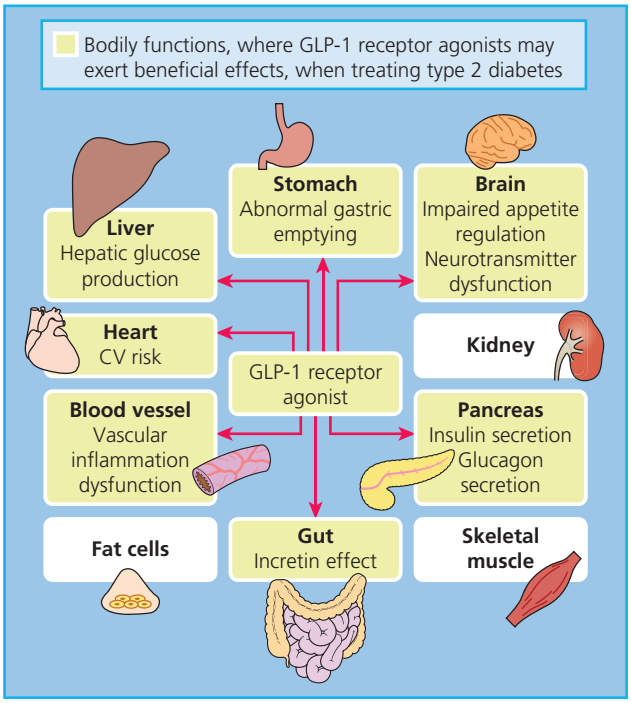

Figure 32.4 GLP-1 receptor agonists act at multiple sites to affect glycemia, weight, and comorbidities of type 2 diabetes.

of the native gut hormone GLP-1, target a broad spectrum of the multifaceted pathophysiology of type 2 diabetes, and improve glucose homeostasis (Figure 32.4) with low risk of hypoglycemia combined with a body weight loss [47]. Furthermore, they exert beneficial effects by reducing cardiovascular events. The introduction of the GLP-1RAs has generated substantial clinical interest and an increasing number of prescriptions have been handed out by clinicians worldwide (Figure 32.5).

As several GLP-1RAs are emerging, it has become apparent that there are clinically relevant differences between them, making the therapeutic field challenging to navigate. Currently, a total of six GLP-1RAs are approved for treating people with type 2 diabetes (Figure 32.6). The major challenge in developing a GLP-1RA is that native GLP-1 is very rapidly degraded by the enzyme DPP-4, resulting in a short half-life (1–1.5 minutes) [48]. To overcome this, GLP-1RAs resistant to degradation by DPP-4 have been developed using two different strategies.

The first strategy is based on the naturally occurring polypeptide exendin-4, which was originally isolated from the saliva of the lizard *Heloderma suspectum*. Exendin-4 is DPP-4 resistant and activates the GLP-1R with equal efficacy as native GLP-1. The other strategy is based on the structure of native GLP-1, with a few amino acid alterations that protect the molecule from being degraded by DPP-4. The main difference between the GLP-1RAs resides in the pharmacokinetic profiles that largely divide them into short-acting and long-acting GLP-1RAs (Figure 32.7). The short-acting GLP-1RAs are readily absorbed after subcutaneous injection and are resistant to degradation by DPP-4, but are still subject to renal elimination, which confers a plasma half-life of

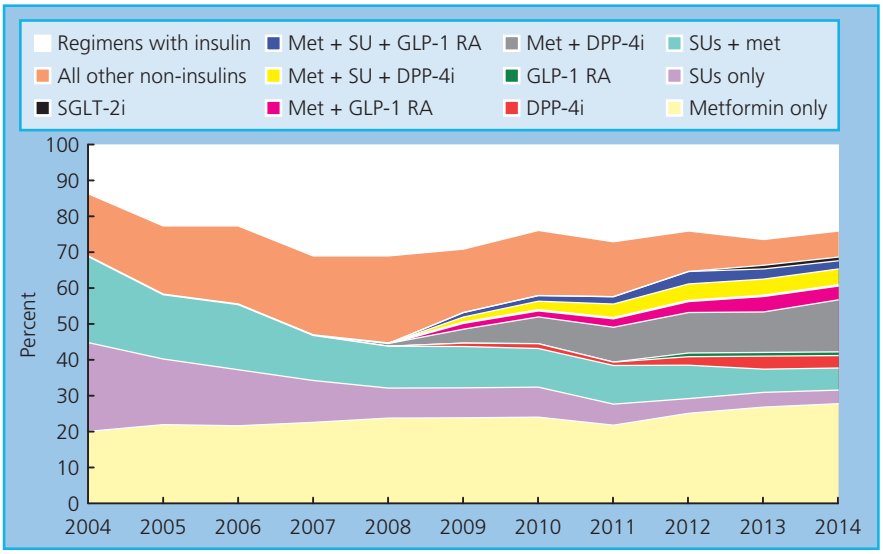

Figure 32.5 Trends of glucose-lowering drugs prescribed by specialists in Europe from 2004 until 2014. SU, sulfonylurea; MET, metformin; DPP-4i, dipeptidyl peptidase 4 inhibitors; GLP-1RA, glucagon-like peptide-1 receptor agonists; SGLT2-i, sodium glucose cotransporter 2 inhibitors.

~2–4 h for these agents [49, 50]. They are administered twice daily (exenatide) or once daily (lixisenatide), which results in relatively large fluctuations in plasma concentrations during the day, and intermittent activation of GLP-1Rs. With regard to the continuous-acting peptides, different modifications have been applied in order to obtain an even longer duration without changing the receptor activation capability. These modifications include (1) incorporation of the GLP-RA in injectable

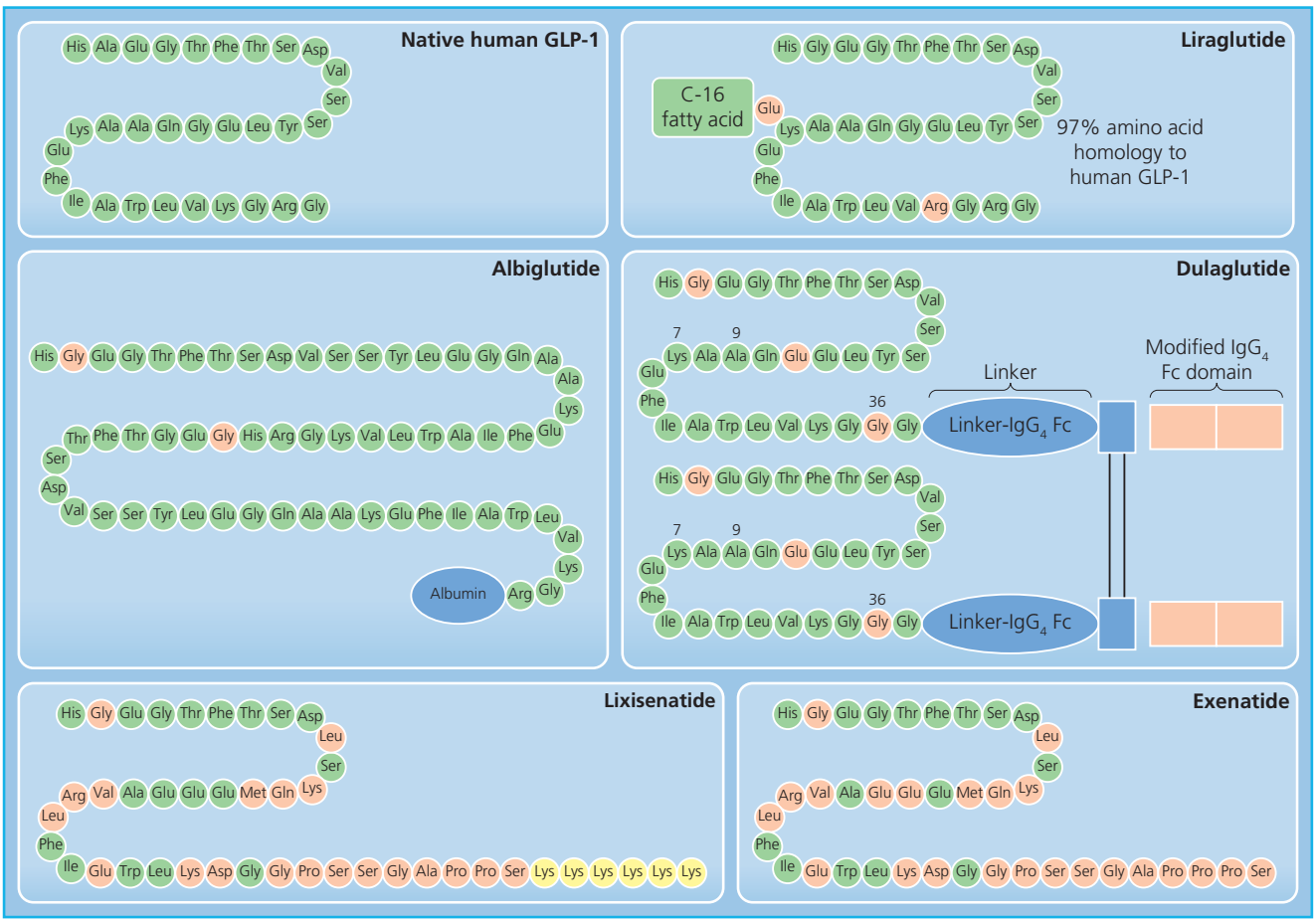

Figure 32.6 Structure comparisons of approved GLP-1 receptor agonists.

Increasing half-life

Category	Agent	Half-life
Short-acting < 24 hours	Exenatide, twice-daily Byetta®	2.4 hours
	Lixisenatide, once-daily Lyxymia®	3 hours
Long-acting ≥ 24 hours	Liraglutide, once-daily Victoza®	13 hours
	Dulaglutide, once-weekly Trulicity®	~4 days
	Albiglutide, once-weekly Tanzeum/Eperzan®	5–8 days
	Exenatide, once-weekly Bydureon®	14 days

Figure 32.7 Glucagon-like peptide-1 receptor agonists pharmacokinetic properties: short- versus long-acting.

microspheres (exenatide once weekly), (2) attachment of a fatty acid side-chain, which allows reversible binding to albumin (liraglutide), and (3) fusion with the Fc fragment of immunoglobulin G (dulaglutide) or larger carrier molecules such as albumin (albiglutide) (Figure 32.6). The longer half-lives of these compounds allows administration with longer intervals while at the same time reducing fluctuations of plasma peptide levels, resulting in continuous activation of the GLP-1Rs. Lastly, the compounds can be subdivided based on their size, as some of the chemical modifications alter the size of the active molecules dramatically. The differences in structure, pharmacokinetics, and size of the GLP-1R agonists are important, as the efficacy and tolerability seem dependent on these differences.

Clinical efficacy and side effects of available GLP-1RA

Short-acting GLP-1RA

Exenatide twice daily

Exenatide, the first available GLP-1RA, was introduced to the market in the United States in 2005 and in Europe in 2007 (Byetta). Exenatide is a synthetic version of exendin-4, which shares only 53% amino acid sequence homology with human GLP-1 (Figure 32.6) [51]. Exenatide is primarily cleared in the kidneys by glomerular filtration [49], and the half-life after subcutaneous (s.c.) injection is ~2.4 h with detectable plasma concentrations up to 10 h after injection [52]. Because of its pharmacokinetics in renal impairment, exenatide should not be used for people with a creatinine clearance of 30 mL/min or less. Exenatide is recommended for twice-daily administration starting at 5 μg twice daily, which may be increased to 10 μg twice daily after one month if well tolerated by the patient. In order to obtain the maximum effect, exenatide should be injected within 60 min before the two main meals. The clinical effects of exenatide twice daily were investigated in the AC2993 Diabetes Management for Improving Glucose Outcome (AMIGO) trials [51, 53, 54]. These trials showed significant reductions in glycated hemoglobin (HbA_{1c}) of ~1.0–1.2% compared with placebo, and a modest reduction in fasting plasma glucose of ~1.0–1.4 mmol/L compared with placebo. Interestingly, the postprandial plasma glucose excursions were blunted in the exenatide-treated participants compared with the placebo group, presumably driven primarily by a substantial deceleration in gastric emptying. Importantly, the effect on postprandial plasma glucose was only evident during meals with concomitant drug administration, i.e. not during lunch where no drug was administered [55]. The effect on gastric emptying and postprandial plasma glucose excursions of exenatide twice daily has been shown to be sustained over a 30-week treatment period [54]. The average weight loss amounted to 1.6 kg in the exenatide-treated groups. In obese people with type 2 diabetes treated with insulin plus oral antidiabetes drugs, addition of exenatide generally caused body weight loss of more than 5 kg, improved glycemic control over 26 weeks, and decreased total daily doses of insulin [56]. Significant reductions in systolic blood pressure compared with placebo (a difference of 2.8 mmHg) have been reported after 6 months of treatment with exenatide [57]. There were no counter-regulatory increases in heart rate likely because of the short half-life of exenatide [58]. The main side effects of exenatide are mild to moderate nausea, diarrhea, and vomiting [59]. The risk of hypoglycemia is low with exenatide in monotherapy and as add-on to metformin because of the glucose-dependent insulinotropic and glucagonostatic effects. In most exenatide trials, when combined with a sulfonylurea the incidence of minor hypoglycemic events increased compared with placebo (14–36%). No cardiovascular outcome trial with twice-weekly exenatide has been reported or is ongoing, perhaps owing to its introduction to the market before this was mandatory.

Lixisenatide once daily

Lixisenatide was approved for the treatment of type 2 diabetes in Europe in 2013 (Lyxumia) and in the USA in July 2016 (Adlyxin) [60]. As with exenatide, lixisenatide is based on exendin-4, but with a deletion of a proline and an addition of six lysine amino acids at the C-terminus [61] (Figure 32.6). These alterations result in a half-life of 2–3 h after s.c. injection, which would normally favor a twice-daily dosing treatment-regimen (Figure 32.7). However, clinical trials have demonstrated efficacy and tolerability with a once-daily dose of 20 μg [50, 62] as evaluated in the clinical trial program GetGoal [62–65]. These trials showed that lixisenatide significantly lowered mean HbA_{1c} levels by 0.5–0.9% (mean baseline of 8.0%) and resulted in moderate reductions of fasting plasma glucose (0.8–1.2 mmol/L) compared with placebo. Lixisenatide showed pronounced effects on postprandial plasma glucose with a 75% (~5 mmol/L) reduction in postprandial plasma glucose excursions during a standardized meal test compared with placebo, but only when the drug was administered immediately before food ingestion [59]. As with exenatide, this marked effect on one meal is presumably driven by the prominent effect of lixisenatide to decelerate gastric emptying, an effect shown to be substantial and sustained also after 4 weeks of treatment [66]. A dose-dependent decrease in body weight ranging from 0 to 3 kg with the 20 μg once-daily dosing, in some

studies not superior to placebo [67], was observed with lixisenatide [68]. The most common side effects of lixisenatide treatment are of gastrointestinal origin (nausea and diarrhea), consistent with other GLP-1RA [60]. A head-to-head trial of lixisenatide versus exenatide twice daily reported non-inferiority of lixisenatide with regard to HbA_{1c} reduction and slightly better tolerability with nausea (25 vs. 35%), diarrhea (10 vs. 13%), and vomiting (10 vs. 13%), and fewer episodes of symptomatic hypoglycemia (3 vs. 8%) with lixisenatide treatment. However, lixisenatide treatment was inferior with regard to weight loss (3 vs. 4 kg, respectively) [64].

The ELIXA (Evaluation of Cardiovascular Outcomes in Patients With Type 2 Diabetes After Acute Coronary Syndrome During Treatment With Lixisenatide) was the first event-driven cardiovascular outcomes study to provide data for a GLP-1RA [69]. The trial was designed to evaluate cardiovascular risk, comparing lixisenatide with placebo in a high-risk population of adults with type 2 diabetes. A total of 6068 individuals with type 2 diabetes and recent spontaneous acute coronary syndrome event participated in the trial. The composite primary endpoint, which was evaluated for non-inferiority and superiority, comprised cardiovascular death, non-fatal myocardial infarction, non-fatal stroke, and hospitalization for unstable angina [69]. The trial demonstrated that lixisenatide did not affect the incidence of cardiovascular events compared with placebo.

Continuous-acting GLP-1RA

Exenatide once weekly

Exenatide was developed as an extended-release formulation approved in Europe in 2011 and in the USA in the beginning of 2012 (Bydureon). Exenatide once weekly contains exendin-4 (i.e. the same active substance as exenatide twice daily) encased in microspheres made of biodegradable polymer poly(D,L-lactide-*co*-glycolide) (Figure 32.6) [70]. The peptide has a sustained release from the microspheres in three phases: initial release (first 48 h), diffusion (~2 weeks), and erosion release (~7 weeks) [71]. The pharmacokinetic profile depends almost solely on the absorption, and over time the biologically active exenatide given as a weekly injection is derived from multiple previous injections undergoing different phases of microsphere dissolution (Figure 32.7). When administered once weekly (2 mg per dose), the mean plasma concentrations of exenatide reach therapeutic levels after ~2–4 weeks, and steady-state levels are obtained once microsphere dissolution begins after ~6–7 weeks [70, 72]. Plasma levels of exenatide gradually decrease over 3 months once treatment is discontinued [72]. The exenatide-filled microspheres require suspension in an aqueous diluent immediately before injection. Recently, a new dual-chamber pen was developed for administration of exenatide once weekly, aiming to simplify microsphere reconstitution, increase usability, and reduce user errors [73, 74]. The extended-release formulation of exenatide once weekly was examined in the clinical trial program DURATION (Diabetes therapy Utilization: Researching changes in HbA_{1c} weight And other factors Through Intervention with exenatide ONce weekly) [75–80]. In these trials, once-weekly exenatide was compared with the twice-daily formulation of exenatide in two head-to-head studies [77, 79] and it was demonstrated that once-weekly exenatide was superior to twice-daily exenatide (HbA_{1c} reductions, 1.6 vs. 0.9% and 1.9 vs. 1.5%; fasting plasma glucose reductions, 1.9 vs. 0.7 mmol/L and 2.3 vs. 1.4 mmol/L). Although both therapies reduced postprandial plasma glucose excursions, the absolute reduction in postprandial plasma glucose excursions was greatest with the twice-daily compound, driven by a greater effect during the morning and evening meals (related to the twice-daily administrations of exenatide) [79]. The lesser effect on gastric emptying and postprandial plasma glucose excursions of the continuous-acting compound is not explained by differences in plasma exenatide concentrations [79, 80]. Similar reductions in body weight were apparent with both formulations of exenatide, which were generally well tolerated. The most frequent adverse event, nausea, was less common with the once-weekly than the twice-daily compound (14 vs. 35%) [78]. Exenatide once weekly was also compared in a head-to-head trial with the continuous-acting compound liraglutide [78], with greater reductions in HbA_{1c} (1.5 vs. 1.3%) and a greater weight loss (3.9 vs. 2.7 kg) in the liraglutide-treated group compared with the once-weekly exenatide-treated group, but once-weekly exenatide was better tolerated than liraglutide (nausea 9 vs. 21%; diarrhea 6 vs. 13%; vomiting 4 vs. 11%, respectively) [78].

In June 2010, the first participant out of around 14,000 was recruited in to the EXSCEL study (EXenatide Study of Cardiovascular Event Lowering). The trial is ongoing and data are expected to be presented in 2018 [81]. The study will compare the impact of adding exenatide once weekly to usual care versus usual care without exenatide with respect to major cardiovascular outcomes (as measured by a primary composite endpoint of cardiovascular-related death, non-fatal myocardial infarction, or non-fatal stroke).

Liraglutide once daily

Liraglutide was approved for clinical use in Europe in 2009 and in the USA in 2010 (Victoza). The structure of liraglutide is based on native GLP-1 with an Arg34Lys substitution and an addition of a 16-carbon fatty acid side-chain at Lys26, leaving liraglutide with a 97% homology with native GLP-1 [82] (Figure 32.6). The fatty acid side-chain enables the compound to be bound non-covalently to albumin and ensures that only 1–2% of liraglutide is circulating as free peptide in plasma after s.c. injection [83]. As a result, the half-life of liraglutide is ~11–15 h and a once-daily dosing ensures continuous activation of GLP-1Rs (Figure 32.7). Liraglutide is administered as an injection of 0.6 mg/day as the starting dose for 1 week and thereafter titrated to 1.2 mg/day. If it is well tolerated and further effect is needed, the dose can be further uptitrated to 1.8 mg/ day. The effects of liraglutide have been investigated in the clinical trial program LEAD (Liraglutide Effect and Action in Diabetes) [84–90]. Liraglutide significantly lowered HbA_{1c} by 0.8–1.5%, fasting plasma glucose by up to 2.6 mmol/L, and induced a weight loss in the range 2–3 kg compared with

the placebo-treated group. Liraglutide also reduced postprandial plasma glucose excursions by ~1.7–2.5 mmol/L compared with placebo; this effect was, however, primarily mediated by a decrease in preprandial (e.g. fasting) glucose values, which is consistent with the observation that liraglutide has small to moderate effects on gastric emptying [90]. The LEAD studies reported significant reductions in systolic blood pressure of up to 6 mmHg, but also a small increase in heart rate of 2–4 beats per minute (bpm) in the liraglutide-treated group [58, 88, 90]. The most frequently reported adverse events were gastrointestinal (nausea; mild and less persistent compared with treatment with exenatide twice daily) [91]. Rates of minor hypoglycemia (plasma glucose <3.1 mmol/L) ranged from 8% with liraglutide monotherapy to 24% in combination with a sulfonylurea [92]. Liraglutide has been compared in head-to-head trials with the two short-acting GLP-1RAs exenatide twice daily and lixisenatide [91, 93]. Compared with exenatide twice daily, significantly greater reductions of HbA_{1c} levels with liraglutide were observed (0.8 vs. 1.1%), and also greater reductions in fasting plasma glucose (0.6 vs. 1.6 mmol/L). Postprandial plasma glucose control was better with exenatide twice daily than with liraglutide after breakfast and dinner (estimated treatment difference of 1.3 and 1.9 mmol/L, respectively), with insignificant differences after lunch [91]. Body weight reductions were equal between the two groups (3.2 kg with liraglutide vs. 2.9 kg with exenatide) [91]. In a head-to-head trial, in which liraglutide was compared with lixisenatide, lixisenatide reduced postprandial plasma glucose excursions to a greater extent after breakfast than liraglutide, but HbA_{1c} reductions (0.5 vs. 0.3%) and fasting plasma glucose reductions (1.3 vs. 0.3 mmol/L) were significantly greater with liraglutide [93]. A significant reduction in systolic blood pressure was apparent in both groups, whereas heart rate decreased with lixisenatide, but increased with liraglutide (–3.6 vs. 5.3 bpm). Body weight reductions were apparent in both groups, but significantly greater in the participants treated with liraglutide (2.4 vs. 1.6 kg). Liraglutide has also been compared in head-to-head trials with two continuous-acting GLP-1RAs. Both trials demonstrated superiority for liraglutide compared with once-weekly dulaglutide (body weight [94]) and once-weekly albiglutide (glycemic control and body weight [95]).

The LEADER (Liraglutide Effect and Action in Diabetes: Evaluation of Cardiovascular Outcome Results–A Long Term Evaluation) trial was initiated in 2010 [96, 97] and the results were presented in June 2016 [38]. The trial was designed to examine the cardiovascular effect of treatment with liraglutide compared to placebo in a population of adults with type 2 diabetes and high cardiovascular risk. In this double-blind trial, the participants were randomized to receive liraglutide (titrated to 1.8 mg once daily) or placebo. The primary composite outcome was the first occurrence of death from cardiovascular cause, non-fatal myocardial infarction, or non-fatal stroke. 9,340 people underwent randomization and the median follow-up was 3.8 years. The primary outcome occurred in significantly fewer participants in the liraglutide group (608 of 4,668 [13.0%]) than in the placebo group (694 of 4,672 [14.9%]) (hazard ratio, 0.87; 95% CI, 0.78 to 0.97; P<0.001). Furthermore, fewer people died from cardiovascular causes in the liraglutide group than in the placebo group, and all-cause mortality was lower in the liraglutide group. The rates of nonfatal myocardial infarction, nonfatal stroke, and hospitalization for heart failure were non-significantly lower in the liraglutide group than in the placebo group. 66 participants would need to be treated with liraglutide for 3 years to prevent one event included in the primary outcome and 98 would need to be treated to prevent a death from any cause.

Dulaglutide once weekly

Dulaglutide (Trulicity) was approved in 2014 by the FDA and 2015 by EMA. It consists of two GLP-1 moieties covalently linked to a human immunoglobulin G (IgG) 4-Fc heavy chain, which acts as an inert plasma carrier (Figure 32.6). The combination of dulaglutide's large size, which limits renal clearance, and three amino acid substitutions (compared with native human GLP-1), which promote DPP-4 resistance, substantially prolongs biological activity [98]. As a result, the half-life of dulaglutide is ~90 h, and a once-weekly dosing ensures continued exposure of the GLP-1Rs (Figure 32.7). The recommended starting dose of Dulaglutide is 0.75 mg, which can be increased to 1.5 mg dose for additional glycemic control. A phase II study examining the efficacy and safety of dulaglutide in doses ranging from 0.5 to 2.0 mg reported significant reductions in HbA_{1c} ranging from 1.3 to 1.5% compared with a reduction of 0.3% in the placebo group [99]. Dulaglutide, used as a 1.5-mg once-weekly dose, has been examined in the clinical trial program AWARD (Assessment of Weekly AdministRation of LY2189265 in Diabetes), and has also been compared head-to-head with exenatide twice daily and liraglutide. Clinical trials showed dose-dependent reductions of HbA_{1c} of up to 1.6%, reductions in fasting plasma glucose of up to 2.7 mmol/L, and weight reductions of up to 3.2 kg. Safety data indicate a low incidence of hypoglycemia and the most frequently reported adverse events were gastrointestinal, primarily nausea, which seemed to reduce over time. AWARD-4 was a randomized, open-label, 52-week comparison of the effects of dulaglutide and insulin glargine, both in combination with insulin lispro, in 884 people with type 2 diabetes. The dulaglutide 1.5-mg dose in combination with insulin lispro showed a statistically superior reduction in HbA_{1c} from baseline compared with insulin glargine in combination with insulin lispro at 26 weeks [100]. AWARD-6 was a randomized, open-label, 52-week, parallel-arm study comparing the effects of dulaglutide with those of once-daily liraglutide in 599 people with type 2 diabetes on concomitant metformin. Dulaglutide 1.5 mg showed non-inferiority to liraglutide 1.8 mg for HbA_{1c} reduction after 26 weeks, but a greater weight loss was seen in the liraglutide-treated group (3.9 kg) compared with the once-weekly dulaglutide-treated group (2.7 kg) [94]. The most common adverse events were nausea (10–15%) and diarrhea (9%). As for the other continuous-acting GLP-1RA, a sustained increase in heart rate by up to 5 bpm was seen in the dulaglutide-treated participants included in the AWARD program. The REWIND (Researching Cardiovascular Events With a Weekly Incretin in

Diabetes) trial (to be completed in 2019) is set to assess the effect of 1.5 mg dulaglutide on cardiovascular outcomes when added to existing glucose-lowering regimens [101]. The primary objective is to test whether dulaglutide (compared with placebo) can reduce the occurrence of death from cardiovascular causes, non-fatal myocardial infarction, or non-fatal stroke in people with type 2 diabetes.

Albiglutide once weekly

Albiglutide is a once-weekly GLP-1RA for s.c. administration approved in 2014 in both the USA (Tanzeum) and Europe (Eperzan). Albiglutide (previously named albugon) is generated in the yeast species *Saccaromyces cerevisiae* by recombinant DNA technology and the resulting therapeutic fusion protein consists of two sequential copies of modified human GLP-1 linked to human albumin, which owing to molecular size limits the renal elimination (Figure 32.6) [102]. Peak plasma levels of albiglutide are achieved 2–5 days after s.c. injection, and the half-life is ~5–8 days, making it suitable for once-weekly dosing [103] (Figure 32.7). The recommended weekly dose is 30 mg, with the possibility of up-titration to 50 mg based on individual glycemic response. A clinical phase II study showed that treatment with albiglutide (30 mg once weekly) reduced HbA_{1c} and fasting plasma glucose levels significantly greater than treatment with twice-daily exenatide (HbA_{1c} reductions of 0.9 vs. 0.5% and fasting plasma glucose reductions of 1.4 vs. 0.8 mmol/L, respectively) [104]. However, the weight loss (1.4 kg) was significantly less with albiglutide than with twice-daily exenatide (2.4 kg). Albiglutide has been examined in the clinical-trial program HARMONY, including a head-to-head comparison with liraglutide [95]. This study reported superiority of liraglutide compared with albiglutide with respect to HbA_{1c} reductions (1.0 vs. 0.8 mmol/L), fasting plasma glucose reductions (1.7 vs. 1.2 mmol/L), and body weight loss (2.2 vs. 0.6 kg). Albiglutide was, however, better tolerated than liraglutide with fewer gastrointestinal side effects (nausea, 10 vs. 29%; vomiting, 5 vs. 9%) and a lower incidence of mild hypoglycemia (16 vs. 21%). Local skin reactions at the injection site were more common in the group treated with albiglutide (13 vs. 5%). A study to determine the effect of albiglutide, when added to standard blood glucose-lowering therapies, on major cardiovascular events in individuals with type 2 diabetes (HARMONY Outcomes) was initiated in July 2014; 9400 participants will be enrolled, and data are expected in 2019 [105].

Safety issues

The safety of GLP-1RAs has been extensively studied in preclinical studies and large clinical trial programs. The most common adverse events observed in clinical trials with GLP-1RAs involve the gastrointestinal system, mainly nausea, vomiting, and diarrhea, and these events diminish over time. Differences exist in the reported occurrence of these gastrointestinal effects between each GLP-1RA (as described above). Other identified potential safety issues include hypoglycemia, pancreatic adverse events, thyroid neoplasms, immunogenicity issues, and interactions with other medicinal products [52, 71, 83, 106–108].

Hypoglycemia

In monotherapy or combination with other antidiabetes agents that have a low risk of hypoglycemia, e.g. metformin and pioglitazone, the GLP-1RAs causes minor hypoglycemia in 1–7% of treated individuals (with almost no severe hypoglycemia events) depending on the study population and GLP-1RA [52, 71, 83, 107, 108]. In trials in which the GLP-1RAs were combined with a hypoglycemia-prone antidiabetes agent, e.g. a sulfonylurea or insulin, the incidence of minor hypoglycemia was, as expected, significantly higher (up to one-third of participants), again depending on trial duration, glycemic control, and study population and also the dose of insulin and/or sulfonylurea.

Pancreatic adverse events

Acute pancreatitis is listed as an adverse event for all GLP-1RAs [52, 71, 83, 107, 108]. Since the introduction of GLP-1-based therapy, pancreatic adverse effects, in particular pancreatitis and pancreatic cancer, have been a major concern. So far there are no data to suggest differences in adverse pancreatic effects between the GLP-1RAs (e.g. between short- and continuous-acting agents [109]). Reports of acute pancreatitis and pancreatic cancer were reported extremely rarely in the clinical trials with the GLP-1RAs [110]. However, there have been numerous postmarketing reports of pancreatitis and pancreatic cancer associated with the GLP-1-based therapy. The causality in these mainly spontaneous reports is difficult to interpret, as persons with type 2 diabetes generally have an up to three times higher risk of pancreatitis than those without diabetes [111]. According to an analysis of the FDA adverse event reporting database conducted by Elashoff et al. [112], pancreatitis was reported as an adverse event more than six times as frequently for people administered exenatide compared with other (non-GLP-1-based) therapies for diabetes. Based on these uncertainties, the regulatory agencies in Europe (EMA) and the USA (FDA) in 2013–2014 undertook an extensive appraisal of the existing preclinical and clinical safety data together with the observational evidence. The conclusion was that data were inconsistent with a causal association between GLP-1R activation and pancreatic adverse effects, but owing to the uncertainty of the estimates, a causal role could not be completely excluded [106]. At present, it remains uncertain whether the frequent reporting is the product of reporting bias or represents a slightly increased risk of pancreatitis with the treatment. Data from ELIXA trial and the LEADER trial after 25 months and 3.8 years of exposure to lixisenatide and liraglutide, respectively, showed that the incidence of pancreatitis was numerically but not statistically significantly lower in the GLP-1RA groups than in the placebo groups [38, 39]. Individuals started on treatment with any of the GLP-1RAs should be informed of the potential risk and characteristic symptoms of acute pancreatitis; and caution is advised when prescribing GLP-1RAs to those with a risk of or a history of pancreatitis [52, 71, 83, 107, 108].

Thyroid adverse events

The preclinical development program of several GLP-1RAs exposed significant increases in thyroid C-cell tumors in rodents

[52, 71, 83, 107, 108]. The fact that these C-cell neoplasms were not detected in monkeys [113] suggests important species differences. Accordingly, in comparison with the situation in rodent thyroid glands, human C cells are much less abundant in human thyroid tissue and, importantly, GLP-1Rs are present in much lower amounts per C cell [113]. Thyroid events were closely monitored (by repeated measurements of calcitonin) in the clinical trial programs and in postmarketing surveillance and cardiovascular outcome trials. Today, no safety signals are pointing towards the risk of thyroid cancers in humans [38, 114].

Immunogenicity issues

The GLP-1RAs are fairly large molecules that raise an immune response in some individuals, evidenced by increasing titers of antibodies directed against epitopes on the GLP-1RA. Generally, the GLP-1RAs that are based on exendin-4 (exenatide and lixisenatide) raise more antibodies, which can be detected in 25–74% of those treated, than the GLP-1RAs based on native human GLP-1 (liraglutide, albiglutide, and dulaglutide) (antibodies detected in 1–9%). There is conflicting evidence on the clinical relevance of these antibodies [67, 94, 115, 116], but particularly high levels (titers) of antibodies, which when measured are present in 1–6% of patients, may limit the clinical effects of at least some of the GLP-1RAs (as is evident with exenatide) [116, 117]. Interestingly, injection-site reactions are more frequent in people who develop antibodies compared with those who did not [71]. However, other excipients in the drug formulation (e.g. the prolonged-release delivery systems in the GLP-1RA for once-weekly administration) are also important factors in the development of injection-site reactions. Thus, exenatide once weekly caused much more injection site pruritus than exenatide twice daily (18 vs. 1%) [79], and injection-site reactions occurred in more people given albiglutide than in those given liraglutide (13 vs. 5%) [95].

Interactions with other medical products

None of the GLP-1RAs interact with the hepatic metabolism of other medicinal products; specific interactions with acetaminophen, digoxin, oral contraceptives, lisinopril, metformin, hydroxymethylglutaryl-coenzyme A (HMG-CoA) reductase inhibitors, and warfarin have been studied in clinical trials [52, 71, 83, 107, 108]. However, all of the GLP-1RAs delay gastric emptying with acute dosing, and therefore have the potential to prolong and increase or decrease the absorption of concomitantly administered oral medicinal products [52, 71, 83, 107, 108]. Importantly, the effect on gastric emptying diminishes with time for the continuous-acting GLP-1RAs owing to fairly rapid tachyphylaxis already evident from the first day of treatment [29, 109]. Therefore, the interaction through delayed gastric emptying is clinically relevant only with the short-acting GLP-1RAs and concomitant administration of medicinal products with a narrow therapeutic–toxic ratio that require careful clinical or biochemical monitoring. The interaction can be alleviated by the administration of the other medicinal product 1 h before or 4 h after the administration of the short-acting GLP-1RAs [52, 60].

Perspectives for the GLP-1RAs

Dulaglutide was the fifth GLP-1RA to reach the market since exenatide twice daily was introduced in 2005. A few other GLP-1RAs are in clinical development. A promising one is semaglutide, which essentially is a further development of liraglutide. Semaglutide is based on native GLP-1 with further modifications in the N-terminus and prolongation of the fatty acid side-chain compared to liraglutide, which increase affinity to albumin and prolong the half-life to ~6–7 days, making it suitable for once-weekly dosing. Interestingly, in late 2016, results were published showing that semaglutide significantly reduces the risk of major adverse cardiovascular events in the SUSTAIN 6 trial, which included approximately 3300 people with type 2 diabetes (ClinicalTrials.gov number, NCT01720446). Semaglutide is also in clinical development as an oral version combined with a small-molecule transporter protein to increase bioavailability [118]. Additionally, several multifunctional peptides that combine GLP-1R agonism with affinity towards other peptide hormone receptors involved in human metabolism (e.g. GIP, cholecystokinin [CCK] and/or glucagon (for a review, see [119]) are also in very early clinical development, which may broaden the scope of the GLP-1RAs.

What will be the future for these drugs? There is already widespread clinical use of GLP-1RAs, in particular liraglutide. The LEADER cardiovascular outcome trial with liraglutide [38] demonstrated the long sought macrovascular benefit that is actually the main incentive for treatment with a second-line antidiabetes agent. The only completed cardiovascular outcome trial in a short-acting GLP-1RA, the ELIXA study investigating lixisenatide [69, 120], showed no beneficial effects on cardiovascular events or mortality, while microvascular endpoints have not been reported. In retrospect, the ELIXA trial, by including only individuals with severe cardiovascular disease and a recent acute coronary event, could be construed as being designed to accrue cardiovascular events rapidly in both groups, but at the cost of limiting the possibility of finding a beneficial effect. Nevertheless, the uniformity of the GLP-1RAs as a drug class is now questioned. Whether other short or long acting GLP-1RAs are able to demonstrate benefits of similar size will be crucial in determining their position in clinical use and the future revisions of treatment guidelines [121]. Solid clinical data exist only for some of the long-acting GLP-1RAs, and these data show clear benefit in terms of reducing mortality and support their clinical use and even prioritization in the clinical guidelines.

Conclusion

The GLP-1RAs target the multifaceted pathophysiology of type 2 diabetes with positive effects on both α- and β-cell dysfunction and provide improvements in fasting plasma glucose, postprandial plasma glucose, and HbA_{1c} with a relatively low risk of hypoglycemia and notably accompanied by a weight loss. There are some clinically relevant differences between the GLP-1RAs. The continuous-acting GLP-1RAs seem to be preferable if a large reduction in HbA_{1c} is the primary therapeutic aim, and when frequent administration and daily timing of injections are

undesirable for the person with diabetes. On the other hand, the short-acting compounds may be preferable if postprandial plasma glucose excursions are the major problem. Additionally, the need for weight reduction and the individual tolerability of the compounds should be considered when choosing between the GLP-1RAs. The differences between the GLP-1RAs enable physicians to choose the compound with the clinical profile that is most likely to benefit the patient. At the moment there is no distinction between the various GLP-1RAs in the position statement from the ADA and the EASD [1, 2]. So far one cardiovascular outcome study (ELIXA) showed non-inferiority to placebo using a short acting GLP-1RA (lixisenatide) compared to placebo. However, two trials (LEADER and SUSTAIN6) using continuous acting GLP-1RA in people with type 2 diabetes at high cardiovascular risk have demonstrated a reduction in cardiovascular events in those treated with the GLP-1RA compared with placebo on a background of standard care. Several other studies are currently underway for the available and emerging GLP-1RAs including head-to-head trials, trials evaluating safety and long-term effects, combinations with insulin preparations, and anti-obesity studies.

Amylin and amylin analogs

Introduction and historical overview

Amylin's precursor, a 67 amino acid polypeptide, is produced in pancreatic β cells and processed by prohormone convertase 2 and prohormone convertase 1/3 to the mature 37 amino acid hormone [122]. Amylin is the major constituent of amyloid deposits in the pancreatic islets of Langerhans in type 2 diabetes. Amyloid deposits were discovered a century ago and described as a pathological feature of people with diabetes and those with insulinomas. In 1987, two research groups, independently of each other, isolated amylin from amyloid deposits and speculated on whether it had important endocrine effects, hence the initial name of amylin: islet amyloid polypeptide (IAPP) [123, 124]. The hormone is stored and secreted together with insulin from the pancreatic β cells [125]. Thus, type 1 diabetes is considered an amylin-deficient state owing to the destruction of β cells. Amylin and insulin exhibit complementary roles in the regulation of plasma glucose [126]. The physiological actions of amylin involve inhibition of appetite and gastric emptying along with suppression of glucagon secretion in relation to meal intake. With the development of amylin analogs, the physiological actions are used to obtain clinically beneficial effects on glycemic control and body weight in the treatment of type 1 and type 2 diabetes.

Amylin physiology

Amylin release, metabolism, and regulation of secretion

Amylin and insulin share the same processing enzymes, are stored together in secretory granules, and are co-released from the pancreatic β cells [127]. The release of amylin is stimulated by ingestion of nutrients and gut-derived incretin hormones (GLP-1 and GIP) and through neural signaling. Thus, under physiological conditions, amylin is acutely released during a meal. Amylin is released together with insulin in a corresponding high-frequency pulsatile pattern, but at a 1:100 ratio. Deviation from this secretion pattern has been observed in morbid conditions such as pancreas cancer, diabetes, and obesity in humans and with pharmacological intervention (e.g. dexamethasone). The underlying mechanisms of the altered amylin secretion pattern and its potential implications are unknown at present [128]. Amylin circulates in equimolar amounts in a biologically active non-glycosylated form and an inactive glycosylated form. In contrast to insulin, which is eliminated primarily in the liver, amylin is eliminated mainly through renal metabolism [125].

The amylin receptor

Amylin is similar in amino acid sequence and structure to other important peptide hormones such as calcitonin, which regulates calcium and phosphorus metabolism, calcitonin gene-related peptide, and adrenomedullin, both of which impart vasodilation. Together they are grouped as the CT peptide family. Amylin acts on a composite receptor comprised of two parts. The "core" part consists of a calcitonin receptor (CR), which is a transmembrane class B G protein-coupled receptor (GPR) [129, 130]. Two splice variants of the CR (a and b) exist, and they are complexed with one of three receptor activity modifying proteins (RAMP1, RAMP2, or RAMP3), creating diverse amylin receptors (AMY1, AMY2, and AMY3) [131]. Amylin appears to bind with high affinity to all of the six different receptors emerging (Table 32.1) [130].

Central effects of amylin on appetite and food intake

Amylin and the gut-derived incretin hormone GLP-1 share many characteristics and have overlapping physiological properties. Both peptide hormones slow nutrient delivery to the small intestine by decelerating gastric emptying, they suppress postprandial glucagon secretion and they reduce appetite, albeit through seemingly different pathways [132]. Dose–response studies performed in rats investigating the influence on gastric emptying exerted

Table 32.1 Amylin stimulates receptors comprised of a class B G protein-coupled receptor (GPR) and a receptor activity-modifying protein (RAMP). The GPR component is a splice variant of the calcitonin receptor, $CT_{(a)}/CT_{(b)}$, complexed with either RAMP1, RAMP2, or RAMP3. The dimerized receptor is referred to as AMY1, AMY2, and AMY3 corresponding to each respective RAMP with either an (a) or (b) in the subscript to define which splice variant of the calcitonin receptor is in the complex.

	CT receptor	
RAMP	$CT_{(a)}$	$CT_{(b)}$
RAMP1	$AMY1_{(a)}$	$AMY1_{(b)}$
RAMP2	$AMY2_{(a)}$	$AMY2_{(b)}$
RAMP3	$AMY3_{(a)}$	$AMY3_{(b)}$

by several different subcutaneously injected gastrointestinal hormones (GLP-1, GIP, cholecystokinin octapeptide [CCK-8], glucagon, and pancreatic peptide) showed that amylin was the most potent inhibitor of these [133]. In contrast, s.c. injection of a selective amylin antagonist in rats revealed an acceleration of gastric emptying [134]. Importantly, it has been demonstrated that the ability of amylin to inhibit gastric emptying is overridden by the occurrence of hypoglycemia [135]. The best characterized anorectic function of amylin is to reduce meal size. A solid argument indicating that amylin is a physiological regulator of meal size is provided by studies showing that peripherally or centrally infused amylin antagonists produce an opposite effect to that of amylin, i.e. an increase in food intake, mainly via a meal size effect. It remains to be clarified whether amylin also has an effect on postprandial satiety [136, 137]. Whereas the feeding inhibitory actions of endogenous GLP-1 seem to be both centrally and peripherally mediated (given that intact vagal afferent signaling from the intestines is required), amylin appears to exert its actions via direct effects on the CNS only [132]. c-Fos expression (a marker of neuronal activity) is induced by amylin in target neurons in different brain regions involved with metabolic control. The area postrema located in the hindbrain is considered to be the primary and most important site of amylin action. This assumption is based on studies of rodents undergoing area postrema ablation, which demonstrated a complete abrogation of amylin's anorexigenic effects [138, 139]. Subsequent to area postrema activation, the amylin signal is conveyed to the forebrain via distinct relay stations and to regions of hypothalamus known to be involved in feeding behavior. Within the lateral hypothalamic area, amylin diminishes the expression of orexigenic neuropeptides such as orexin and MCH (melanin-concentrating hormone) [128, 139, 140]. The area postrema is favorably located as a target of central hormone action owing to the permeable blood–brain barrier in this region [141]. Other brain sites suggested to be important contributors to amylin's anorexic effects include the subfornical organ, nucleus accumbens, and the dorsal raphe of the brainstem [138, 139]. Whether amylin also exerts peripheral actions has been investigated in muscle, liver, and adipose tissue of mice and adipose tissue of humans by Moon et al. [142, 143], and physiological effects were clearly evident with stimulation of distinct signaling pathways after application of amylin. However, no studies have confirmed the presence of amylin receptors in these peripheral tissues [139].

Amylin analogs

In the treatment of diabetes

The discovery of amylin's glucose- and body weight-lowering effects makes it attractive for medical purposes. However, the instability and propensity to self-aggregate made the clinical use of human amylin difficult [125]. The problem was solved by substituting a few amino acids in the human sequence of amylin with proline residues (at positions 25, 28, and 29) [132]. This enhanced the solubility and markedly reduced amyloid fibril formation of the bioactive peptide [144]. The actions and pharmacokinetic and pharmacodynamic properties of a synthetic amylin analog, pramlintide, were found to be very similar to those of native amylin [125]. Numerous clinical trials tested the efficacy and safety of pramlintide ahead of its approval by the FDA in March 2005. Currently, pramlintide, the only available amylin analog, is marketed in the USA as Symlin. The drug is approved for adjunct treatment of type 1 and type 2 diabetes, when optimal glucose control is not achieved with insulin administration alone or combined with other glucose-lowering drugs [145]. Pramlintide is administered parallel to meal-time insulin therapy [144]. The plasma half-life is ~48 min when injected s.c. in the thigh or the abdomen. The drug is primarily eliminated by the kidneys, like native amylin [146]. The most common adverse events related to pramlintide treatment are of gastrointestinal origin, e.g. decreased appetite, vomiting, and stomach pain with mild-to-moderate nausea being most frequent. However, these effects are generally transient and can be minimized by starting with a low dose and slow titration. No direct correlation between gastrointestinal symptoms and the therapy-induced weight loss has been found [147]. Although pramlintide is considered to be well tolerated overall, it is associated with an increased risk of insulin-induced severe hypoglycemia, particularly in people with type 1 diabetes [148]. Another second-generation amylin analog, davalintide, was subsequently developed. Since phase II studies did not demonstrate superiority of davalintide in terms of efficacy, and showed a tolerability profile and body weight-lowering effect similar to pramlintide, the drug was discontinued in development but has been used in clinical studies investigating the effects of amylin [149].

Studies evaluating pramlintide therapy in humans

In the mid-1990s, several clinical studies investigating the acute and short-term effects of pramlintide were performed, e.g. Kolterman investigated pramlintide given prior to a liquid meal (consisting of 350 kcal with 24% protein, 21% fat, and 55% carbohydrate) to individuals with type 1 or type 2 diabetes [150]. Considerable reductions in postprandial glucose excursions and 24-h glucose profile were demonstrated following pramlintide administration in both diabetes groups. These glycemic improvements were observed in acute studies and also with continued dosing for 2–4 weeks and are likely due to decreased gastric emptying and reduced glucagon release. The suppression of gastric emptying in diabetes exerted by amylin is well documented, although the specific mechanisms behind are still unknown [151]. Chapman et al. demonstrated that the acute hypophagic effects of pramlintide do not only apply to people who are obese or diagnosed with diabetes: a single low-dose (30 μg) pramlintide injection in healthy, normal-weight volunteers induced reduction in food intake and meal duration compared with placebo [152].

Several larger long-term trials with pramlintide have also been conducted. Hollander et al. [153] investigated HbA_{1c} and weight control with adjuvant pramlintide therapy in individuals with type 2 diabetes ($n = 656$) with $HbA_{1c} \geq 8\%$ and who were requiring insulin treatment either alone or combined with oral antidiabetes

medications at baseline. Participants were randomized to receive pramlintide at different doses or placebo for 52 weeks. Treatment with pramlintide 120 µg twice daily led to a reduction from baseline in HbA_{1c} of −0.68%, which was sustained at week 52 (HbA_{1c} −0.62%). This was significantly greater than what was observed with placebo (HbA_{1c} ~0.25%). At week 26, the body weight in participants receiving pramlintide was significantly and dose-dependently decreased from baseline by −0.7 kg with 90 µg twice daily and −1.1 kg with 120 µg twice daily, whereas placebo-treated participants experienced a +0.3 kg change in body weight. At week 52, the body weight change from baseline was sustained in those receiving 120 µg twice daily (−1.4 kg), whereas this was not achieved in people treated with 90 µg twice daily (−0.5 kg) or placebo (+0.7 kg) [153]. The overweight participants (BMI >25 kg/m^2) with type 2 diabetes, who received pramlintide 120 µg twice daily in the study, were included in a pooled post hoc analysis with corresponding participants from another large-scale trial (total $n = 1155$) [154]. Significant reductions in both HbA_{1c} (−0.43%) and body weight (−2.0 kg) from baseline to week 26 (compared with placebo) were found with adjunctive pramlintide therapy. These data indicate that pramlintide added to insulin therapy yields further reductions in HbA_{1c} and a concomitant weight loss in individuals with type 2 diabetes. Furthermore, the risk of severe hypoglycemia was not increased [155].

Future perspectives: amylin incorporated in dual agonist?

Since pramlintide is indicated solely as a supplement to insulin and both peptides must be administered several times per day with s.c. injections, a combination of the two therapies is desirable for people with diabetes in order to reduce the number of injections. At present it is not possible to mix insulin and pramlintide and administer the two drugs in one pen owing to biochemical incompatibility. Perhaps in the future, advanced biotechnology might produce a dual-chamber, double-gauged pen delivering both peptides simultaneously. A novel approach in the pharmaceutical industry is to chemically design multifunctional peptides, e.g. by making a hybrid of two peptides bound together directly or via a linker. These so called "phybrids" are able to act on two (or more) distinct receptors and thereby induce additive or even synergistic beneficial effects and potentially limiting adverse effects [119]. Interestingly, Trevaskis et al. designed two kinds of phybrids combining GLP-1 (exenatide) and amylin (davalintide) modules with different covalent links [141]. The individual phybrids were administered via subcutaneously implanted minipumps in an obese diabetic mouse model (Lep^{ob}/Lep^{ob}). Sustained infusions reduced blood glucose and HbA_{1c} equivalently to exenatide, but both phybrids induced greater weight loss compared with exenatide administration alone. The phybrids reduced food intake and body weight in a dose-dependent manner in diet-induced obese rats. The body weight loss was equal to that with co-infusion of davalintide and exenatide, but greater than that achieved using davalintide and exenatide administration alone. These preclinical data suggest that a single-molecule phybrid approach involving amylin and GLP-1 dual agonism may be just as efficient as co-administration of the individual peptides [141, 156]. In the search into renewing and optimizing the treatment of diabetes and obesity, such co-agonists are likely to go into clinical development.

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33 How to Use Type 2 Diabetes Treatments in Clinical Practice: Combination Therapies

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Key points

- Twelve drug classes (including insulin) are now available to lower glucose in individuals with type 2 diabetes.
- Each antihyperglycemic drug class has a unique mechanism of action, a specific glucose-lowering efficacy, and certain side effects and risks, and some categories also carry specific non-glycemic benefits.
- Metformin is the standard initial drug therapy; in people not achieving control with metformin alone, other drugs are added in sequence—most people will eventually require 2–3 agents for optimal control.
- To achieve glycemic control, many people, particularly those with longer standing disease, will ultimately require insulin, usually beginning with a single injection of a basal formulation once daily.
- In order to arrive at the best regimen for each patient, the clinician should weigh the glucose-lowering efficacy of each drug, with its potential risks and benefits, in addition to its cost.
- The ADA–EASD position statement (2012, updated in 2015) provides rational recommendations for initial and combination glucose-lowering therapy in type 2 diabetes.

Introduction

Optimal care of the person with diabetes involves a comprehensive, multisystem approach to address not only hyperglycemia, but also the frequent companion comorbidities of obesity, hypertension, and dyslipidemia. The main goals of therapy are to avoid symptoms of hyperosmolality and to prevent or delay the long-term sequelae of the disease, including both microvascular and macrovascular complications. At the same time, the potential negative impact of treatments on quality of life should be minimized (See Chapter 23). This composite outcome is not necessarily easy to achieve owing to the limitations of our current therapies, each of which carries some risk of adverse effects, requires adherence on the patient's part, and involves some measurable cost, to either the person with diabetes, insurers, or governments. In this chapter, we review combination pharmacological therapies for people with type 2 diabetes mellitus (T2DM), with a focus on non-insulin glucose-lowering medications. Of course, such treatments cannot be considered as stand-alone therapies. They are always a component of a comprehensive risk-reduction strategy that includes treatments to lower blood pressure, improve circulating lipid concentrations, and reduce platelet hyperactivity. When one considers the significant polypharmacy that this may involve, it is contingent on the practitioner to recommend the proper *balance* of medications, trying to minimize side effects, complexity, and cost, while encouraging adherence to prescription medicines and to the lifestyle choices that are so important in optimizing clinical outcomes.

Reducing glucose concentrations towards the normal range has been unequivocally proven to reduce the incidence and progression of microvascular complications in both type 1 diabetes (T1DM) [1] and T2DM [2]. The most consistent data pertain to the prevention or stabilization of retinopathy and nephropathy. The evidence of an impact of diabetes management on neuropathy is less robust. Moreover, preventing cardiovascular events from improving glycemic control (with the surrogate endpoint of glycated hemoglobin [HbA_{1c}]) has not been unequivocally demonstrated, although there may be certain benefits in this regard from specific drug strategies used to lower glucose [3], but, crucially, interventions to improve cardiovascular outcomes include the management of hypertension and hyperlipidemia. Glucose lowering plays a role in the prevention of cardiovascular disease, and especially so early in the disease process [4]. The effects are probably mediated by slowing the atherosclerotic process and therefore are slow, i.e. measured over years rather than months. The early effect of reducing glucose to or towards the normal range is undoubtedly the prevention of microvascular disease.

Textbook of Diabetes, Fifth Edition. Edited by R. Holt, C. Cockram, A. Flyvbjerg and B. Goldstein.

Efforts to lower glucose are often thwarted by drug side effects, particularly unwanted hypoglycemia when sulfonylurea drugs or insulin are used. Progressive β-cell failure [5] means that therapies often need to be uptitrated even to maintain the status quo. A pragmatic approach is to recommend that glucose levels be lowered as much as is feasible, taking into account overall goals of care, patient capacities and support structure, and the adverse effects and costs of treatments. Even in the hands of the specialist, the optimal titration of an effective, well-tolerated antihyperglycemic regimen is frequently a great challenge, especially in those with long-standing disease.

Pathophysiological rationale for using multiple therapies

Combination glucose-lowering therapy is frequently required in individuals with T2DM because of the multiplicity of pathophysiological defects that lead to increased blood glucose concentrations [6] (Figure 33.1). A proper understanding of optimal pharmacological approaches requires an appreciation of the metabolic abnormalities that characterize the disease.

One of the earliest of such features detected in persons at risk for T2DM was resistance to the action of insulin in peripheral tissues, mainly skeletal muscle and adipocytes. This appears to be driven by obesity and also genetic factors and involves molecular abnormalities in post-receptor insulin signaling, probably related to the build-up of fatty acid metabolites within the cell leading to deranged mitochondrial function [7]. Initially, the pancreatic response to insulin resistance is to augment insulin secretion in a homeostatic drive to maintain blood glucose concentrations within the normal range. However, in some individuals, such a response cannot be sustained over time. As a result, there is a gradual diminution in pancreatic insulin secretion, leading to a slow but predictable increase in circulating blood glucose levels [6].

This is readily detected in the postprandial setting or with glucose tolerance testing, when the demand for increased insulin significantly outstrips the β-cell's secretory capacity. However, basal glucose concentrations also reflect this defect [8], and fasting hyperglycemia is now most frequently used as an appropriate index, rather than the more complex oral glucose challenge.

The molecular mechanisms underlying β-cell dysfunction remain controversial, with evidence for a variety of potential factors, including glucotoxicity, lipotoxicity, oxidative stress, and the extracellular accumulation of amorphous islet amylin polypeptide (IAPP) [9]. It is important to emphasize that although insulin resistance provides a fertile condition for diabetes to develop, it is islet dysfunction that determines the progression to diabetes. This includes both relative insulin secretory deficiency of the β cell and failure to suppress glucagon secretion by the α cell. Abnormalities in the incretin system have also been recognized as a contributing factor to abnormal islet cell behavior [10].

The liver plays a major role in the increased blood glucose concentrations in T2DM. Augmented endogenous glucose production, a manifestation of *hepatic* insulin resistance, contributes to hyperglycemia in both fasting and postprandial settings [11]. This may also partly relate to hyperglucagonemia, given that this islet hormone is a significant driver of hepatic glycogenolysis and gluconeogenesis.

Finally, urinary excretion can be a compensatory mechanism to rid the body of excess glucose when pathological hyperglycemia occurs above the normal renal threshold. This threshold is paradoxically raised in people with T2DM, who are consequently *less* glucosuric than would be expected based on their prevailing circulating blood glucose concentrations [12]. This may relate

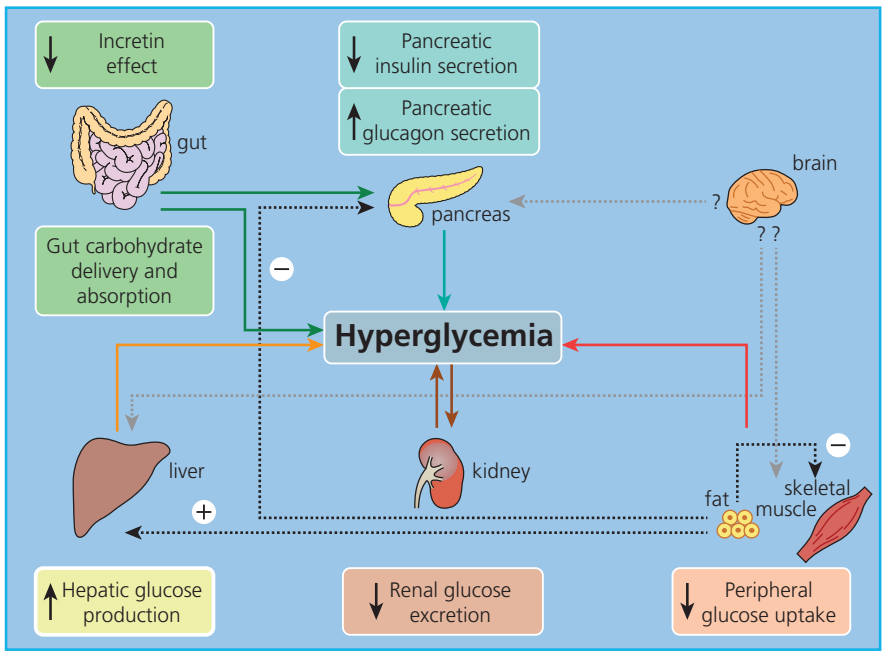

Figure 33.1 The multiple pathophysiological defects that lead to T2DM. The abnormalities described are expressed variably in patients. Most individuals with T2DM have derangements in both insulin supply and insulin action. More recently, abnormal incretin system has been described in addition to inadequate renal clearance of glucose. Many of these metabolic axes are in part driven by the brain but the link to diabetes remains unclear.

to overexpression of the main glucose transporter on the luminal side of the nephron, the sodium–glucose co-transporter-2 (SGLT-2) [13].

Because T2DM is a heterogeneous disease, these abnormalities are present to a variable extent from one individual to another. In practice, clinicians do not necessarily test for their presence or severity, although there are certain clinical features that might suggest greater or lesser perturbation in a specific a domain. For example, those with "metabolic syndrome," a classical constellation of physical and biochemical characteristics that include abdominal obesity, hypertension, hypertriglyceridemia, hyperglycemia, inflammation, and increased risk of atherosclerosis, usually demonstrate significant insulin resistance [14]. The contributions of insulin resistance and β-cell dysfunction vary to some extent by ethnic group [15–17]. Individuals with relatively higher fasting blood glucose levels achieve that through the augmentation of hepatic glucose production. In contradistinction, those with predominant postprandial hyperglycemia exhibit more peripheral insulin resistance and/or more significant β-cell dysfunction. Irrespective of the dominant feature, which is difficult to measure outside a clinical research center, *most* people with T2DM exhibit *both* insulin resistance *and* insulin deficiency [6]. Accordingly, most drugs will reduce glucose to some extent in the majority of individuals, although certain agents (and therefore certain combinations) may be more efficacious in certain people. Understanding the pathogenesis of diabetes will provide the clinician with a framework to understand how each of the drug categories (and their combinations) reduces glycemia based on their unique mechanism of action. This will not only lead to a deeper understanding of the disease and its treatment, but may also allow for more refined, individualized approaches to patient care. Admittedly, however, there are few data to support the notion that attempting to match a drug's mechanism to a patient's predominant pathophysiological defect results in any better control than a more traditional, iterative approach during the longitudinal care of the person with diabetes.

Individual glucose-lowering drug classes

A further description of each of the individual antidiabetes drug classes is given in chapters 29, 31 and 30 (Table 33.1).

Major classes

Sulfonylureas

Sulfonylureas have been available since the early 1950s and remain one of the standard therapies for T2DM [18]. Their mechanism of action involves binding to the sulfonylurea receptor on the cell surface of pancreatic β cells, leading to closure of ATP-sensitive K^+ (K-ATP) channels. This, in turn, depolarizes the plasma membrane, allowing an influx of calcium ions and consequent insulin secretion. Notably, the effects of sulfonylureas are not glucose dependent, and therefore this drug class carries the risk of hypoglycemia, which in some circumstances can be severe and prolonged.

First-generation agents (chlorpropamide, tolbutamide, tolazamide, and acetohexamide) are no longer in widespread use. Currently available second-generation sulfonylureas include glyburide/glibenclamide, glipizide, and glimepiride, with subtle differences in their durations of action and metabolic fates. Glyburide has the longest receptor binding half-life (although its plasma half-life is short). It has a significantly active glucose-lowering hepatic metabolite that is renally cleared. Accordingly, this agent is associated with a high risk of hypoglycemia and should generally be avoided in older persons and those with compromised renal disease [19]. An additional side effect of sulfonylureas is modest weight gain (2–3 kg.) This category is also associated with a higher secondary failure rate than for other drugs, such as metformin and thiazolidinediones, an effect ascribed by some to "pancreatic exhaustion" [20]. Hence they are considered less durable than these other agents in most people with diabetes. In the UK Prospective Diabetes Study (UKPDS) [2], involving 5102 individuals newly diagnosed with T2DM, those treated with sulfonylureas (analyzed in conjunction with those assigned to initial insulin therapy) experienced significantly better microvascular outcomes (–25%; $p = 0.001$; mainly retinopathy, albuminuria) than those treated with diet alone. There was an insignificant trend towards fewer myocardial infarctions (MI) (–15%; $p = 0.052$) and no effect on either all-cause or diabetes-related mortality.

In some observational studies, sulfonylureas have been associated with increased cardiovascular events compared with metformin and, at times, other oral antihyperglycemic drugs [21, 22]. Interestingly, in an older study, the UGDP, tolbutamide was associated with greater cardiovascular mortality than insulin therapy [23]. Dating from this observation, although the study had many methodological limitations (including large imbalances in the randomization relating to ECG abnormalities and angina [24]), the sulfonylurea drug class carries a "black-box" US Food and Drug Administration (FDA) warning [25]. Importantly, although sulfonylureas were not associated with a significant reduction in MI in the main UKPDS, in its follow-up study, during which the originally assigned participants were not necessarily still on their study treatment, the benefit regarding MI became significant, owing to the accumulation of more events [26]. The point estimate for the effect showed a 15% reduced risk (hazard ratio 0.85; $p = 0.01$).

Sulfonylureas may be used in combination with metformin and most other antihyperglycemic categories with the exception of the less commonly used drug class known as meglitinides, which are similar in their mechanism of action. Since the first combination therapy trial published by Defronzo and Goodman [27] (see Dual combination therapy), many additional studies involving combinations with thiazolidinediones, dipeptidyl peptidase (DPP)-4 inhibitors, glucagon-like peptide (GLP)-1 receptor agonists, and SGLT-2 inhibitors have consistently shown improved glycemic control compared with baseline therapies, either with or without metformin [28–31]. Combinations with insulin have also been studied extensively [32], although this specific pairing has become less popular over time (see Combinations with insulin).

Table 33.1 Specific properties of available glucose-lowering agents that guide combination therapy choices in patients with T2DM.

Class	Compound(s)	Cellular mechanism	Primary physiological action(s)	Advantages	Disadvantages	Cost
Biguanides	• Metformin	Activates AMP-kinase; inhibition of mitochondrial GDP; increase in intestinal GLP-1 release	↓ Hepatic glucose production	• Extensive experience • No hypoglycemia • Likely ↓ CVD events (UKPDS)	• Gastrointestinal side effects (diarrhea, abdominal cramping) • Lactic acidosis risk (rare) • Vitamin B_{12} deficiency • Multiple contraindications: CKD, acidosis, hypoxia, dehydration, etc.	Low
Sulfonylureas	• Glyburide/ glibenclamide • Glipizide • Gliclazide[a] • Glimepiride	Closes K_{ATP} channels on β-Cell plasma membranes	↑ Insulin secretion	• Extensive experience • ↓ Microvascular risk (UKPDS)	• Hypoglycemia • ↑ Weight • ? Blunts myocardial ischemic preconditioning • Low durability	Low
Meglitinides (glinides)	• Repaglinide • Nateglinide	Closes K_{ATP} channels on β-cell plasma membranes	↑ Insulin secretion	• ↓ Postprandial glucose excursions • Dosing flexibility	• Hypoglycemia • ↑ Weight • ? Blunts myocardial ischemic preconditioning • Frequent dosing schedule	High
Thiazolidinediones	• Pioglitazone • Rosiglitazone[b]	Activates the nuclear transcription factor PPAR-γ	↑ Insulin sensitivity	• No hypoglycemia • Durability • ↑ HDL-C • ↓ Triglycerides (pioglitazone) • ? ↓ CVD events (ProACTIVE, pioglitazone)	• ↑ Weight • Edema/HF • Bone fractures • ↑ LDL-C (rosiglitazone) • ? ↑ MI (meta-analyses, rosiglitazone)	Low
α-Glucosidase inhibitors[a]	• Acarbose • Miglitol	Inhibits intestinal α-glucosidase	Slows intestinal carbohydrate digestion/absorption	• No hypoglycemia • ↓ Postprandial glucose excursions • ? ↓ CVD events (STOP-NIDDM) • Non-systemic	• Generally modest HbA_{1c} efficacy • Gastrointestinal side effects (flatulence, diarrhea) • Frequent dosing schedule	Moderate
DPP-4 inhibitors	• Sitagliptin • Vildagliptin[a] • Saxagliptin • Linagliptin • Alogliptin	Inhibits DPP-4 activity, increasing postprandial active incretin (GLP-1, GIP) concentrations	↑ Insulin secretion (glucose-dependent) ↓ Glucagon secretion (glucose-dependent)	• No hypoglycemia • Well tolerated	• Generally modest HbA_{1c} efficacy • Urticaria/angioedema • ? Acute pancreatitis • ? ↑ HF hospitalization (saxagliptin)	High

[a]Not licensed in the USA.
[b]Limited use in the USA/Europe.
AMP, adenosine monophosphate; CKD, chronic kidney disease; CVD, cardiovascular disease; DPP-4, dipeptidyl peptidase 4; GLP-1, glucagon-like peptide 1; HDL-C, high-density lipoprotein cholesterol; HF, heart failure; LDL-C, low-density lipoprotein cholesterol; PPAR, peroxisome proliferator-activated receptor; ProACTIVE, Prospective Pioglitazone Clinical Trial in Macrovascular Events; UKPDS, United Kingdom Prospective Diabetes Study.

(continued)

Bile acid sequestrants	• Colesevelam	Binds bile acids in intestinal tract, increasing hepatic bile acid production; ? activation of farnesoid X receptor (FXR) in liver; ? activation of TGR5 receptor in GI tract	? ↓ Hepatic glucose production ? ↑ Incretin levels	• No hypoglycemia • ↓ LDL-C	• Generally modest A1c efficacy • Constipation • ↑ Triglycerides • May ↓ absorption of other medications	High
Dopamine-2 agonists	• Bromocriptine (quick-release)[c]	Activates dopaminergic receptors	Modulates hypothalamic regulation of metabolism ↑ Insulin sensitivity	• No hypoglycemia • ? ↓ CVD events (Cycloset Safety Trial)	• Generally modest HbA_{1c} efficacy • Dizziness/syncope • Nausea • Fatigue • Rhinitis	High
SGLT-2 inhibitors	• Canagliflozin • Dapagliflozin • Empagliflozin	Inhibits the sodium–glucose co-transporter 2 in the proximal nephron	Blocks glucose reabsorption by the kidney, increasing glucosuria	• No hypoglycemia • ↓ Weight • ↓ Blood pressure • Effective at all stages of T2DM • ↓ CV mortality and HF hospitalization (EMPA-REG Outcome, empagliflozin)	• Genitourinary infections • Polyuria • Volume depletion/hypotension/dizziness • ↑ Risk of DKA • ↑ LDL-C • ↑ Creatinine (transient) • ? ↑ Fractures (canagliflozin)	High
GLP-1 receptor agonists	• Exenatide • Exenatide extended release • Liraglutide • Albiglutide • Lixisenatide[a] • Dulaglutide	Activates GLP-1 receptors	↑ Insulin secretion (glucose-dependent) ↓ Glucagon secretion (glucose-dependent) Slows gastric emptying ↑ Satiety	• No hypoglycemia • ↓ Weight • ↓ Postprandial glucose excursions • ? Potential for improved β-cell mass/function (preliminary data) • ? Cardiovascular protective actions	• Gastrointestinal side effects (nausea/ vomiting) • ? Acute pancreatitis • C-cell hyperplasia/medullary thyroid tumors in animals • Injectable • Training requirements	High

[c]Not licensed in Europe.
CVD, cardiovascular disease; DKA, diabetic ketoacidosis; GLP-1, glucagon-like peptide 1; LDL-C, low-density lipoprotein cholesterol

(continued)

Table 33.1 (*Continued*)

Class	Compound(s)	Cellular mechanism	Primary physiological action(s)	Advantages	Disadvantages	Cost
Amylin mimetics	• Pramlintide[c]	Activates amylin receptors	↓ Glucagon secretion Slows gastric emptying ↑ Satiety	• ↓ Postprandial glucose excursions • ↓ Weight	• Generally modest HbA_{1c} efficacy • Gastrointestinal side effects (nausea/ vomiting) • Hypoglycemia unless insulin dose is simultaneously reduced • Injectable • Frequent dosing schedule • Training requirements	High
Insulins	• Rapid-acting analogs – Lispro – Aspart – Glulisine • Short-acting – Human Regular • Intermediate-acting – Human NPH • Basal insulin analogs – Glargine – Detemir – Degludec • Pre-mixed (several types)	Activates insulin receptors	Glucose disposal Hepatic glucose production Other	• Nearly universal response • Theoretically unlimited efficacy • Microvascular risk (UKPDS)	• Hypoglycemia • Weight gain • ? Mitogenic effects • Injectable • Training requirements • Patient reluctance	Variable[d]

[c]Not licensed in Europe.
[d]Depends on type (analogs ≫ human insulins) and dosage.
LEADER, Liraglutide Effect and Action in Diabetes: Evaluation of Cardiovascular Outcome Results; UKPDS, United Kingdom Prospective Diabetes Study.

In the 2012 American Diabetes Association (ADA) and European Association for the Study of Diabetes (EASD) position statement on the management of hyperglycemia in type 2 diabetes [33] and its 2015 update [34], the sulfonylureas were included as an option for dual therapy after metformin (Figure 33.2). This was based on this class's low cost, wide accessibility, and documented efficacy, and the evidence of benefit on microvascular complications. However, the writing group included cautionary statements about hypoglycemia risk. With the advent and growing popularity of several drug classes that do not (by themselves) increase the risk of hypoglycemia and which have been proven to at least be safe from a cardiovascular standpoint, this class of medication is likely to be used less frequently in the future. In most studies involving people on baseline sulfonylurea treatment, the addition of a drug that may not itself be associated with hypoglycemia still increases the risk of hypoglycemia. Accordingly, in people whose glycemic control is close to target, the addition of a second agent may require some adjustment in the secretagogue dose.

Some sulfonylureas are available in fixed-dose combinations with metformin (short-acting) and thiazolidinediones (see Table 33.2).

Metformin

Metformin, a member of the biguanide class, has been used clinically since the 1950s, and has been available in the United States since 1995. Its mechanism of action still remains incompletely understood. The drug reduces hepatic glucose production [35]. This may be through activation of AMP-kinase [36], although more recent data suggest an effect through the inhibition of mitochondrial glycerolphosphate dehydrogenase (mGDP), blocking ingress of hydrogen ions into the mitochondria [37]. This increases the cytosolic redox state, suppressing gluconeogenesis. Other investigators have found that metformin increases the release of intestinal GLP-1 [38]. The glucose-lowering effect of metformin may therefore be multidimensional and may vary to some extent with dose. With HbA_{1c} reducing potency on a par with sulfonylureas, the major advantage of metformin is its ability to lower glucose without inducing hypoglycemia. Although often considered as a drug that results in weight loss, over time metformin is actually weight neutral in most people. The drug has been associated with several benefits on certain cardiovascular risk factors, such as proatherogenic lipoproteins and the inflammatory mediator C-reactive protein [39]. In fact, to date, it is the only glucose-lowering agent to be linked to a reduction in MI in people with newly diagnosed T2DM, an effect demonstrated in a sub-study within the UKPDS in which 753 drug-naive, overweight people with T2DM were randomized to metformin monotherapy versus diet therapy or sulfonylurea/insulin [40]. The metformin group experienced a 49% reduction ($p = 0.01$) in MI compared with the diet-controlled control group, a trend towards fewer such events compared with the sulfonylurea/insulin group (whose glucose levels were lowered to an equivalent degree), and statistically significantly fewer stroke events compared with the sulfonylurea/insulin group. This apparent macrovascular effect of metformin on MI persisted in the UKPDS study, with follow-up extending out an additional decade (relative risk reduction 43%; $p = 0.005$) [26].

Another sub-study within the UKPDS, however, focused on individuals who were not controlled on sulfonylurea monotherapy. They were then randomized to the addition of metformin in combination with the sulfonylurea or continued sulfonylurea monotherapy. For reasons that are still unclear, those assigned to combination therapy experienced a nearly twofold increase in diabetes-related mortality to those left on secretagogue monotherapy (relative risk [RR] 1.96; $p = 0.039$) [41]. In a post hoc epidemiological analysis of the UKPDS, such a risk could not be documented in all people treated with this combination in the entire study. Moreover, in the UKPDS follow-up, the risk in those originally randomized to combination metformin–sulfonylurea disappeared over time [42]. Most have therefore concluded that the initial finding that raised concerns about a deleterious effect of the combination was likely to be a chance finding.

Another smaller, randomized trial (HOME) showed less cardiovascular disease (CVD) (RR 0.61; $p = 0.02$) events in people with insulin-treated T2DM who had metformin added to their regimen versus further titration of the insulin dose [43]. These findings have been buttressed by several large, retrospective trials that showed fewer CVD events in those treated with metformin monotherapy versus sulfonylurea monotherapy [44–47].

Data such as these have resulted in metformin being considered, by most professional organizations, as the optimal initial therapy for individuals with T2DM who are not able to control their glucose levels through lifestyle change alone. In the ADA–EASD position statement on the management of hyperglycemia in T2DM [33, 34], metformin has a prominent role as foundation therapy, to which other drugs are added if additional glucose-lowering is necessary (Figure 33.2). Since the original combination therapy trial that demonstrated an additional glucose-lowering effect from adding metformin to failing glyburide therapy [27], dozens of trials have resulted in similar conclusions, whether from adding metformin to other glucose-lowering drugs (e.g. insulin) or, more commonly, adding another agent (e.g. thiazolidinediones, DPP-4 inhibitors, GLP-1 receptor agonists, SGLT-2 inhibitors, or insulin) to baseline metformin therapy [48–51]. In fact, all new T2DM therapies are now tested early on in their course of development as add-on to metformin, given the latter's established role as the optimal initial therapy.

There are several contraindications to metformin that deserve mention, some of which pertain to other drugs with which it may be prescribed. Because of their effects on mitochondrial respiration, members of the biguanide group have been linked to increased risk of lactic acidosis [52] (the original biguanide, phenformin, was actually removed from the market owing to excessive rates of this often lethal metabolic complication). Lactic acidosis is typically observed in the setting of other medical illness, especially those that result in hemodynamic collapse and renal failure. Because metformin is excreted unchanged in the urine, its circulating levels increase potentially into a toxic range when renal

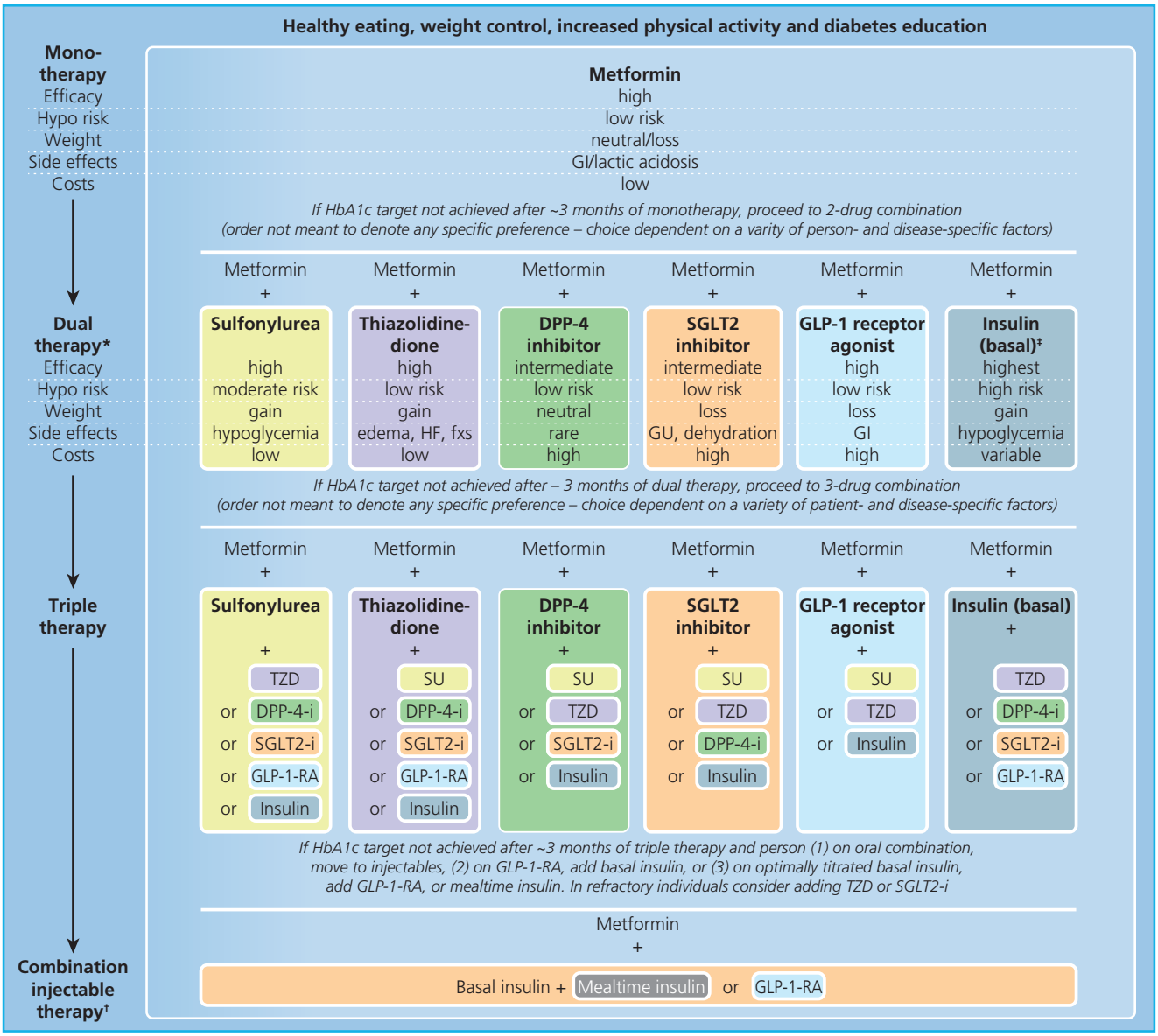

Figure 33.2 General recommendations from the 2015 update to the ADA–EASD position statement on management of hyperglycemia in T2DM [34]. Potential sequences of antihyperglycemic therapy for people with T2DM are displayed, the usual transition being vertical, from top to bottom (although horizontal movement with therapy stages is also possible, depending on the circumstances.) In most people, begin with lifestyle changes; metformin monotherapy is added at, or soon after, diagnosis, unless there are contraindications. If the HbA_{1c} target is not achieved after ~3 months, consider one of the six treatment options combined with metformin: SU, TZD, DPP-4-i, SGLT-2-i, GLP-1-RA, or basal insulin—the order in the chart not meant to denote any specific preference. Drug choice is based on patient preferences in addition to various patient, disease, and drug characteristics, the goal being to reduce glucose concentrations while minimizing side effects, especially hypoglycemia. The figure emphasizes drugs in common use in the USA and/or Europe. In patients intolerant of or with contraindications for metformin, consider initial drug from other classes depicted under *Dual therapy* and proceed accordingly. Consider initiating therapy with a dual combination when the HbA_{1c} ≥9% to achieve glycemic targets more rapidly. Insulin has the advantage of being effective where other agents may not be and should be considered a part of any combination regimen when hyperglycemia is severe, especially if the individual is symptomatic or if any catabolic features (weight loss, any ketosis) are evident. Consider initiating combination insulin injectable therapy when BG ≥300–350 mg/dL (16.7–19.4 mmol/l) and/or HbA_{1c} ≥10–12%. As the patient's glucose toxicity resolves, the regimen can potentially be subsequently simplified. *Consider initial therapy at this stage when HbA_{1c} ≥9%. †Consider initial therapy at this stage when BG ≥300–350 mg/dL (16.7–19.4 mmol/l) and/or HbA_{1c} ≥10–12%, especially if the person is symptomatic or if catabolic features are present, in which case basal insulin + mealtime insulin is the preferred initial regimen. ‡Usually a basal insulin (NPH, glargine, detemir, degludec). Abbreviations: DPP-4-i, DPP-4 inhibitor; Fxs, bone fractures; GI, gastrointestinal; SGLT-2, sodium–glucose co-transporter 2; GLP-1-RA, GLP-1 receptor agonist; HF, heart failure; SU, sulfonylurea; BG, blood glucose. Source: Inzucchi et al. 2015 [34]. Copyright 2015 American Diabetes Association. Reproduced with permission.

Table 33.2 Available fixed-dose combinations of glucose-lowering agents of different classes.

Combination	Components
Secretagogue-Biguanide	**Secretagogue-Thiazolidinedione**
Glyburide-Metformin	Glimepiride-Rosiglitazone
Glipizide-Metformin	Glimepiride-Pioglitazone
Repaglinide-Metformin	
Thiazolidinedione-Biguanide	**DPP-4 inhibitor-Thiazolidinedione**
Rosiglitazone-Metformin	Alogliptin-Pioglitazone
Pioglitazone-Metformin	
DPP-4 inhibitor-Biguanide	**DPP-4 inhibitor-SGLT2 inhibitor**
Sitagliptin-Metformin	Linagliptin-Empagliflozin
Saxagliptin-Metformin	
Alogliptin-Metformin	
Linagliptin-Metformin	
SGLT2 inhibitor-Biguanide	**GLP-1 Receptor Agonist-Insulin**
Canagliflozin-Metformin	Lixisenatide-Glargine
Dapagliflozin-Metformin	Liraglutide-Degludec
Empagliflozin-Metformin	

function is severely impaired. In the USA, the prescribing guidelines contraindicate use of metformin when the serum creatinine reaches 1.5 mg/dL or higher in men and 1.4 mg/dL or higher in women [53]. In the United Kingdom, prescribing guidelines are based on estimated glomerular filtration rate (eGFR), with the drug allowed down to 45 mL/min, dose adjustments between 30 and 45 mL/min, and discontinuation after the eGFR falls below 30 mL/min (or when the serum creatinine exceeds 1.7 mg/dL) [54]. There have recently been calls in the USA to harmonize the prescribing label with that used in the UK, given the paucity of evidence that metformin poses risk when used in those with mild to moderate chronic kidney disease (CKD) [55]. Indeed, some observational data suggest an actual mortality *benefit* in these individuals [56]. Since many other drugs with which metformin is used in combination (such as sulfonylureas, certain DPP-4 inhibitors, certain GLP-1 receptor agonists, and SGLT-2 inhibitors) have prescribing stipulations for individuals with decreased kidney function, great care is needed when using most combination glucose-lowering therapy in T2DM. In addition to advanced renal disease, metformin should also not be used in those with acidosis, dehydration, severe heart failure, or liver disease, or in chronic alcoholics, all due to an increased risk of developing lactic acidosis.

Thiazolidinediones

The thiazolidinediones, or glitazones, became available in the mid-1990s amidst substantial interest in their potential not only to reduce insulin resistance but also to improve cardiovascular outcomes [57]. The original thiazolidinedione, troglitazone, was removed from the market owing to hepatotoxicity, after rosiglitazone and pioglitazone had become available. These insulin-sensitizing drugs activate the nuclear hormone receptor peroxisome proliferator-activated receptor (PPAR-γ), with predominant metabolic effects in adipocytes (promotion of differentiation and modulation of adipokine secretion) and skeletal muscle (augmentation of insulin-mediated peripheral glucose uptake) [58]. There may also be a beneficial effect on the efficiency of β-cell function [59]. The thiazolidinediones thus reduce both blood glucose and insulin levels and are not associated with hypoglycemia when used as monotherapy. Preclinical data and studies in humans involving surrogate markers of atherosclerosis had suggested a potentially important effect on reducing cardiovascular complications [60]. However, the results from studies that examined actual clinical macrovascular events have been mixed. Pioglitazone, when added to background T2DM therapy, was associated with a 16% reduction in major adverse cardiovascular events (MACE) in the PROactive study, although the study's primary outcome, which was a broad composite that included peripheral vascular complications, proved neutral [61]. Rosiglitazone has had a highly controversial history. In 2007, a meta-analysis of phase III and IV studies suggested an actual *increase* (43%) in MI risk [62]. These data led to a rapid curtailment of the prescriptions of this once popular drug across the world and many countries proceeded to withdraw this thiazolidinedione from their markets. By contrast, and consistent with the PROactive study results, a similarly designed meta-analysis of pioglitazone trials found a benefit (–18%) on cardiovascular events [63]. Subsequently, however, a randomized clinical trial (RECORD) demonstrated a neutral effect of rosiglitazone on cardiovascular events, although this information came too late to reinvigorate interest in the compound [64].

There have been additional concerns that have rendered the entire thiazolidinedione drug class less popular over time. The most important concerns the weight gain that characterizes thiazolidinedione therapy, usually of the order of 4 kg over the first year [65]. The more recent availability of glucose-lowering drugs that lead to weight loss (GLP-1 receptor agonists, SGLT-2 inhibitors) or are at least weight neutral (DPP-4 inhibitors) has contributed to decreased use of this class. The thiazolidinediones are also associated with increased rates of peripheral edema, the result of activation of sodium retention at the distal renal tubule [66]. For this reason, the risk of heart failure and heart failure hospitalization is also increased [67]. There is no known deleterious effect on ventricular function, however. Bone loss and an increase in fracture rates in women have been found in multiple studies [68]. Finally, the question of an increased risk of carcinoma of the bladder has been raised with pioglitazone, although a recent 10-year follow-up review involving nearly 200,000 people with T2DM within the Kaiser Permanente of Northern California system found no such risk [69].

In spite of these considerable concerns, the thiazolidinediones are unique amongst diabetes therapies in that they have been demonstrated to have greater durability in glycemic effectiveness compared with metformin and sulfonylureas [70], perhaps

reflecting an overall beneficial effect on β-cell function due to decreasing insulin secretory demands.

Thiazolidinediones lower glucose and HbA_{1c} to similar extents to metformin and sulfonylureas (1–1.5%). Since their inception, the thiazolidinediones have been used almost exclusively in combination regimens. One early study demonstrated efficacy in combination with metformin [71] and, since then, they have been tested and used in combinations with most other major antihyperglycemic drug classes, including sulfonylureas, DPP-4 inhibitors, GLP-1 receptor agonists (RAs), SGLT-2 inhibitors, and insulin [72–76]. The thiazolidinediones are also available in fixed-dose combinations with metformin (short-acting), sulfonylureas, and a DPP-4 inhibitor (pioglitazone–alogliptin.)

As with metformin and all sulfonylureas, pioglitazone is now available in cost-effective generic formulations. Despite the concerns raised over the years about safety, these remain endorsed as reasonable second-line agents by in the latest ADA–EASD position statement on the management of hyperglycemia in type 2 diabetes (see Guidelines and Figure 33.2) [33, 34].

Incretin-based therapy

The incretin system is represented by the intestinal hormones GLP-1 and glucose-dependent insulinotropic peptide (GIP), which stimulate glucose-dependent pancreatic insulin secretion and suppress glucagon secretion. GLP-1 also delays gastric emptying and enhances satiety [77]. The incretins are secreted in response to meal ingestion. They are rapidly degraded by the widely expressed protease DPP-4, rendering biological half-lives of just a few minutes. Developers of glucose-lowering medicines have taken two approaches to capitalize on this physiology. One is to synthesize injectable GLP-1 receptor (R) agonists (A) that are resistant to DPP-4, and the other is to produce oral inhibitors of DPP-4. Both classes are referred to as *incretin enhancers*.

GLP-1 receptor agonists

GLP-1 receptor agonists (exenatide, liraglutide, lixisenatide, albiglutide, dulaglutide) are injectable agents that mimic the effects of endogenous GLP-1 [78]. They thereby increase insulin secretion in a glucose-dependent fashion, decrease glucagon secretion, and delay gastric emptying, the last being an effect that appears to wane over time. Their use is characterized by decreased appetite, lower calorie consumption, and weight loss. The class is associated with small reductions in blood pressure, and some beneficial lipid and anti-inflammatory effects (decreased triglycerides and C-reactive protein). Although a specific formulation of liraglutide (high-dose) is now available as an antiobesity drug, the GLP-1RAs are almost exclusively used in combination therapy for those with T2DM, classically with metformin with or without additional oral agents. A common scenario is their use as a third-line agent after failure to control blood glucose with two agents, such as metformin–sulfonylurea or metformin–thiazolidinedione. At the time of this writing, there are no published studies on the combination of GLP-1RA plus an SGLT-2 inhibitor, an obviously attractive regimen with potentially enhanced weight loss effects. The class should not be used in conjunction with DPP-4 inhibitors given their overlapping mechanisms of action and the inherent resistance of the GLP-1RAs to enzymatic breakdown by DPP-4.

The GLP-1RAs have also been studied extensively with insulin and two products in fixed-ratio combination products with basal insulin analogs (liraglutide–insulin degludec, lixisentatide–insulin glargine) have been approved or submitted to the regulatory approval process.

Most of the members of this class reduce HbA_{1c} by ~1–2% over placebo, with larger changes noted with the longer-acting formulations [79], perhaps a reflection of better adherence. Their efficacy is therefore generally on a par with those of the other three older medications used in T2DM, metformin, sulfonylureas, and thiazolidinediones. The GLP-1RAs appear to be more efficacious than the class of glucose-lowering drugs with which they are often compared, the DPP-4 inhibitors. The GLP-1RAs result in a body weight loss of 2–4 kg over the first 6–12 months of therapy, which appears to be sustained over long-term use [80]. This category of diabetes medication is becoming an increasingly favored option in obese individuals.

The GLP-1RAs are gaining in popularity in combination with basal insulin, with studies demonstrating equal efficacy on HbA_{1c}, with weight loss instead of weight gain, and less hypoglycemia risk, as compared with the addition of mealtime insulin—the usual strategy in people not controlled with basal insulin alone [81]. (see Combinations with insulin). The longer-acting formulations are more convenient, although the ease of use of the various injection pen devices differs to some extent from product to product. Accordingly, good patient instruction on proper pen use is important.

Side effects mainly relate to the gastrointestinal system. Particularly during the initiation of therapy, many people will develop nausea and in some cases vomiting. These symptoms generally abate over time. Slow dose uptitration is important for minimizing these effects, which probably relate to a slowing of gastric emptying. The agents should not be used in individuals with gastroparesis. There have been some lingering concerns about the risk of pancreatitis or even pancreatic malignancy with the GLP-1RAs, with animal studies showing subtle changes of unknown significance in the exocrine pancreas at very high doses. Observational studies have demonstrated no measurable increase in rates of pancreatitis in cohorts treated with these agents, although in randomized trials, small imbalances have been reported. Nevertheless, the overall incidence remains low [82]. Notably, people with T2DM, particularly those who are obese (in whom the drug may be used to a greater extent), are predisposed to both biliary disease and hypertriglyceridemia, both themselves risk factors for pancreatitis. The GLP-1RAs remain contraindicated in anyone with a prior history of pancreatitis.

This class of drug is extremely expensive, ~100 times the cost of generically available diabetes drugs. In addition, they are available only in injectable forms. They are therefore typically reserved for those individuals who have adequate insurance coverage and when other agents have failed.

There is substantial evidence from preclinical studies in animal models, investigations involving cardiovascular risk surrogates and/or markers in humans, and also some small mechanistic human studies to suggest that GLP-1RA therapy may advantageous for the cardiovascular system [83]. Whether this may relate to direct cardiac and/or vascular effects of the drugs, or the ability to lower glucose with weight gain and without hypoglycemia, or some other off-target effect is not clear. After the 2008 *Guidance to Industry* from the US Food and Drug Administration (FDA) concerning cardiovascular safety of diabetes therapies [84], the GLP-1RAs are currently under investigation in large outcomes trials of 2–4 years' duration for their effects on cardiovascular outcomes in high-risk individuals. Most of the trials have been additionally powered to demonstrate cardiovascular effectiveness. The initial cardiovascular outcome trial to report involved lixisenatide in people with recent acute coronary syndrome—the ELIXA trial, involving 6075 participants studied over 2 years [85]. The MACE rates were equivalent between the group assigned to lixisenatide versus placebo, added to background diabetes therapy. (Notably, in light of the concerns described below regarding DPP-4 inhibitors and possible heart failure risk, there was no signal of such an effect in this trial.) At the time of publication, the LEADER trial results were released. In 9340 participants at high CV risk, treatment with the GLP-1RA liraglutide resulted in a 13% relative risk reduction (HR = 0.87; 95% CI 0.78–0.97; $p = 0.011$) in MACE and a 22% reduction CV death (HR = 0.78; 95% CI 0.66–0.93; $p = 0.007$). In contrast to EMPA-REG, each component of 3-point MACE appeared to contribute to the composite outcome [85a]. Time will tell whether any of the other GLP-1RAs will prove to be both safe and potentially beneficial on hard cardiac outcomes. The trials currently under way include, EXSCEL (weekly exenatide), SUSTAIN (weekly semaglutide), and REWIND (weekly dulaglutide). GLP-1RA of even longer duration of action are also under investigation.

GLP-1RAs were endorsed as options in combination regimens after metformin by the 2012 ADA–EASD position statement on the management of hyperglycemia in type 2 diabetes [33]. The position statement's update in 2015 underscored the growing importance of the class in combination regimens with basal insulin (Figure 33.2) [34] (see Combinations with insulin).

DPP-4 inhibitors

These oral agents are potent and durable inhibitors of the protease enzyme that rapidly degrades the endogenous incretin hormones GLP-1 and GIP [86]. They thereby allow endogenous incretin hormone levels to rise to a higher concentration and in a more sustained fashion in the postprandial setting. The levels of incretin hormones achieved after DPP-4 inhibition, however, are substantially lower than the more pharmacological concentrations reached through the administration of GLP-1RAs. Currently available compounds include sitagliptin, vildagliptin, saxagliptin, alogliptin, and linagliptin. In monotherapy, they appear to be somewhat less potent than other agents, with HbA_{1c} reductions in the 0.6–0.8% range [87, 88]. As with other glucose-lowering drugs, efficacy is greater in those individuals with higher baseline HbA_{1c} levels. When compared directly, in head-to-head trials, with sulfonylureas and thiazolidinediones, the DPP-4 inhibitors reduce HbA_{1c} equivalently, but to a lesser extent than metformin, GLP-1RAs, and SGLT-2 inhibitors [87–91]. One advantage of this class of glucose-lowering drug is fewer side effects than with most other categories, with no significant hypoglycemia, weight gain, gastrointestinal intolerance, or edema. In fact, they are now widely viewed as the best tolerated of the most commonly used antihyperglycemic agents.

The DPP-4 inhibitors are not commonly used as monotherapy and are often prescribed in conjunction with metformin or other drugs, such as sulfonylureas, thiazolidinediones, SGLT-2 inhibitors, and sometimes basal insulin [92–95]. They should not be used in conjunction with GLP-1RAs, which share a similar mechanism of action. Most of the currently available DPP-4 inhibitors are available in fixed-dose combinations with metformin, both short-acting and in some circumstances long-acting formulations. A single fixed-dose combination with a thiazolidinedione exists (aloglipin–pioglitazone). Recently, fixed-dose combinations with SGLT-2 inhibitors have also become available.

The adverse effect profile of the DPP-4 inhibitors is similar to that of placebo. Urticaria and other allergic skin eruptions are the most commonly reported effects. As with the GLP-1RAs, there remains some concern about possible pancreatitis risk, but large retrospective studies have not found any distinct increase in the incidence of pancreatitis in people using this drug class [96]. In some clinical trials, a slightly greater number of pancreatitis cases have been reported in the DPP-4 inhibitor arm but, as with the GLP-1RAs, the frequency remains very low. These drugs should not be used in anyone with a prior history of pancreatitis.

Preclinical studies had suggested a possible beneficial effect on atherosclerosis, either via direct effects on the vasculature and/or heart from DPP-4 inhibition or from higher levels of GLP-1 [97]. Three large cardiovascular outcome studies (SAVOR, EXAMINE, and TECOS) have unequivocally demonstrated these drugs to be essentially neutral on MACE, at least over the relatively brief time course (1–2-year median follow-up) of these types of trials [98–100]. In one of these investigations, SAVOR, participants assigned to saxagliptin experienced a 27% greater risk ($p = 0.007$) of hospitalization for heart failure [98]. The precise etiology of such an effect, if it is more than a chance finding, remains elusive. DPP-4 inhibition is not known to increase the circulating concentrations of any molecule that serves as a natriuretic factor or any that might have effects on cardiac contractility. Notably, in both EXAMINE (which used alogliptin) and TECOS (sitagliptin), no increase in heart failure was detected in the active therapy group. One cardiovascular outcome study with a DPP-4 inhibitor, CAROLINA (using linagliptin), is still ongoing [101].

The DPP-4 inhibitors are as all available members of the class are branded products. These drugs were also been endorsed as options in combination regimens after metformin in the 2012 ADA–EASD position statement on the management of hyperglycemia in type 2 diabetes [33] and its update in 2015 (Figure 33.2) [34].

SGLT-2 inhibitors

The newest glucose-lowering category is the sodium–glucose co-transporter (SGLT)-2 inhibitors (canagliflozin, dapagliflozin, and empagliflozin.) These drugs inhibit SGLT-2 in the proximal nephron, thereby blocking glucose reclamation and increasing glucosuria [102]. This transporter is responsible for ~90% of glucose reabsorption from the glomerular filtrate (SGLT-1, which is more highly expressed in the gut, modulating glucose absorption, comprises the remaining 10%). In people treated with drugs of this type, urinary glucose losses are in the 60–80 g/day range, resulting in a daily calorie reduction of about 400 kcal and an average weight reduction of 2–3 kg over the course of 6–12 months. This is a sustained effect but, interestingly, not progressive with longer-term use. Because of a mild osmotic diuretic effect, these agents can also decrease blood pressure (by 3–4 mmHg systolic and 1–2 mmHg diastolic). HbA_{1c} reductions range between 0.6 and 1.0%; as with all antihyperglycemic drugs, greater reductions are seen in those with higher baseline values [103, 104].

Adverse effects relate mainly to the genitourinary system. Owing to increased glucose concentration in the urine, an increase in genital mycotic (yeast) infections is seen, most frequently in women (vulvo-vaginitis), but also in men (balanitis). In some but not all studies, an increase in urinary tract infections has also been detected. Owing to the drugs' mechanism of action, individuals tend to perceive an increase in urine frequency and flow, and this may become a challenge in those with urinary incontinence or in men with bladder outlet obstruction from prostatic hypertrophy. Symptoms of volume contraction may also occur (dehydration, orthostasis). A mild increase in serum creatinine can also be measured soon after medication initiation, but this effect is not a toxic effect per se, but one that reflects decreased vascular volume and renal perfusion. Importantly, it reverses upon drug discontinuation. In fact, these agents appear to decrease urinary albumin : creatinine ratios [105], although their long-term effects on renal preservation are unknown. Fracture rates have also been reported to be increased with at least one member of this class, possibly the result of increase urinary calcium losses and secondary hyperparathyroidism [106].

One unique aspect of the SGLT-2 inhibitors is that their mode of action is independent of insulin. Hence they can be effective across the various stages of diabetes, from recent-onset to late-stage disease. One the other hand, because their mechanism requires both adequate filtration of glucose and sufficient urinary delivery of drug compound to the luminal surface of renal proximal tubular cells, they are less effective in lowering glucose in people with reduced kidney function (eGFR <45–60 mL/min).

As with all newer agents for T2DM, their impact on cardiovascular complications of diabetes is also under study. Because they improve several cardiovascular risk factors (glucose, blood pressure, weight, and albuminuria) without inducing hypoglycemia, there was some anticipation of a benefit by some [107]. The first cardiovascular outcomes trial to report with this class was with epagiflozin (EMPA-REG OUTCOME) [108], in which 7020 participants with T2DM and overt CVD (mean age 63 years, HbA_{1c} 8.1%) were randomized to empagliflozin or placebo, on a background antihyperglycemia therapy. Glycemic control improved and there was a 1–2 kg weight loss and a reduction in systolic blood pressure of 2–3 mmHg in the active therapy groups. The primary cardiovascular outcome (3-point major adverse cardiovascular events) was reduced by 14% in the empagliflozin group (hazard ratio [HR] 0.86; 95% confidence interval [CI]: 0.74–0.99; $p = 0.038$). This appeared to be driven mainly by a reduction in CVD death of 38% (HR 0.62; 95% CI: 0.49–0.77; $p < 0.0001$). Heart failure hospitalization was reduced with empagliflozin (HR 0.65; 95% CI: 0.50–0.85; $p = 0.0017$), as was all-cause mortality (HR 0.68; 95% CI: 0.57–0.82; $p < 0.0001$). The cumulative incidence curves for each of the positive outcomes began to diverge at about 2–3 months, suggesting a rapid effect, unlikely to have been driven by glucose or attenuation of atherosclerosis. The mechanisms of the benefit remains unclear, but may partially relate to the drug's osmotic diuretic effect.

Several other large cardiovascular outcome trials with SGLT-2 inhibitors are currently under way, including CANVAS (using canagliflozin) and DECLARE (dapagliflozin).

The SGLT-2 inhibitors are mainly used in combination regimens with metformin [109] or other antihyperglycemic drugs, including insulin [31, 75, 95, 110], and rarely as monotherapy. Most are available in fixed-dose combinations with metformin or with DPP-4 inhibitors. According to the updated ADA–EASD position statement on the management of hyperglycemia in type 2 diabetes [34], they may be used in combination with virtually any other drug, although combined therapy with GLP-1RAs could not be endorsed due to lack of clinical trial reports at the time of publication (Figure 33.2).

Insulins

Insulin therapy is unique among all T2DM treatments because of its theoretically limitless ability to lower blood glucose concentrations and HbA_{1c}, restrained only by the development of hypoglycemia. Of all glucose-lowering therapies, insulin is associated with the highest rates of this complication, which in certain circumstances can be severe and life threatening. Other notable side effects include weight gain, which appears to correlate with the amount of HbA_{1c} lowering. Since most insulin products are injectables and have a relatively narrow therapeutic window, and a very wide range of possible dosages, significant patient education is required for effective and safe use. Modern disposable, prefilled pen devices have made the administration of insulin easier than with traditional vials and syringes. Recently, an inhaled insulin product for mealtime use has become available. Irrespective of the modality of administration, insulin therapy in general requires more frequent self-monitoring of blood glucose (SMBG) with home capillary blood glucose meters and comprehensive instruction regarding the detection, documentation, and treatment of hypoglycemic episodes.

An extensive discussion of the various insulin formulations and strategies is beyond the scope of this chapter (see Chapter 29). for more information.) Dose timing and frequency are generally

based on pharmacokinetic properties. For example, the longer acting basal insulin analogues (glargine, detemir, degludec) are administered once daily (detemir can sometimes require twice daily injections.) Rapid-acting insulin analogues (lispro, aspart, glulisine), with their fast onset and brief time course of action are optimally timed just before meals to prevent or minimize postprandial glucose excursions.

In T1DM, combination insulin therapy using the so-called "basal-bolus" approach comprises a basal insulin dose once or twice daily along with mealtime rapid-acting insulin three times daily. An increasingly popular alternative is an insulin pump (continuous subcutaneous insulin infusion [CSII]) to deliver both basal rates and mealtime boluses with a single insulin type, in almost all circumstances a rapid-acting analog. In T2DM, in contrast, the insulin deficiency is, by definition, relative and usually not profound, that is, some endogenous insulin secretion persists well into late stages of disease. As a result, many people who no longer respond to non-insulin therapies (e.g. oral glucose-lowering agents and/or a GLP-1RA injectable) will experience satisfactory control with a single injection of a basal insulin alone [111]. This strategy can be used alone, or more commonly with metformin, to blunt weight gain and minimize the insulin dose required [112, 113]. Other agents in addition to metformin can also be paired with insulin, but their continued use should take into account both complexity and cost, and in some circumstances side effects. The use of secretagogues with insulin has decreasing popularity, but thiazolidinediones, DPP-4 inhibitors, SGLT-2 inhibitors and GLP-1RAs are used appropriately [33, 34].

In T2DM, when basal insulin is no longer sufficient to achieve HbA_{1c} targets, the next step is *combination injectable therapy*. There are several choices here, as described in the updated 2012 ADA–EASD position statement on the management of hyperglycemia in type 2 diabetes (Figure 33.3). The simplest is to switch the basal insulin to a *premixed insulin*, typically dosed twice daily before breakfast and the evening meal [33]. These fixed combinations of intermediate and either short- or rapid-acting insulin provide some basal insulin with mealtime coverage at two meal sittings, with lunchtime coverage being omitted. The formulations available include 70:30, 75:25, and 50:50 ratios of intermediate to short- or rapid-acting insulin, depending on the specific product. Since the ratios are fixed, they are less flexible than in other insulin strategies.

A second approach is more complex but ostensibly more flexible and appropriate for those individuals who have the capacity to handle two separate insulins. This is the classical basal bolus approach as used in T1DM, with the option of less frequent (two per day) injections—sometimes referred to as "basal plus": a combination of a basal insulin once daily with coverage of the *main* meal (i.e. that of the highest caloric content) with a rapid-acting insulin [33]. The dose of the basal insulin is more or less fixed, but that of the mealtime insulin can be (and ideally should be) adjusted according to the planned carbohydrate content of the meal (more insulin for more grams), typically in ratios of 1 unit to 10–20 g of carbohydrate. The dose can also be adjusted to the premeal blood glucose reading, such as adding a "correction" amount of insulin to the calculated mealtime dose. For example, an additional 1–2 units can be administered for every 3 mmol/L (~50 mg/dL) starting at a threshold of 9 mmol/L (~150 mg/dL). A third adjustment is to the anticipated activity level after the meal (e.g. reducing by 25% if physical exertion is planned). Of course, not everyone is able to make these more complex treatment decisions safely. Therefore, many people administer bolus insulin therapy more simply with *fixed* doses, which is successful provided that the carbohydrate content is roughly equivalent from meal to meal and from day to day. As the individual on basal plus becomes familiar with mealtime insulin administration, if the HbA_{1c} remains above target, additional preprandial injections can be encouraged before other meals. Of course, the greater the number of injections the more likely it is there will be weight gain and hypoglycemic episodes (and also errors in dosing), and so a comprehensive educational program is mandatory for anyone proceeding to these more complex regimens.

A third and emerging approach to combination injectable therapy is the use of a GLP-1RA in conjunction with a basal insulin. A recent meta-analysis demonstrated as good glucose control with less hypoglycemia and, in contrast with most insulin therapy, with weight *loss* [81]. In selected individuals, this strategy may be not only successful but also simpler to conduct. Of course, there are substantial cost concerns. See below (Combinations with insulin) for more discussion about this specific combination strategy.

With regard to cardiovascular complications, the role of insulin therapy has been somewhat controversial, with evidence for both benefit and harm. This area is complex, particularly since endogenous hyperinsulinemia, classically apparent in obesity and raised insulin resistance, has been associated with increased cardiovascular events and mortality. From the UKPDS [2] and ORIGIN [114] trials, we have learned that insulin therapy in T2DM is either neutral or mildly beneficial towards macrovascular events. Importantly, however, hypoglycemia, which is itself associated with adverse cardiovascular outcomes, should be avoided as much as possible. Some have proposed that the evidently harmful effects of stringent glucose control in the ACCORD trial, involving older patients with long-standing T2DM at high cardiovascular risk, may have been related to unrecognized hypoglycemia [115, 116].

Minor classes

Beyond the major glucose-lowering drugs for T2DM described above, there are four additional categories that are used uncommonly, predominantely owing to relatively modest HbA_{1c} reductions, the need for frequent administration, lack of robust outcome trials, higher cost, and/or side-effect profile. They are generally used as niche agents, and may be considered in specific scenarios when other more popular agents cannot be used.

Meglitinides (or glinides)

Meglitinides (repaglinide, nateglinide) are rapid-acting insulin secretagogues that are occasionally used in lieu of sulfonylureas [117]. Their rapid onset and resolution of action result in better

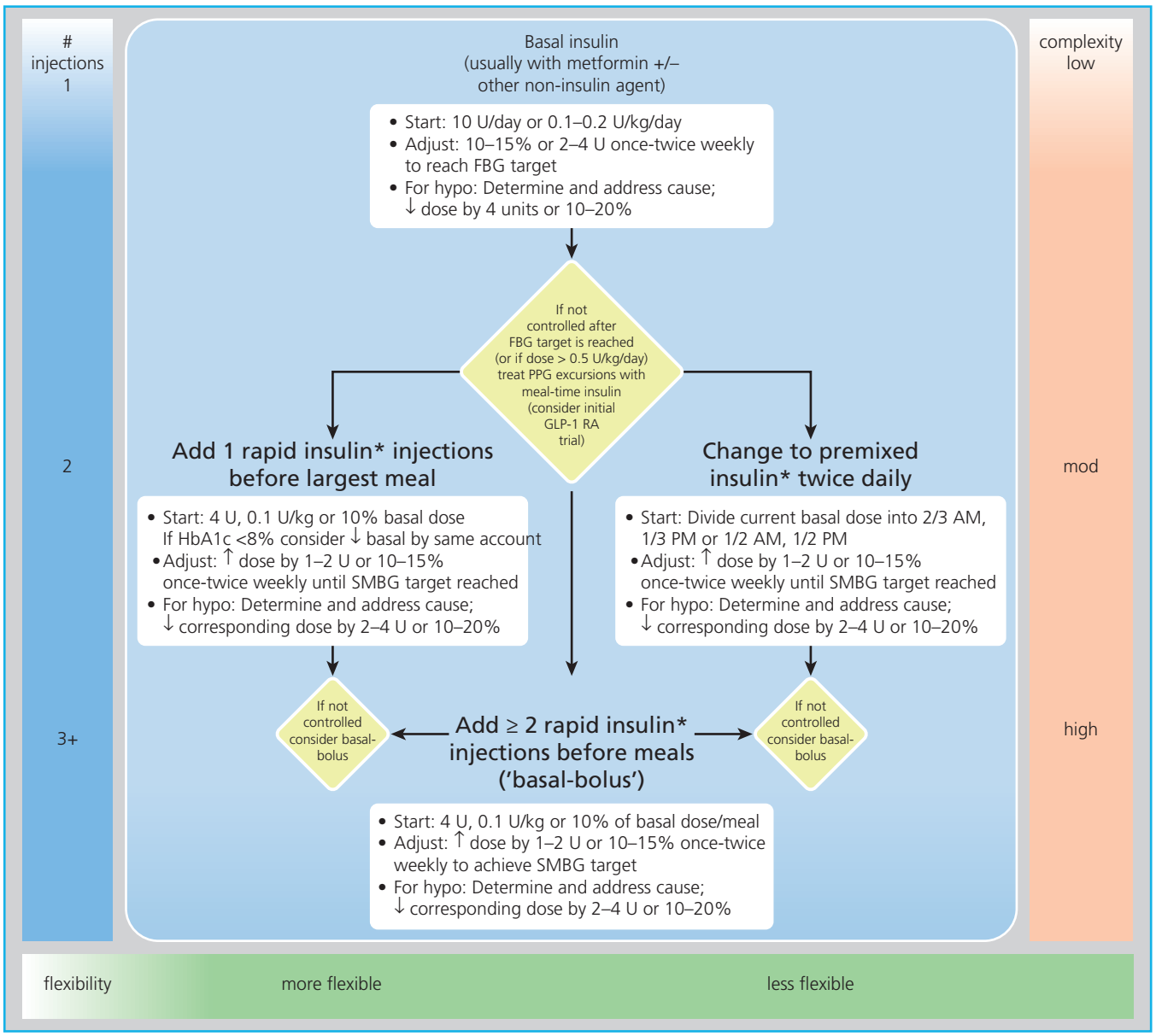

Figure 33.3 Insulin initiation and adjustment recommendations from the 2015 update to the ADA–EASD position statement on management of hyperglycemia in T2DM [34]. Sequential insulin strategies are described, with the number of injections and the relative complexity and flexibility of each stage presented. Basal insulin alone is the most convenient initial regimen, beginning at 10 units or 0.1–0.2 units/kg, depending on the degree of hyperglycemia. It is usually prescribed in conjunction with metformin and possibly one additional non-insulin agent. When basal insulin has been titrated to an acceptable fasting blood glucose but the HbA_{1c} remains above target, consider proceeding to combination injectable therapy (see Figure 33.2) to cover postprandial glucose excursions. Options include adding a GLP-1-RA, adding mealtime insulin, consisting of 1–3 injections of a rapid-acting insulin analog* (lispro, aspart or glulisine) administered just before eating, or switching to twice-daily premixed (or biphasic) insulin analog* (70:30 aspart mix, 75:25 or 50:50 lispro mix). Once any insulin regimen is initiated, dose titration is important, with adjustments made in both mealtime and basal insulins based on the prevailing blood glucose levels, with knowledge of the pharmacodynamic profile of each formulation used. Non-insulin agents may be continued, although sulfonylureas, DPP-4 inhibitors, and GLP-1RA are typically stopped once insulin regimens more complex than basal are utilized. In refractory patients, however, especially in those requiring escalating insulin doses, adjunctive therapy with metformin and pioglitazone or an SGLT-2-inhibitor may be helpful in improving control and reducing the amount of insulin required. Comprehensive education regarding self-monitoring of blood glucose, diet, exercise, and the avoidance of and response to hypoglycemia are very important in any insulin-treated patient. *Regular human insulin and human NPH-Regular premixed formulations (70:30) are less costly alternatives to rapid-acting insulin analogs and premixed insulin analogs, but their pharmacodynamic profiles makes them suboptimal for the coverage of postprandial glucose excursions. †A less commonly used and more costly alternative to basal bolus therapy with multiple daily injections is continuous subcutaneous insulin infusion (CSII, insulin pump.) ‡In addition to the suggestions provided for determining the starting dose of mealtime insulin under "basal-bolus," another method consists of adding up the total current daily insulin dose and then providing half of this amount as basal and half as mealtime insulin, the latter split evenly between three meals. Abbreviations: #, number; U, units; FBG, fasting blood glucose; hypo, hypoglycemia; PPG, postprandial glucose; GLP-1RA, GLP-1 receptor agonist; Mod., moderate; SMBG, self-monitoring of blood glucose. Source: Inzucchi et al. 2015 [34]. Copyright 2015 American Diabetes Association. Reproduced with permission.

postprandial control of blood glucose, but their overall efficacy is similar to that of the more traditional sulfonylureas. Nateglinide is somewhat weaker. These agents are not used commonly because of their need for frequent dosing, higher cost than generic sulfonylureas, and lack of any coherent evidence base. They can be used in a variety of combinations with other agents, having been studied predominantly in combination with metformin [118]. Meglitinides cannot, of course, be used in conjunction with sulfonylureas. They are associated with hypoglycemia and weight gain, but possibly to a lesser extent than the longer-acting sulfonylureas. They might be considered in people with erratic meal schedules.

α-Glucosidase inhibitors

The α-glucosidase inhibitors (acarbose, miglitol, voglibose) retard carbohydrate absorption by inhibiting the breakdown of disaccharides and polysaccharides in the proximal small bowel, thereby damping postprandial glucose excursions [119]. These drugs remain more popular in East Asian countries than in the rest of the world. Particularly at higher doses and during initial drug titration, they are associated with substantial gastrointestinal side effects, such as flatulence and diarrhea. These result from distal colonic delivery of undigested carbohydrates. The α-glucosidase inhibitors do not by themselves increase the risk of hypoglycemia. They have been tested mainly in conjunction with metformin, sulfonylureas, and insulin [120–122]. Their HbA_{1c}-lowering efficacy is generally low, in the 0.5% range. They could be considered in people with very mild hyperglycemia whose glucose profiles indicate predominately postprandial hyperglycemia.

Bile acid sequestrants

Although its mechanism of action on glycemia is poorly understood, colesevelam, an older cholesterol-lowering drug that binds intestinal bile acids, is approved as a glucose-lowering agent [123]. A modest antihyperglycemic effect (HbA_{1c} –0.5%) has been demonstrated. This class has been associated with constipation and may increase circulating triglyceride levels. They have been studied either as monotherapy or in combination with metformin [124]. One additional benefit is a modest reduction in low-density lipoprotein cholesterol (LDL-C). They might be considered in people requiring a small reduction in HbA_{1c} whose LDL-C is in need of additional lowering without other options (e.g. statin intolerant).

Dopamine-2 agonists

A quick-release form of the dopamine-2 agonist bromocriptine is now available as an antihyperglycemic agent [125]. The drug is usually used in people with hyperprolactinemia from pituitary neoplasms. The HbA_{1c}-lowering capacity is in the 0.5% range. It may exert its metabolic effect through the daily resetting of hypothalamic centers that appear to modulate peripheral insulin sensitivity. Side effects include nausea, fatigue, dizziness, and headache. It has not been extensively studied with specific other treatments and is rarely used.

Amylinomimetics

Amylin is an islet-derived peptide that is co-secreted with insulin. Its apparent physiological role is to suppress glucagon secretion and delay gastric emptying. The amylin receptor agonist pramlintide is an injectable pharmacological agent that is used infrequently but mainly in people with T1DM [126]. It is even less commonly employed in those with T2DM. Pramlintide requires dosing three times per day with meals and its glucose-lowering effect is modest, typically in the 0.5% range. Pramlintide is associated with nausea and vomiting but also weight loss. It may be considered in insulin-requiring individuals who cannot otherwise gain control of postprandial glucose levels, especially if gaining weight. It has not been extensively studied in T2DM in combination with other therapies.

Combination therapy: uses and evidence

In people with T2DM, hyperglycemia tends to progress over time, the result of worsening β-cell function and further decrements in insulin secretory capacity. As a result, most people are not able to maintain adequate glucose control with one agent alone. The value of using medications with complementary mechanisms in combination, thereby targeting different aspects of the disease's complex pathogenesis, is now a standard therapeutic approach and serves three practical purposes:

1 to lower blood glucose to a greater extent than with monotherapy;
2 to allow for lower doses of drugs to minimize their side effects;
3 to use the benefits of one drug to counterbalance the adverse effects of another.

The *first* purpose is to lower blood glucose to a greater extent with two (or three) drugs than can be accomplished with a single agent. This additive effect can be demonstrated with either initial combination therapy (i.e. starting with two drugs from the original prescription) or with sequential therapy, a second drug added to the first after initial failure to lower blood glucose to the extent required or after the first agent fails over time to maintain blood glucose in the targeted range [33, 34]. For example, a person with a baseline HbA_{1c} of 7.9% might respond well to metformin initially, with HbA_{1c} decreasing to 6.7%. The HbA_{1c} might subsequently climb above the targeted range (e.g. to 7.4%) over a period of 2 years. In this circumstance, adding a second agent (i.e. sulfonylurea, thiazolidinedione, DPP-4 inhibitor, SGLT-2 inhibitor, GLP-1RA or basal insulin [see Guidelines, below]) would reduce glucose levels, allowing the individual to attain the HbA_{1c} goal once again. A related scenario would involve a person with a starting HbA_{1c} of 9.2%, which was reduced to 7.7% with metformin monotherapy, and who then requires a second agent to achieve an HbA_{1c} of <7%. This individual, of course, could also have been treated with both metformin plus the second agent from the outset (see Initial combination therapy, below.)

The *second* purpose of combination therapy is to allow for lower doses of each component, in an effort to minimize side effects

or to lessen the cost of a more expensive, branded medication. An example would be someone who experiences protracted diarrhea each time they exceed a metformin dose of 1000 mg. With an HbA_{1c} of 7.5%, this person could perhaps achieve glycemic targets with a higher dose of metformin were it to be tolerated. Instead, a second agent could be added to allow the achievement of the glycemic goal. Another example is an individual already on a full dose of metformin (2 g) and a moderate dose of pioglitazone (30 mg) who is close to but not at their target (e.g. last HbA_{1c}, 7.3%). Each time the pioglitazone is increased to 45 mg, the person develops edema. In this circumstance, an alternative strategy would be the addition of a third agent, while maintaining the pioglitazone at the lower dose.

The *third* potential purpose of combination therapy is for one agent to counteract directly the side effects of another. For example, people often gain weight after basal insulin is added to the glucose-lowering regimen. The addition of metformin, a GLP-1RA, or an SGLT-2 inhibitor (with perhaps a concurrent reduction in the insulin dose) might attenuate weight gain [33, 34, 112, 113]. A similar strategy could be considered if weight gain occurred with the addition of a thiazolidinedione. Theoretically, an SGLT-2 inhibitor could also be used to counteract edema from a thiazolidinedione. Of course, the clinician should strive to make the therapeutic regimen as simple and as cost-effective as possible, and simply abandoning the agent that is leading to adverse effects should also be strongly considered.

The evidence basis

Most of the available antihyperglycemic agents for T2DM have been shown to have additional efficacy when used in combination with each other, with the exception of two insulin secretagogues (i.e. sulfonylurea plus meglitinide) and two incretin enhancers (i.e. DPP-4 inhibitor plus GLP-1RA). The most commonly studied combination is that with metformin [27, 48–51, 71, 112, 113], owing to its widely viewed role as foundation pharmacological therapy for this condition. Most glucose-lowering drugs have also been tested in conjunction with sulfonylureas [27–32], thiazolidinediones [48, 71–76], and insulin [32–34, 76, 81, 112, 113]. SGLT-2 inhibitors have also been assessed in conjunction with DPP-4 inhibitors [95]. In the majority of these clinical trials, typically conducted in phase III of drug development, the added benefit on HbA_{1c} is equivalent to or somewhat slightly less than the efficacy of that drug when used as monotherapy. The reader is referred to two excellent reviews on this topic [127, 128].

In the past, few studies examined long-term clinical outcomes of combination therapy, such as durability of glycemic control or the effect on micro- and/or macrovascular complications. Since 2009, however, in an effort to guarantee drug safety, the US Food and Drug Administration (FDA) and the European Medicines Agency (EMA) have mandated large cardiovascular outcome trials before or soon after regulatory drug approval [84, 129]. Their methodologies have focused on ensuring that MACE are not *increased* when the drugs are used on the backdrop of other glucose-lowering therapies. Most, however, have not contrasted MACE between the study drug and another. One exception is the aforementioned CAROLINA, which will assess the relative cardiovascular effects of the DPP-4 inhibitor linagliptin versus glimepiride [101]. A second is GRADE, funded by the US National Institutes of Health [130] (see Future research, below). In summary, there is a paucity of prospective long-term randomized trials that might inform treatment decisions as to which combinations are better than others on issues beyond glucose-lowering efficacy and adverse effects.

This was the conclusion of an important meta-analysis by Bennett et al., who examined 140 randomized clinical trials and 26 observational studies and compared the efficacies and relative side effects of six antihyperglycemic drug classes both in monotherapy and in dual combination regimens in T2DM [131]. The medication categories were metformin, sulfonylureas, meglitinides, thiazolidinediones, DPP-4 inhibitors, and GLP-1RAs. The authors concluded that most of agents lowered HbA_{1c} by ~1% whether used as monotherapy or in two-drug combinations. They found minor differences in efficacy, with metformin having more powerful effects than DPP-4 inhibitors on HbA_{1c}. Metformin therapy also demonstrated a mean difference in body weight of −2.5 kg compared with sulfonylureas or thiazolidinediones. Metformin treatment was also associated with a beneficial effect on LDL-C when compared with pioglitazone, sulfonylureas, and DPP-4 inhibitors. Sulfonylurea therapy was associated with a more than fourfold greater risk of hypoglycemia than metformin. Thiazolidinediones increased the risk of heart failure compared with sulfonylureas and were associated with bone fractures compared with metformin. However, there was insufficient evidence regarding important long-term clinical outcomes such as mortality, CVD, and microvascular complications such as nephropathy and neuropathy.

Combination therapy: specific strategies

Dual combination therapy

Most glucose-lowering drug categories can be combined with any other, owing to their distinct and complementary actions. Dozens of clinical trials have demonstrated HbA_{1c}-reducing benefit from combining agents in dual combinations. In the USA, FDA-approved prescribing labels no longer endorse specific drug combinations, but now provide broader indications for a specific medication "as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus," the implication being that the drug may be used either as monotherapy or in combination with other glucose-lowering drugs. Certain combinations are widely viewed as particularly effective, such as combinations that target the opposing defects of impaired insulin sensitivity (e.g. metformin, thiazolidinediones) paired with drugs that augment deficient insulin secretion (sulfonylureas, DPP-4 inhibitors, GLP-1RAs). However, even combinations that focus on insulin sensitivity alone (metformin plus a thiazolidinedione)

or insulin secretion (sulfonylurea plus an incretin enhancer) have been shown to be efficacious.

The first major trial to assess the value of dual combination therapy was by DeFronzo and Goodman, who studied 788 participants not adequately controlled with the sulfonylurea glyburide as monotherapy [27]. Study participants were randomized to three arms (continued glyburide alone, switched to metformin monotherapy, or combined glyburide–metformin) and followed for 29 weeks. There was no difference in either fasting glucose or HbA_{1c} between the first two groups. In the combination group, however, a notable decrease in glycemic variables occurred, with a 63 mg/dL decrease in fasting glucose and a 1.7% fall in HbA_{1c}. In a second, much smaller study, Inzucchi et al. tested the effect of combining metformin and troglitazone—an early thiazolidinedione (Figure 33.4) [71]. Whereas the combination of metformin and a sulfonylurea was expected to have greater efficacy than either drug in monotherapy, there was clinical equipoise as to whether combining two drugs that addressed insulin resistance would behave similarly. Both drugs reduced glucose to a similar extent in 29 participants who were withdrawn from their baseline therapy and randomized to one of the two medications. This was mediated through distinct mechanisms, with metformin predominantly reducing hepatic glucose production and troglitazone mainly increasing peripheral glucose disposal. These complementary actions result in a further reduction in HbA_{1c} of 1.2% when the drugs were combined for an additional 3 months. Hence these two insulin-sensitizing drugs appeared to be useful in combination, as had already been demonstrated with metformin and glyburide in the earlier study.

With the advent of the DPP-4 inhibitors, the GLP-1RAs and the SGLT-2 inhibitors, initial clinical trials required for drug approval have routinely tested the agents not only as monotherapy but also in combination with metformin, in addition to, in most cases, sulfonylureas or thiazolidinediones. More recently, the combination of DPP-4 inhibitors with SGLT-2 inhibitors has been studied. Not surprisingly, each combination proved more powerful than either single drug alone.

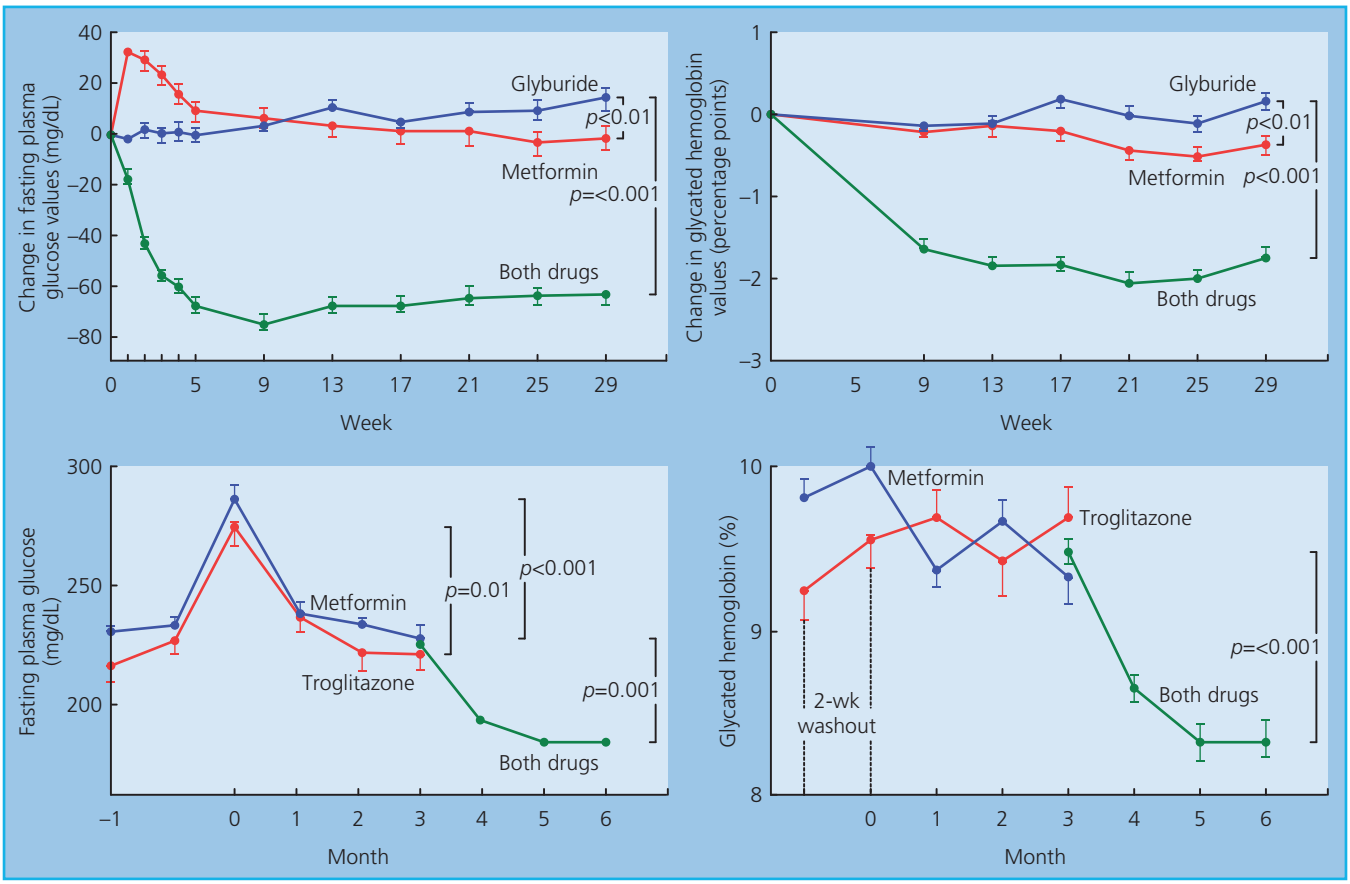

Figure 33.4 Glucose lowering effects from (a,b) adding metformin to baseline glyburide, and (c,d) from combining metformin with a thiazolidedione. (a,b) In people with T2DM who were suboptimally controlled on maximal dose glyburide, continuation of the sulfonylurea resulted in no improvement. Similarly, a switch from glyburide to metformin had no benefit. Instead, when metformin was added to glyburide, patients experience a significant lowering of both fasting glucose and HbA_{1c}. This study exemplifies the general principle that adding agents in combination is preferable to switching one agent for another. Source: Based on Defronzo RA, Goodman AM. *N Engl J Med* 1995; 333:541-549. (c,d) In a small trial, the addition of troglitazone to metformin (and vice-versa) resulted in further significant lowering of fasting glucose and HbA_{1c}. This study underscored the benefits of using drugs with complementary mechanisms of action in combination. Source: Inzucchi et al. 1998 [71]. Copyright 1998 Massachusetts Medical Society. Reproduced with permission.

Triple combination therapy

Although the evidence base is not as extensive, several trials have now clearly documented the additional benefit of three drugs in combination versus baseline therapy using two drugs [132–134]. Of course, side effects and cost must be a major consideration as more complex diabetes regimens are contemplated. Therefore, strong consideration at this juncture should be given to the use of insulin, which has less of an efficacy "ceiling" than other drugs.

Combinations with insulin

An older combination strategy dates back to the time before the widespread availability of metformin: insulin injections paired with an sulfonylurea. Although not an intuitively obvious combination, some people with T2DM who had progressed to insulin requirements do maintain a degree of pancreatic β-cell function. It should also be considered that endogenous insulin has the advantage over exogenous insulin of being secreted in the portal vein, thereby allowing for better control of hepatic glucose production. At this time, the concept of "bedtime insulin–daytime SU" had gained popularity in those people who were no longer responding adequately to sulfonylurea monotherapy [135]. The insulin injected at night was of intermediate duration (i.e. insulin NPH or Lente) to control overnight and fasting hyperglycemia, and the secretagogue was administered in the morning in order to control daytime glucose levels. The additional benefit to glucose control was slight, and the strategy was never properly compared with aggressive insulin titration using multiple daily injections. More recent analyses of the sulfonylurea–insulin paired strategy suggest that it is associated with more hypoglycemia than insulin alone [136]. As a result, and with the advent of additional categories of oral agents, this specific combination has become less popular.

Several other combinations with insulin, particularly using a single injection of a basal insulin, have emerged over the past two decades. The most popular is with metformin. The first indication for a thiazolidinedione was in combination with insulin, with trials showing that the addition of a thiazolidinedione to baseline insulin therapy also improved HbA_{1c} and allowed for a reduction in the insulin dose, the latter to a greater extent than with metformin [137]. However, the thiazolidinedione–insulin pairing was also found to increase the likelihood of weight gain and edema and the risk of heart failure. Accordingly, when used, the thiazolidinedione should be started at the lowest dose with careful titration and clinical follow-up. Both DPP-4 and SGLT-2 inhibitors provide a modest additional HbA_{1c} lowering effect when added to insulin [138, 139]. Most drugs, despite not being associated with hypoglycemia as monotherapy, may still increase the risk of hypoglycemia when added to insulin. However, this effect is probably no greater than would be observed had the insulin dose been titrated to the same HbA_{1c} target. Nonetheless, if the HbA_{1c} is close to target, consideration should be given to lowering the insulin dose by 10–20% upon initiation of adjunctive therapy.

A more recent insulin combination gaining in popularity is that with a GLP-1RA. An important meta-analysis by Eng et al. found that this strategy was associated with a mean change in HbA_{1c} of –0.44% (95% CI: –0.60 to –0.29) compared with the comparator groups, in which other drugs were added to achieve glycemic control [81]. Notably, this was achieved with a mean loss of 3.22 kg (95% CI: 4.90–1.54). In addition, a handful of clinical trials had compared the addition of a GLP-1RA to basal insulin with the standard "basal bolus" insulin approach of adding three injections of a mealtime rapid-acting insulin analog. It was found that the HbA_{1c} was slightly lower with the GLP-1RA (0.10%; 95% CI: –0.17 to –0.02), and this was achieved with weight loss instead of weight gain (mean difference –5.66 kg; 95% CI: –9.80 to –1.51 kg) and with less hypoglycemia risk (RR 0.67; 95% CI: 0.56–0.80) [81]. Given the once-daily or even once-weekly injection frequency of most of the GLP-1RAs available and less need for glucose monitoring, using this approach instead of adding multiple daily injections of insulin before meals may be more convenient for patients. Of course, this comes with a higher cost, depending on the insulin dose required.

Is combination therapy synergistic?

Conceptually, two drugs with complementary mechanisms of action could have synergistic effects, that is, resulting in a better glycemic response than the sum of the responses to each drug individually. In fact, when drugs are added, HbA_{1c} reductions tend to be somewhat less robust than one might predict from the reported efficacy with the individual components in monotherapy. This phenomenon may result from the well-described reduced glycemic reduction at lower baseline HbA_{1c} levels [140]. Irrespective of the reason, no drug combination has demonstrated true synergism. Instead, drugs are said to have additive or complementary effects.

Early versus sequential combination therapy

Traditionally, people with T2DM are prescribed a glucose-lowering agent, which is then titrated to the maximally tolerated dose and, if glucose levels are not adequately controlled, a second drug is added. However, some have proposed that, owing to the multiple pathophysiological defects of the disease, two drugs should be prescribed at the initiation of therapy [6, 141]. Several studies have in fact demonstrated the quicker achievement of the HbA_{1c} target using two instead of one drug in drug-naïve individuals over a relatively short term of 3–6 months [142, 143]. It would be fairly likely that the usual sequential approach would achieve an equivalent HbA_{1c} reduction after 1 year as with initial combination therapy. Given the chronic nature of diabetes, the more rapid attainment of a glycemic goal may have little advantage. If the clinician predicts, based on the baseline HbA_{1c} level, that the target is unlikely to be achieved with one drug, initial combination therapy is reasonable. Initial monotherapy, followed by a combination, also has the advantage of being able to discern which potential side effect is attributable to which agent. However, the side effect profiles of glucose-lowering agents are reasonably distinct, so this is rarely a problem with combination therapy.

One controversial strategy that has been proposed is "triple combination" therapy at diagnoses, i.e. treating all people

initially with the combination of metformin, pioglitazone, and a GLP-1RA [6]. The goal is to address each of the fundamental pathophysiological derangements associated with T2DM, namely excess hepatic glucose production (with metformin), decreased insulin sensitivity in skeletal muscle (with pioglitazone), and insufficient insulin secretion and excess glucagon secretion (with the GLP-1RA). In a small, randomized trial that had significant methodological limitations, investigators compared this strategy (metformin–pioglitazone–exenatide) with the conventional approach of metformin followed sequentially by glyburide and insulin glargine in 249 drug-naïve, recently diagnosed individuals [144]. From a baseline of 8.6%, the investigators found that those randomized to triple therapy achieved a significantly better HbA_{1c} (5.95 vs. 6.50% with conventional therapy; $p < 0.001$). Moreover, the treatment goal of HbA_{1c} <6.5% was not achieved in significantly more conventional therapy participants (44 vs. 17% in the triple therapy group; $p = 0.003$.) Triple therapy participants also experienced 7.5 times fewer hypoglycemic events (all mild). Finally, the between-groups weight difference was 5.3 kg in favor of triple therapy. The study, however, had a high dropout rate in both arms, presenting interpretive challenges. Also, the sulfonylurea chosen in this trial was one associated with the greatest risk of hypoglycemia. One conclusion that could be made from this study is that the traditional sequential approach resulted in fairly good glycemic control, albeit at some cost of hypoglycemia and weight gain. Accordingly, it remains unclear if such an initially more complex and expensive triple therapy approach is warranted in such mildly hyperglycemic individuals.

Fixed-dose combinations

For at least 15 years, beginning with metformin–sulfonylurea pairings, two glucose-lowering drugs have been available as so-called "fixed-dose combination" (FDC) tablets. These provide additional convenience for people, who are often on multiple tablets for a variety of other conditions, such as hypertension and dyslipidemia. The combinations may also make drug errors less likely. The clinician should take care to prescribe the most cost-effective medicinal regimens and this may not necessarily be in the form of these FDCs, since generic constituents of these therapies are often available as less expensive products. As with all aspects of diabetes care, individualization is key. The practitioner and office staff must also be cautious during medication reconciliations, since many of the FDC tablets have trade names very similar to those of the parent compounds (see Table 33.2).

Guidelines

Combination therapy played a prominent role in the 2012 ADA–EASD position statement on the management of hyperglycemia in type 2 diabetes, which was updated in 2015 [33, 34]. This statement, as have other sets of recommendations from various professional societies, emphasized the role of lifestyle changes and also the fundamental role of metformin as initial monotherapy. Beyond metformin, if glycemic control remained suboptimal, the statement endorsed the use of one of six potential therapies to be used in combination with metformin (Figure 33.2): sulfonylureas, thiazolidinediones (specifically, pioglitazone), DPP-4 inhibitors, SGLT-2 inhibitors, GLP-1RAs, and basal insulin. The specific choice depends on a variety of factors, including cost, side-effect profile, comorbidities, and anticipated additional benefits in that individual. Reassessment of the quality of glycemic control should be undertaken every 3 months with intensification of therapy made at that interval. After dual combination therapy, if an additional glucose-lowering effect was required, a third agent from one of the aforementioned classes could be used, although basal insulin becomes an increasingly important constituent of the treatment regimen. In those situations where additional glucose-lowering is necessary, the position statement suggested proceeding to combination injectable therapy, either basal bolus insulin or basal insulin with a GLP-1RA (Figure 33.3).

Other published T2DM treatment guidelines that deal with the issue of combination therapy include those from the National Institute for Health and Care Excellence (NICE) in the UK [145], the International Diabetes Federation (IDF) [146], the American College of Physicians (ACP) [147], and the American Association of Clinical Endocrinologists (AACE) [148]. These guidelines differ to some extent based on the intensiveness of glucose control and which specific drugs to add in sequence, but, similarly to the ADA–EASD position statement, generally they focus on several key points:

1 Lifestyle changes are an important component of therapy.
2 Start drug therapy with metformin.
3 Add another oral or injectable agent if metformin monotherapy is insufficient to control glucose.
4 Move towards insulin therapy alone or in combination with other agents if glucose remains controlled.
5 Avoid "glucocentricity": treat blood pressure (favor angiotensin-converting enzyme inhibitors or angiotensin II receptor blockers and lipids (with statins) aggressively, and use antiplatelet therapy where indicated.

Future research needs

There is a paucity of comparative effectiveness research on long-term clinical outcomes with glucose-lowering therapies used in combination in T2DM. Most clinical trials are relatively brief (6–12 months) and focus on glycemic reductions alone after metformin monotherapy. As noted above, since 2009, pharmaceutical companies have been mandated to present cardiovascular safety data prior to or shortly consequent on new drug approval. This necessitates the conduct of large cardiovascular safety trials from which extensive safety data emerge. Unfortunately, the typical methodology of these investigations is to add the compound in question upon a variety of backdrop antihyperglycemic therapies, including a variety of oral agents and insulin. Hence these trials

can determine the safety and potential effectiveness of a strategy involving a particular drug, but cannot in general compare clinical outcomes of that agent with those of another agent of a different class. One exception is CAROLINA, which is assessing cardiovascular and other outcomes between a specific DPP-4 inhibitor and a sulfonylurea [101]. Another major ongoing clinical trial, GRADE, is a comparative effectiveness study, examining the relative effects of four common strategies added to metformin, when the latter is no longer controlling blood glucose adequately: a sulfonylurea (glimepiride), a DPP-4 inhibitor (sitagliptin), a GLP-1RA (liraglutide), or basal insulin (glargine) [148]. The primary outcome is time-to-treatment failure, and so GRADE is essentially a durability study. However, a variety of secondary outcomes are planned, including micro- and macrovascular complications and adverse effects and other safety measures.

Conclusions

Combination therapy is a method commonly used in the management of individuals with T2DM, mainly out of necessity, given the inadequacy of most individual therapies over time. Newer strategies, however, have focused on earlier use of combinations, particularly in those with higher HbA_{1c} values at baseline. There are few data to inform the clinician about the preference for one drug over another after metformin monotherapy, although recently reported cardiovascular benefits with empagliflozin, especially if confirmed with other SGLT-2 inhibitors, may result in a reordering of drug choices, at least for people with established CVD and/or heart failure. The ultimate choice of drug, however, should rely on a comprehensive assessment of expected drug efficacy, side-effect profiles including contraindications, additional benefits, and cost. Recently, the wide availability of fixed-dose combinations has made combination therapy easier for patients. Finally, newer strategies of GLP-1RA plus basal insulin is an emerging strategy in selected individuals with T2DM who would normally require mealtime injections of rapid-acting insulin to attain control.

The future is also likely to yield new devices for improving drug delivery and the long-acting nature of new drugs is likely to transform our approach to therapy. We still cannot reverse β-cell failure, although our developing understanding of the β cell and its pathology may yield a solution even to this, the most pressing of our therapeutic hopes.

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34 In-Hospital Treatment and Surgery in People with Diabetes

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Key points

- The numbers of inpatients with diabetes continues to increase.
- Hyperglycemia (in particular in those people who were not known to have diabetes prior to hospital admission or those experiencing "stress hyperglycemia") and hypoglycemia are associated with increased levels of harm, using whatever measure is chosen.
- Levels of knowledge among heathcare staff remain poor, and levels of satisfaction among inpatients with diabetes remain low.
- The importance of the early involvement of the diabetes inpatient specialist team is stressed as being an important factor in the education of patients and staff.
- A number of national and international guidelines are now available to help teams manage this increasingly complex cohort of patients, aiming to achieve suitable glycemic control, avoiding symptomatic hyperglycemia or debilitating hypoglycemia.

Introduction

Known diabetes in hospital

The prevalence of diabetes in the general population of Western Europe is in the region of 6–7%, and is expected to rise significantly over the next 20–30 years [1]. The prevalence of diabetes in other parts of the world is much higher; in the United States it is reported to be between 9.3 and 10.9% [1, 2]. It has been recognized that having diabetes more than doubles the risk of being hospitalized for any given condition [3], which is reflected in the high prevalence of diabetes in hospitalized patients. Data from the 2015 UK National Diabetes Inpatient Audit (NaDIA) showed that the prevalence of hospital inpatients with diabetes ranged from 4% to over 35% [4]. Previous work has shown that people with diabetes have a longer length of hospital stay and higher mortality rates than those without the condition [5]. This translates to greater costs. In the United Kingdom, it has been estimated that diabetes accounts for over 10% of the entire budget of the National Health Service (NHS), with the excess costs of inpatients with diabetes equating to between £573 million and £686 million per annum [6]. In the USA, data suggest that in 2012, 20% of the health budget was spent on diabetes, equating to $245 billion, with over 40% of this being attributed to direct inpatient costs [7].

Undiagnosed diabetes and stress hyperglycemia in hospital

In addition to the admissions of people who are known to have diabetes prior to admission, a number of people with hyperglycemia are admitted without a prior diagnosis of diabetes. These include those people not previously known to have diabetes but who continued to have it after they were discharged. However, some patients may develop transient hyperglycemia (a fasting glucose level of >7.0 mmol/L, 126 mg/dL or a random blood glucose level of >11.1 mmol/L, 200 mg/dL) during their inpatient stay that normalizes after discharge—so-called stress hyperglycemia [8, 9]. Taken together, the number of people in hospital with either diabetes or transient hyperglycemia is very large, with observational data indicating a prevalence of between 32 and 38% on general wards [10, 11] and between 28 and 80% of patients with critical illness or undergoing cardiac surgery [11–13].

Pathophysiology of hyperglycemia in acute illness

In healthy individuals who are fasting, glucose levels are usually maintained between 3.9 and 5.6 mmol/L (70 and 100 mg/dL). Levels are finely controlled to match appropriately endogenous glucose production from the liver (and to a lesser extent the

Textbook of Diabetes, Fifth Edition. Edited by R. Holt, C. Cockram, A. Flyvbjerg and B. Goldstein.

kidneys) and glucose utilization by peripheral tissues [14–16]. The glucose levels are controlled by the balance of insulin and the counter-regulatory hormones, glucagon, catecholamines, growth hormone, and cortisol. At relatively low levels, insulin is a potent inhibitor of lipolysis, free fatty acid oxidation, and ketogenesis. As insulin concentrations increase, glucose levels decrease first by inhibiting hepatic gluconeogenesis and glycogenolysis, and then by increasing peripheral glucose uptake and promoting glycogen synthesis. At even higher concentrations, insulin prevents protein breakdown. Finally, at the highest doses, insulin is an anabolic hormone, promoting skeletal muscle formation [17, 18].

Hyperglycemia develops as a result of an imbalance between the glucose-lowering effect of insulin and the counter-regulatory response. Hyperglycemia occurs by three processes: increased gluconeogenesis, accelerated glycogenolysis, and impaired glucose utilization by peripheral tissues [19]. Of these, the first two constitute the major contribution to hyperglycemia. Skeletal muscle breakdown leads to an increased delivery of gluconeogenic precursors in the form of amino acids. Fat breakdown leads to an increased level of free fatty acids delivered to the liver. These effects may be exacerbated by prolonged starvation in the perioperative period. In people without diabetes, a compensatory increase in insulin secretion helps to mediate against these catabolic effects. Without the glucose-lowering effects of insulin, the activity of gluconeogenic enzymes, in particular phosphoenolpyruvate carboxykinase, fructose-1,6-bisphosphatase, and pyruvate carboxylase, is also increased [16, 20]. During times of illness or stress, the increased levels of counter-regulatory hormones alter carbohydrate metabolism by inducing insulin resistance, increasing hepatic glucose production, and reducing peripheral glucose utilization [8, 9]. A major consequence of severe hyperglycemia is osmotic diuresis accompanied by dehydration and electrolyte disturbances (in particular sodium, potassium, magnesium, and phosphate). This increased osmolality leads to a pro-coagulant state. In addition, hyperglycemia results in raised levels of inflammatory cytokines and markers of oxidative stress such as tumor necrosis factor α, interleukin (IL)-6, IL-1β, and IL-8, and C-reactive protein [21, 22]. These pro-inflammatory cytokines have been shown to be associated with the development of insulin resistance by interfering with intracellular pathways, downstream of the insulin receptor [21, 23, 24]. Furthermore, levels fall when the glucose concentrations return to normal [21].

There are other causes of hyperglycemia, which may be more specifically related to the hospital admission [25]. These include co-administered medications such as corticosteroids, although a guideline from the Joint British Diabetes Societies (JBDS) Inpatient Care Group in the UK now exists to help tackle this issue [26].

Evidence of harm from in-hospital hyperglycemia and effect of glucose lowering

Prior to the publication of large, randomized controlled trials in the 1990s, it had been well recognized that poor diabetes control in ambulatory people with either type 1 or type 2 diabetes was associated with poor outcomes. It was only with the publication of the DCCT [27] and UKPDS [28] study results that it was shown that interventions to improve glycemic control maintained over many years were associated with improved outcomes. In the world of inpatient diabetes, there is compelling evidence that high blood glucose levels are associated with higher in-hospital morbidity and mortality, prolonged length of stay, unfavorable post-discharge outcomes, and significant excess healthcare costs in medical and surgical specialities [10, 29–32]. Umpierrez et al. showed that patients with new hyperglycemia had a striking 18-fold increase in in-hospital mortality, whereas patients with known diabetes had a 2.7-fold increase in in-hospital mortality, compared with people with normoglycaemia [10]. In 2004, a joint position statement from the American College of Endocrinology (ACE) and the American Association of Clinical Endocrinologists (AACE) on inpatient diabetes and metabolic control concluded that hyperglycemia in hospitalized patients is a common, serious, and costly healthcare problem. There was a strong recommendation for early detection of hyperglycemia and an aggressive management approach to improve outcomes [3]. In the UK, the JBDS have produced a series of guidelines on managing various aspects of inpatient diabetes care, which also recommend aggressive glucose control [26].

For surgical patients, there are data to show that hyperglycemia in the perioperative period is associated with poor outcomes in several surgical specialities [31–33]. These can be measured as a variety of outcomes, such as length of hospital stay, development of urinary tract infections, surgical site infections, time in the intensive care unit (ICU), and mortality. The reasons for these adverse outcomes are multifactorial, but include failure to identify patients with diabetes and/or hyperglycemia [34, 35]; multiple comorbidities, including microvascular and macrovascular complications [36–42]; complex polypharmacy and insulin prescribing errors [43]; increased perioperative and postoperative infections [32, 44, 45]; associated hypoglycemia and hyperglycemia [32]; lack or inadequate institutional guidelines for management of inpatient diabetes and/or hyperglycemia [32, 46]; and inadequate knowledge of diabetes and hyperglycemia management among staff delivering care [47].

There are also data to show that having a diagnosis of diabetes prior to having surgery is associated with a lowering of risk [31], despite having a high glucose level. Hence the knowledge that a individual has diabetes is somehow protective. It may well be that people with diabetes have more attention paid to them, and thus have more contact with nursing and medical staff, which may mean that postoperative problems are picked up sooner. What remains to be determined is whether it is the high glucose level per se that causes the increased harm, or whether the high glucose is a marker for underlying disease severity.

Whereas there are reasonably robust data showing that high perioperative glucose levels are associated with harm, data showing an association with high preoperative HbA_{1c} are currently lacking [48]. There have been very few good-quality prospective

observational studies in the area of preoperative glycemic control, as measured by HbA_{1c}, as a predictive factor of postoperative morbidity and mortality. Recent work has suggested that risks increase when preoperative HbA_{1c} is >64 mmol/mol (8%), and the UK JBDS guideline also recommends a preoperative level of <69 mmol/mol (8.5%) [33].

Disappointingly, to date, despite the findings that high glucose levels are associated with harm for medical and surgical patients, except for a very few clinical specialities such as cardiac surgery, any convincing evidence to show that achieving good glycemic control while an inpatient is associated with improved outcomes remains to be forthcoming [49].

Glycemic targets for hospitalized inpatients

It has been recognized that hypoglycemia is associated with increased morbidity and mortality [50]. To reduce the impact of hypoglycemia, there is a general consensus that glucose levels should not be allowed to fall below 4.0 mmol/L (72 mg/dL). However, given the lack of robust data showing that aggressive glucose lowering helps reduce the excess morbidity and mortality associated with hyperglycemia, it has been difficult to reach an agreed consensus on what the target glucose levels should be in the hospitalized inpatient. Different targets have been suggested for different categories of patient, e.g. those on the ICU compared with those on a general ward, or those due to undergo surgery.

The intensive care unit (ICU)

A lot of work has been carried out to try to establish the level of glycemic control that is associated with the lowest morbidity and mortality since the first study published in 2001 on patients in the surgical ICU in Belgium [13]. That study compared outcomes in over 1500 patients randomized to a group given "usual care," i.e. glucose levels maintained between 10.0 and 11.1 mmol/L (180–200 mg/dL), or treated with "intensive insulin therapy," i.e. glucose levels maintained between 4.4 and 6.1 mmol/L (80–110 mg/dL) with intravenous insulin given using an infusion pump. The mean glucose concentration in the usual care group was 8.5 mmol/L (153 mg/dL) and the mean concentration in the intensively treated arm was 5.7 mmol/L (103 mg/dL). It was shown that those randomized to the intensive insulin group did significantly better in all outcomes. In particular, their mortality was reduced by 34%, but other measures of outcome were also significantly improved, including less bacteremia, less antibiotic use, shorter length of time on a ventilator, and fewer days on the ICU [13]. The authors then repeated the study in a medical ICU, with a mean glucose concentration in the intensively treated arm of 6.2 mmol/L (111 mg/dL), and showed that intensive insulin therapy was associated with a reduction in overall morbidity and a reduction in mortality if the stay on the ICU was over 3 days [51]. As a result of these two seminal studies, it had been suggested that the target for this cohort of patients should be between 4.4 and 6.1 mmol/L (80 and110 mg/dL). However, subsequent attempts to reproduce these data have proved inconclusive, with most similar studies being unable to achieve similar reductions in morbidity or mortality [52–56], and with some of these studies being stopped early because of the significantly increased risk of harm due to the high frequency of severe hypoglycemia [52, 54, 55]. In a review of the literature in 2013, the lead author of the initial Belgian study concurred that there was still work to be done, and that given the increased mortality in the intensively treated arms of these studies, it remained unclear whether tight glycemic control in the ICU was appropriate [57].

In view of these and other findings, in 2014 a joint statement from the American Diabetes Association (ADA) and the AACE recommended specific glycemic targets in the ICU. They advocated for the initiation of insulin when glucose levels are persistently greater than 10.0 mmol/L (180 mg/dL), aiming for a glucose level between 7.8 and 10.0 mmol/L (140 and 180 mg/dL) [58]. They also suggested that in those centers with more experience in glucose control, a lower target of 6.1–7.8 mmol/L (110–140 mg/dL) may be aimed for provided that there is no increase in the incidence of severe hypoglycemia [58]. The Society of Critical Care Medicine in the USA recommends that glucose-lowering therapy be started once levels rise above 8.3 mmol/L (150 mg/dL), and glucose levels should not be allowed to rise above 10.0 mmol/L (180 mg/dL) or drop below 3.9 mmol/L (70 mg/dL) [59].

General ward patients

There are data from a variety of specialities to show that hyperglycemia in hospitalized patients is associated with poor outcomes [30, 60–63]. Despite this, there remains a paucity of good-quality data on what the ideal target for blood glucose should be in patients on a general ward in hospital, with no data currently available showing if good glycemic control reduces the excess morbidity and mortality seen in hospitalized inpatients with hyperglycemia. The available data are from small cohorts, but show that a lowering of glucose levels is associated with improved outcomes [64]. In the UK, the JBDS has published a series of consensus-based guidelines on a variety of aspects of care for this increasingly large cohort [26]. They advocate that the target glucose level should be between 6.0 and 10.0 mmol/L (108 and180 mg/dL), with a level of 4.0–12.0 mmol/L (72–216 mg/dL) being acceptable for medical patients and for awake surgical patients. These levels are at slight variance with the USA, where the guidelines suggest targets for fasting glucose levels of <7.8 mmol/L (140 mg/dL) and a random glucose target of <10.0 mmol/L (180 mg/dL) [58]. Targets for those who are at the end of life are more relaxed, with the aim of avoiding symptomatic hypoglycemia or hyperglycemia, with levels of 6.0–15.0 mmol/L (108–270 mg/dL) being advocated in the UK [65], and similar but slightly lower levels in the USA [66].

Surgical patients

Several studies have shown that perioperative hyperglycemia is associated with harm [31, 32]. This can be in the form of increased risk of infections of the surgical site or urinary or lower respiratory

tract, increased risk of myocardial infarction and acute kidney injury, time on the ICU or ventilator, and increased risk of mortality. There are data to show that in those individuals who have been previously identified as having diabetes prior to surgery, their risk is significantly lowered, regardless of their glycemic control [31]. This may be because of the increased communication between staff, and if an individual is on an intravenous insulin infusion then it is likely that they will be in contact with nursing staff more frequently (if only to have a capillary glucose measurement taken) than those individuals not previously known to have diabetes. Hence if complications do occur, they may be picked up at an earlier stage. In the UK, the JBDS guideline for the perioperative management of adults with diabetes recommends that the glucose targets for patients undergoing surgery are to keep levels between 6.0 and 10.0 mmol/L (108 and 180 mg/dL), with an acceptable range of 4.0–12.0 mmol/L (72–216 mg/dL) in the awake surgical patient [33]. In those who are asleep, or unable to communicate, the risk of developing hypoglycemia increases at the lower limit, hence the range is recommended to be 6.0–12.0 mmol/L (108–216 mg/dL). The USA and other countries do not yet have similar guidelines, although given the recent evidence that a perioperative HbA_{1c} level of >8.0% (64 mmol/mol) is associated with greater harm, organizations may begin to address this in the future [67, 68].

Given the greatly increased risk of postoperative complications associated with hyperglycemia, it may be necessary for units to adopt a policy to measure a capillary glucose level in at-risk individuals at the preoperative assessment clinic or at the time of acute admission, to ensure that those who have undiagnosed hyperglycemia, either diabetes or stress hyperglycemia, can be identified and appropriately treated.

Surgical patients: potential mechanisms of beneficial effects of glucose lowering in hospital

Although there are few data to show that lowering blood glucose is beneficial, insulin has several beneficial effects on the inflammatory cascade that are independent of its metabolism-regulating effect. These effects include reducing the degree of oxidative stress by its action on free radical production and clearance [69], and also beneficial effects on reducing pro-inflammatory cytokine levels in addition to improving white cell and endothelial function [70–72].

Current recommended standards of care for hospital inpatients with diabetes

Data from the USA in 2012 indicated that 25% of inpatient bed days, accounting for an estimated 43 million days, were attributable to diabetes [7]. In the UK in 2015 people with diabetes occupied between 4 and 35% of hospital beds [73]. Data from NaDIA showed that the majority of patients with diabetes are admitted for reasons other than diabetes, with ~92% admitted as an emergency [74]. In addition, one in four people admitted with heart failure, heart attack, or stroke have diabetes [74].

Professional organizations from different countries publish recommended standards of care for hospital inpatients. The International Diabetes Federation (IDF), an umbrella organization of more than 200 national diabetes associations in over 160 countries, offers a broad perspective on inpatient care relating to people with type 2 diabetes but acknowledges that not all countries have the infrastructure or resources to offer the same care standard for all. They therefore offer three care categories, recommended care, limited care, and comprehensive care, to which member organizations can benchmark [75], as summarized below:

- *Recommended care*. This is evidence-based care that is cost-effective in most nations with a well-developed service base, and with healthcare funding systems consuming a significant part of national wealth. *Recommended care* should be available to all people with diabetes and the aim of any healthcare system should be to achieve this level of care. However, as there are considerable variations in resources throughout the world, other levels of care are described that acknowledge low- and high-resource situations.
- *Limited care*. This is the lowest level of care that anyone with diabetes should receive, as standard medical resources and fully trained health professionals are often unavailable in poorly funded healthcare systems. However, even with limited and cost-effective resources, this level of care aims to achieve a high proportion of what can be achieved by *Recommended care*. Only low-cost or high cost-effectiveness interventions are included at this level.
- *Comprehensive care*. This level of care includes the most up-to-date and complete range of health technologies that can be offered to people with diabetes, with the aim of achieving best possible outcomes. However, the evidence base supporting the use of some of these expensive or new technologies is relatively weak.

This list includes recommendations from other countries including the USA, Australia, Canada, South Africa, and the UK.

Similar themes emerge when reviewing these documents relating to care, including the following:

- A diabetes diagnosis should be clearly identified in the hospital medical case records.
- All people with diabetes admitted to hospital should have their blood glucose level and HbA_{1c} measured, with results available to all members of the healthcare team.
- There should be an emphasis on insulin safety, particularly when using intravenous insulin infusion.
- Recommended blood glucose targets for inpatients should be stated, thereby reducing the risk of hypoglycemia and hyperglycemia.
- Discharge planning should be implemented on admission to hospital.
- Systems and policies should be in place that recognize the specific needs of inpatients with diabetes.
- Each hospital trust should identify a clinical lead for diabetes inpatient care.
- All inpatients with diabetes should have access to a specialist inpatient multidisciplinary diabetes team.
- Staff caring for inpatients with diabetes should be appropriately trained and competent in the management of inpatient diabetes.

The major themes identified in these reports are outlined in the following.

Minimizing length of stay

Reducing excess length of stay is one of the principal aims of good inpatient care. Prolonged length of stay occurs for a multiplicity of reasons, but is often because of diabetes mismanagement secondary to poor staff knowledge and lack of education [47, 76]. Insulin errors are also associated with a longer hospital stay, and although it is recognized that Certified Diabetes Educators (CDEs) and diabetes specialist nurses (DSNs) are effective in reducing length of stay, the majority of diabetes inpatients do not come into contact with these healthcare professionals during admission [77, 78]. The IDF and the ADA are among many institutions that have put discharge planning as a priority at the time of patient admission and not as an afterthought just prior to discharge [75, 79].

Discharge planning defines the agreed management plan for that episode of care, including assessment and prompt referral to the specialist team if necessary, and can aid in anticipating and therefore preventing problems. When possible, this planning should be done in consultation with the patient.

Patient safety

Patient safety for inpatients focuses predominantly on insulin and diabetes management errors and the risks of infection or debilitation associated with extended length of hospital stay. Globally, insulin is one of the five highest risk medications administered [80]. One-third of all inpatient medical errors that cause death within 48 h of the error involve insulin administration. Insulin medication errors can occur at any stage in the process of prescribing, preparing, and delivering the medication to the patient [81]. Errors involving insulin infusion have been highlighted particularly in the last few years [74].

The UK National Patient Safety Agency reviews all medication errors, including those relating to insulin. In 2010, they published a 6-year audit of reported insulin errors described as moderate and severe; 3881 reports were received, and these included inpatient deaths [82]. Following this, a directive was issued stating that all healthcare professionals, including medical staff involved in the prescribing, handling, and administration of insulin, must receive insulin training. In the UK, there is a nationwide initiative to raise the profile of glucose control for inpatients, and also for individual healthcare professionals to take part in a national training program [83, 84]. In recent times there have been a very small number of reports of the development of diabetic ketoacidosis (DKA) in some people with type 1 diabetes, and individuals with type 2 diabetes who are taking SGLT2 inhibitors. In those with type 2 diabetes the blood glucose was only slightly raised. Risk factors for DKA in these people include poor nutrition, reduced insulin, and alcohol abuse. SGLT2 inhibitors should be temporarily discontinued in all patients on admission to hospital for any reason. If the patient is acutely unwell their blood ketones should be tested and they should be assessed for DKA risk.

Diabetes self-management

When not in hospital, people with diabetes are accustomed to managing their own condition. Traditionally, patients are disempowered in the management of their diabetes as soon as they are admitted, and for many people with diabetes, this disempowerment is a negative experience [74, 85]. In 2011, the IDF promoted the need for individuals to be enabled to self-manage their own condition [86]. The USA and UK have set national standards defining the principles of self-management of diabetes, but acknowledge that there is no best practice education program that meets the needs of all people with diabetes [87, 88].

The key principle of self-management is that the person with diabetes has primary responsibility for making the decision about whether they should self-manage their own diabetes. Individuals suitable for self-management in hospital must be competent adults with a stable level of consciousness who successfully manage their diabetes at home. In addition, while in hospital it is advised that these people have the physical skills appropriate to self-administer insulin, be accustomed to performing self-monitoring of blood glucose, and have adequate oral intake. In the event that self-care is deemed unsafe or impossible (e.g. critically ill, post-surgery or unwilling patients), then there must be a governance arrangement to assess patient competency and if necessary supersede patients' right to self-care. Hospitals should have a patient-centered policy for diabetes self-management. Encouraging and supporting individuals to have as much responsibility for their diabetes management as they wish, and their clinical status allows, are likely to enhance the patient experience during a hospital stay [86–88].

Patient satisfaction

Patient experience is important and plays a seminal role when developing local and national guidelines; but there is little in the worldwide literature evaluating inpatient experience. The UK has, however, gathered a large amount of data on patient satisfaction through two sources, as follows.

The Diabetes Inpatient Satisfaction Study was a cross-sectional study measuring inpatient diabetes treatment satisfaction and its relationship to inpatient diabetes care in over 1300 inpatients with insulin-treated diabetes [85]. Patients filled out a validated Diabetes Treatment Satisfaction Questionnaire for Inpatients [89]. Satisfaction with the general diabetes treatment was high, but there were high levels of extreme dissatisfaction with meal choices, meal quality, and lack of similarity of hospital meals to normal domestic choices: 23% would never or rarely have made similar meal choices at home.

Hyperglycemia or hypoglycemia was reported for much of the inpatient stay (20 and 7%, respectively) and 26% reported at least one severe hypoglycemic episode. More frequent inpatient hyperglycemia or hypoglycemia was associated with significantly poorer overall satisfaction scores and negative well-being scores. These groups also had lower satisfaction with the timing of medication in relation to meals. Factors that were significantly associated with the highest levels of satisfaction were the amount

of time spent with a diabetes inpatient specialist nurse (DISN) and self-administration of insulin [85].

Inpatient satisfaction questionnaires were an integral part of the National Diabetes Inpatient Audit, and data were collected over 4 years [74]. In the 2015 audit, 8521 of the 15,229 inpatients included in the audit responded to questionnaires on their inpatient experience, of which 8456 were matched to a corresponding bedside audit form (Box 34.1).

The role of the diabetes specialist team

The patient remains at the heart of the diabetes team. Diabetes specialist inpatient teams are multidisciplinary and should include the consultant in diabetes with a specialist interest in inpatient care, who often is seen at the lead, working closely with DSNs or CDEs, diabetes dieticians, and specialist podiatrists. Extended foot team members should include orthopedic and vascular surgeons, microbiologists, tissue viability nurses, and interventional radiologists. When necessary, rehabilitation teams should also be available. The specialist team should work together by individually contributing their specialist skills to provide a holistic approach to patient care. The success of such team work requires a culture that invests in excellent communication between the person with diabetes, diabetes specialists, and non-specialist teams to activate timely intervention by avoiding glycemic deterioration during the hospital stay.

There is evidence that involvement of the specialist diabetes team, and in particular DISNs and CDEs, significantly reduces length of stay and insulin errors, improves the patient experience, and reduces readmissions [6, 76, 90–92].

A CDE is a health professional in the USA or Canada who possesses comprehensive knowledge of and experience in diabetes management. The role is not exclusive to nursing, but all educators must have a relevant health-related degree and undergo extensive training. They educate and support people affected by diabetes to understand and manage the condition and promote self-management to achieve individualized behavioral and treatment goals that optimize health outcomes. Working in close partnership with social workers, case managers, and home care coordinators, they are able to facilitate a smooth patient pathway from hospital to home at discharge. The DSNs, who work exclusively in diabetes care, and the CDEs are also integral to providing ongoing staff training and may also be prescribers [76, 93]. DSNs deliver patient-centered care wherever required and influence care delivery at every stage of the patient journey, including inpatient care; there is a subgroup of DSNs who specialize in the care of inpatients with diabetes (DISNs). The role of the DISN has evolved in recent times and specifically focuses on supporting inpatients and the ward staff caring for them. Aside from clinical care, DISNs are frequently involved in medical and nursing education. Despite these numerous attributes, almost one-third of UK hospitals do not have a DISN [74]. The same data reveal that the number of hospitals offering inpatient dietetic support is much worse.

Box 34.1 Results from the UK National Diabetes Inpatient Audit 2015.

Patient's ability to self-care

- 27.1% said they had not been able to take control of their own diabetes care in hospital to the extent they would have liked; 17.1% reported they were able to test their own blood glucose levels in hospital. However, the rates of hypoglycemic episodes in those self-testing were higher than in those who did not (27.6% vs. 21.1%).
- 14.2% stated that they were not able to test their own blood glucose levels but would have liked to do so.
- Over half of inpatients (56.5%) taking insulin for their diabetes had been permitted to self-administer insulin while in hospital. The percentage of inpatients who were able to self-administer insulin and who had had one or more hypoglycemic episodes (35.1%) was the same as that among inpatients who were not able to self-administer insulin.
- 9.3% of those taking insulin for their diabetes reported that they were not permitted to self-administer insulin while in hospital but would have liked to do so.
- 30.8% of insulin users stated that they did not want to self-administer while in hospital.
- 23.4% would have liked more involvement in the planning of their diabetes treatment, while 12.5% of inpatients would have preferred to have been less involved in planning their treatment.

Patients' perceptions of ward staff

- 56.4% reported that hospital staff definitely took their treatment preferences into account and 29.5% reported that hospital staff took their treatment preferences into account to some degree
- Inpatients were asked whether they felt the ward staff were knowledgeable about diabetes, 65.7% stated that all or most staff knew enough to meet their needs while they were in hospital. However, 7.7% of inpatients stated that staff did not have sufficient knowledge of diabetes to meet their needs while in hospital; 8.2% of inpatients who had questions about their diabetes reported that hospital staff were not able to answer these questions in a way that they could understand.
- The vast majority of inpatients (84.1%) stated that they were satisfied or very satisfied with the overall care of their diabetes while in hospital.

Staff education

One of the key roles for the specialist diabetes inpatient team is to educate other ward-based generic healthcare professionals. Ward staff may have little or no protected time for education and training other than mandatory training defined by the employing organization. Despite the large numbers of patients with diabetes in

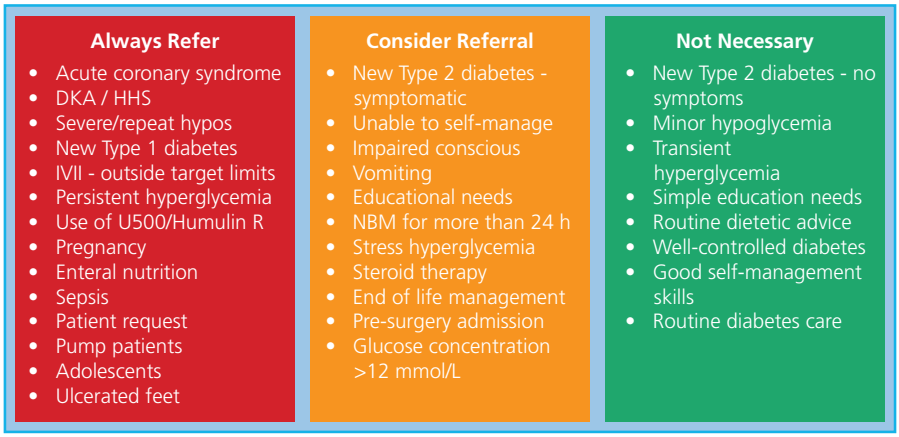

Figure 34.1 Prioritization of patients who should be seen by the diabetes inpatient specialist team. NBM: nil by mouth. Source: Adapted from ThinkGlucose.

hospital, often the only mandatory training in diabetes is in blood glucose monitoring. People with diabetes, who generally have a high level of knowledge about their condition, are therefore frequently being managed by nursing and medical staff who only have only a rudimentary knowledge and training in diabetes care [47, 94]. Hence it is the senior physicians who have the responsibility for educating junior medical staff, whilst the CDE and DSN teams are often best placed to offer education to ward-based staff because they can use the opportunity when reviewing patients to provide education to other non-specialist staff about diabetes management and medication error prevention.

As 10–35% of hospital inpatients have diabetes, it is almost impossible for specialist team members to see every patient on a regular basis. In the UK, specialist teams therefore have drawn up a priority list for which patients should be referred for assessment (Figure 34.1). Ward-based and specialist nursing staff in the UK have to undergo a revalidation process from 2016, which includes ascertaining patient views and demonstrating competency [95].

Management of in-hospital hyperglycemia

"It is as unacceptable for hospitals not to have a glycemic management policy as it is for them not to have an infection control policy" [83]. This statement, from the UK NHS Institute for Innovation and Improvement, echoes similar sentiments from the ADA [58], namely that it is incumbent upon organizations to ensure that diabetes is appropriately managed in the inpatient population.

Hyperglycemia in hospital is a common problem and occurs in around 25% of all hospital inpatients [4]. The majority of people with diabetes are not admitted to hospital to address and treat complications associated with the disease. Control of blood glucose often becomes secondary to the care of the primary diagnosis requiring admission. In people without diabetes who develop hyperglycemia during an acute illness, high or low glucose levels are often ignored or treated inappropriately. Poor glycemic control is common among inpatients with diabetes, for many reasons [4]. Over the last few years, the issue of inpatient diabetes has become a higher priority, with the UK Joint British Diabetes Societies Inpatient Care Group producing a number of different guideline addressing various issues surrounding inpatient glycemic control [26]. In the USA, the PRIDE group has also been set up to address inpatient glycemic control [68].

Medication to manage in-hospital hyperglycemia

For many years, it was thought that it was more straightforward to stop any oral medication that a patient may be taking and to use intravenous insulin because it provided the greatest flexibility in the hospital setting to achieve optimal blood glucose control. However, it has become increasing recognized that the use of insulin is associated with severe hypoglycemia [50, 96]. New strategies are required to manage hyperglycemia, while at the same time keeping the work load of the nursing staff to a minimum, at a reasonable cost. Umpierrez et al. used more flexible insulin regimens either with or without drugs that work by preventing glucose concentrations from rising, with some success in medical and surgical patients [64, 97]. Subcutaneous insulin given as a basal bolus regimen with correction bolus doses have also been used [98]. However, these regimens require a degree of awareness and training among nursing and medical staff. Increasing awareness, such as the use of the ThinkGlucose campaign in the UK, have helped to ensure that nursing staff remain vigilant to the importance of maintaining good glycemic control [83]. Insulin administration errors are very common, and have been classified as a "Never Event" [99]. When incidents occur, they should be regularly audited and staff training put into place as necessary.

Self-management of diabetes in hospital

Self-management describes the whole process of adjusting insulin treatment in response to self-measured capillary glucose values [88]. Although this is an institutional decision, in principle inpatients with diabetes should be given the opportunity to decide whether they wish to self-manage their condition during their admission, provided that they are well enough to do so. Part of this involves institutions providing written information for staff and patients to explain the responsibilities of self-management. For elective surgical patients, this written information may be provided at the time of the preassessment clinic. In addition, for elective admissions, a care plan should be agreed at that time to

establish whether the person with diabetes wishes to self-manage and the circumstances in which this may not be possible should be agreed in advance [88].

At the time of admission, the responsible nurse and the person with diabetes should again agree on the circumstances in which the patient should or should not self-manage. Ideally, an agreement form should be signed by both the person with diabetes and the responsible nurse. People with diabetes should be able to self-monitor their blood glucose but should make the results available to hospital staff. People with diabetes should be allowed to use their own blood glucose monitoring equipment, but ideally this should be quality assessed. In addition, the technique for glucose testing and insulin administration should also be assessed. Once the person with diabetes has administered their own insulin, the dose self-administered should be recorded on the prescription chart, or an entry made on an electronic prescription by a member of staff.

To allow people with diabetes to keep and administer their own insulin, facilities should be available for safe storage of insulin in the ward environment. In addition, the institution should ensure that the timing and content of meals are suitable for the individual with diabetes; this is a common cause of unhappiness and dissatisfaction among inpatients with diabetes [85].

It is important that during the admission, the clinical circumstances should be regularly assessed to ensure that the patient's ability to self-manage has not been compromised by their clinical condition. If there are doubts or disagreements between the person with diabetes and the staff as to whether they can self-manage, then the diabetes specialist team may need to be involved.

Technology

The use of technology to manage inpatient diabetes is still in its infancy, but is likely to play an increasing role in managing glycemic control over the next few years. The use of continuous subcutaneous insulin infusions complemented by implantable real-time glucose sensors has been used successfully in small studies in patients in ICUs [100]. The use of these "closed loops" is likely to become more frequent as the algorithms that they use become more sophisticated, and the cost of the technology falls sufficiently to make it cost-effective to use regularly.

Subcutaneous and intravenous insulin protocols

The use of "sliding-scale" insulin given intravenously or subcutaneously has been soundly discredited, but continues to be used [101, 102]. Umpierrez et al. have published widely on the successful use of subcutaneous insulin to manage glucose levels on the wards in medical and surgical patients [64, 97], and have also shown that the use of the dipeptidyl peptidase inhibitor sitagliptin alone, or in combination with basal insulin, was associated with a lowering of glucose levels in a small, single-center study of 90 general medical and surgical patients [103]. How insulin is given is also a subject of contention. The use of basal bolus or twice-daily mixed subcutaneous insulin regimens has been advocated [3, 104], but to use insulin safely requires a certain level of understanding, and data have shown that among many junior medical staff this is lacking [47]. This may be why there is reluctance among junior medical staff to prescribe subcutaneous insulin earlier, even when glucose levels remain high.

The ideal intravenous or subcutaneous insulin protocol should be safe, understandable, easily ordered, and readily implemented. It should be effective in correcting hyperglycemia quickly and in maintaining glucose levels within a defined target range. If given intravenously, the provision of an easy-to-follow algorithm for making incremental changes to the infusion rate, which can be executed by nursing staff, is likely to improve the efficacy of the protocol. Hypoglycemia is a potential complication of intensified insulin therapy and is associated with poor outcomes. It is for this reason that intravenous insulin infusions should be supported by caloric input when glucose levels drop. In most patients, this is in the form of a simultaneous infusion of dextrose, but calories can be provided by other routes (e.g. enteral, parenteral, or in a dialyzate). The UK JBDS and others have produced comprehensive guidelines on the management of intravenous insulin infusions [98, 105]. It is expected that if the patient was taking a long-acting basal insulin (human or analog) prior to admission, then this should be continued, because continuation of the background insulin prevents rebound hyperglycemia when the intravenous insulin is stopped [106].

Indications for an intravenous insulin infusion

Whether the patient has previously recognized diabetes or not, insulin provides the greatest flexibility to meet rapidly changing requirements in different hospital settings to achieve optimal blood glucose control. Intravenous infusion of insulin is the only insulin treatment strategy specifically developed for use in the hospital setting. The JBDS and the ACE advise that intravenous insulin infusion should be used to control glucose levels in certain circumstances (Box 34.2).

Box 34.2 Indications for an intravenous insulin infusion (variable rate unless stated).

- To treat critical care illness
- Acute coronary syndromes—although owing to the uncertainty here, local guidelines should be followed
- Patients on "nil by mouth" status when more than one meal will be missed
- Type 1 diabetes
- General preoperative, intraoperative and postoperative care
- Stroke
- Hyperglycemia during high-dose corticosteroid therapy
- Labor and delivery
- Other acute illness for which prompt glycemic control is judged important to recovery, such as prevention or treatment of infection
- Diabetes emergencies such as diabetic ketoacidosis or hyperosmolar hyperglycemic syndrome (fixed-rate infusion)

Table 34.1 Insulin infusion table.

Glucose (mmol/L)	Insulin rates (mL/h)[a] (start on standard rate unless otherwise indicated)[b]		
	Reduced rate (for use in insulin sensitive patients, e.g. ≤24 units/day)	Standard rate (first choice in most patients)	Increased rate (for insulin-resistant patients, e.g. ≥100 units/day)
<4.0	0	0	0
4.1–8.0	0.5	1	2
8.1–12.0	1	2	4
12.1–16.0	2	4	6
16.1–20.0	3	5	7
20.1–24.0	4	6	8
>24.1	6	8	10

[a] Using 50 units of human soluble insulin in 49.5 mL of 0.9% sodium chloride solution gives a concentration of 1 unit/mL.
[b] If a patient normally takes basal subcutaneous insulin, continue this alongside the variable rate intravenous insulin infusion.
The scales may be customized as necessary.
Source: George and Stanisstreet 2014 [105].

Preparation and delivery of an intravenous insulin infusion

An intravenous insulin infusion is prepared by adding 50 units of soluble insulin to 49.5 mL of 0.9% sodium chloride solution, which will provide 1 unit of insulin in 1 mL, which is delivered via an infusion pump. This insulin infusion can be piggy-backed into the infusion of dextrose using a three-way connector and a non-return valve. This is most often given as a variable-rate intravenous insulin infusion; it can be given as a fixed-rate intravenous insulin infusion, but this is usually limited to treatment of diabetic ketoacidosis or hyperosmolar hyperglycemic syndrome (Table 34.1). The terms "variable-rate intravenous insulin infusion" (VRIII) and "fixed-rate intravenous insulin infusion" (FRIII), are preferred owing to the potential ambiguity associated with the term "sliding scale."

Transition from intravenous to subcutaneous insulin

Conversion to subcutaneous insulin should only be carried out when the patient is able to eat and drink normally without nausea or emesis. The most appropriate time to switch from intravenous to subcutaneous insulin is at the usual time of the patient's insulin administration, before a meal; however, when possible, this should not be done before the evening meal. People with known type 1 diabetes will become insulin deficient within minutes of the intravenous infusion being stopped because of the short half-life of intravenous insulin. It is therefore good practice to continue the infusion of insulin for 30–60 min after the subcutaneous insulin has been administered to allow time for the insulin to be absorbed [105].

If the patient has been on an established insulin regimen, then this regimen should be restarted, but doses may have to be adjusted depending on the patient's clinical condition. If the patient is new to insulin therapy, then a rough estimation of the total daily dose of insulin can be made from a simple calculation using the hourly rates delivered in the intravenous insulin infusion. Estimation of insulin doses can also be made according to body weight, which is useful in calculating total daily dose requirement in patients who are new to insulin but have not required an insulin infusion (Table 34.2 and Box 34.3).

Avoiding and treating in-hospital hypoglycemia

Hypoglycemia is the commonest side effect of insulin and sulfonylurea treatment, and represents a major barrier to satisfactory long-term glycemic control. The other drug classes, i.e. biguanides, thiazolidinediones, DPP-4 inhibitors, SGLT-2 inhibitors, and GLP-1 receptor agonists, are unlikely to result in hypoglycemia owing to their modes of action, unless co-prescribed with insulin or sulfonylureas. Hypoglycemia should be excluded in any person with diabetes who is acutely unwell, drowsy, unconscious, unable to cooperate, or presenting with aggressive behavior or seizures. In-hospital hypoglycemia is defined as a blood glucose level ≤3.9 mmol/L (70 mg/dL) [58]. There is an increasing body of evidence supporting the widespread occurrence of hypoglycemia in hospitals and poor knowledge of how to detect and manage it [50, 96].

Frequency of hypoglycemia in hospitalized patients

In 2015, the UK National Diabetes Inpatient Audit (NaDIA) data showed 21.8% of inpatients with diabetes experienced one or more hypoglycemic episodes with a blood glucose less than 4.0 mmol/L (72 mg/dL), with 9.3% experiencing one or more hypoglycemic episodes less than 3.0 mmol/L (54 mg/dL) [4].

Farrokhi et al. [107] reported a prevalence of severe hypoglycemia ranging from 5 to 32% in hospital inpatients treated with insulin. In England, the National Diabetes Inpatient Audit data set showed that people with type 1 diabetes had the highest prevalence, with 42.5% experiencing a hypoglycemic episode with a blood glucose less than 4.0 mmol/L (72 mg/dL) and 31.3% experiencing a hypoglycemic episode <3.0 mmol/L (54 mg/dL). Injectable rescue treatment was required by 2.1% of patients [4].

Table 34.2 Transition from intravenous to subcutaneous insulin.

Insulin	Good control, i.e. HbA_{1c} <59 mmol/mol (7.5%)	Suboptimal Control	Monitoring blood glucose for all patients
Basal insulin	Restart usual dose of insulin when it is due (usually with either breakfast or evening meal). Do not stop VRIII until at least 30–60 min after insulin has been given and patient has eaten If it is necessary to stop VRIII but the basal insulin is not due for several hours, give half the usual dose of basal insulin. This will provide background insulin until the usual dose can be recommenced	In addition, discuss with local diabetes inpatient team. Insulin regimen may need adjusting	CBG should be checked 1 h after discontinuing VRIII and at least 4-hourly for the next 24 h, to ensure that there is no rebound hyper- or hypoglycemia
Once- or twice-daily mixed insulin	Restart usual dose of insulin together with a meal (either breakfast or evening meal). Do not stop VRIII until at least 30–60 min after insulin has been given and the patient has eaten If it is necessary to stop VRIII at lunchtime, give half the usual breakfast dose of mixed insulin. This will provide essential background insulin until the usual dose can be recommenced		
Multiple daily insulin injections (MDI or basal bolus)	Restart usual diabetes treatment together with a meal Basal insulin will usually have been continued. Restart bolus dose of insulin together with the next meal. Do not stop VRIII until at least 30–60 min after bolus insulin has been given and the patient has eaten If basal insulin has been stopped, background insulin must be restarted prior to stopping VRIII. Ideally, continue the VRIII until basal insulin is given and a meal is due, and stop at least 30–60 min after basal and bolus insulin is restarted If it is necessary to stop the VRIII, but the basal insulin is not due for several hours, give half the usual daily dose of basal insulin, along with a meal and bolus insulin. This will provide essential background insulin until the usual dose can be recommenced		
Insulin pump (CSII)	Restart usual basal rate via CSII Do not stop VRIII until at least 30 min after insulin has been recommenced via CSII Give bolus insulin according to patient's usual regime. It is not usually necessary to wait until a mealtime to switch back to CSII therapy Avoid restarting CSII at bedtime		

Source: George and Stanisstreet 2014 [105]. CSII, continuous subcutaneous insulin infusion; CBG, capillary blood glucose.

Box 34.3 Converting from intravenous to subcutaneous insulin.

Step 1

Calculate the total daily dose requirement (TDD) using either of two methods: weight based, or using the dose delivered for the last 6 h using a VRIII. The weight-based method suggests that in frail, elderly patients, those with renal failure (CKD stage 4 or 5) or severe hepatic failure, or in those with newly diagnosed type 1 diabetes:

Total daily insulin dose = 0.3 × body weight in kg

All other adult patients:

Total daily insulin dose = 0.5 × body weight in kg

The infusion-based method estimates the daily insulin requirement from the last 6 h of the VRIII as follows:

The total dose of insulin administered in last 6 h of the VRIII is divided by 6 to calculate average hourly dose of insulin. This is then multiplied by 20 (not 24, to reduce risk of hypoglycemia) to estimate the patient's total daily insulin requirement.

Step 2

Using the total daily dose to convert the patient to either a premixed twice daily insulin regimen or a multiple basal bolus dose regimen

For a basal bolus regimen, 50% of the total insulin requirement is usually given as basal insulin, and the remainder as rapid-acting insulin, divided equally between breakfast, lunch, and evening meal

For a twice-daily, premixed insulin regimen, patients usually need 60% of the total insulin requirement at breakfast and the remaining 40% with the evening meal

Source: George and Stanisstreet 2014 [105].

Table 34.3 Potential causes of in-hospital hypoglycemia.

Medical issues	Carbohydrate intake issues
• Inappropriate use of "stat" or "PRN" rapid/short-acting insulin • Acute discontinuation of long-term steroid therapy • Recovery from acute illness/stress • Mobilization after illness • Major amputation of a limb • Incorrect type of insulin or oral hypoglycemic therapy prescribed and administered • Inappropriately timed insulin or oral hypoglycemic therapy in relation to meal or enteral feed • Change of insulin injection site • I.v. insulin infusion with or without glucose infusion • Inadequate mixing of intermediate-acting or mixed insulins • Regular insulin doses or oral hypoglycemia therapy being given in hospital when these are not routinely taken at home	• Missed or delayed meals • Less carbohydrate than normal • Change of the timing of the biggest meal of the day (i.e. main meal at midday rather than evening) • Lack of access to usual between-meal or before-bed snacks • Prolonged starvation time, e.g. "nil by mouth" • Vomiting • Reduced appetite • Reduced carbohydrate intake

Source: Stanisstreet et al. 2013 [119].

The same data showed that the highest proportion of episodes took place overnight (34.3%), between 9 p.m. and 9 a.m., when snack availability was likely to have been lowest; these data have been confirmed elsewhere [108].

The tight glycemic control achieved in ICUs led to much higher reported rates of hypoglycemia, with the incidence of blood glucose ≤2.2 mmol/L (40 mg/dL) ranging from 5 to 18.7% [51, 52, 54, 109].

Causes of in-hospital hypoglycemia

Common causes of inpatient hypoglycemia are listed in Table 34.3. One of the most serious and common causes of inpatient hypoglycemia is insulin prescription errors, including misreading poorly written prescriptions, such as when U is used for units (e.g. 4U becoming 40 units), or confusing the insulin name with the dose (e.g. Humalog Mix25 becoming Humalog 25 units).

Morbidity and mortality associated with in-hospital hypoglycemia

Turchin et al. examined data from 4368 admission episodes for people with diabetes, of whom one-third were on regular insulin therapy [110]. Individuals experiencing inpatient hypoglycemia showed a 66% increased risk of death within 1 year and spent 2.8 days longer in hospital than those not experiencing hypoglycemia. Recent data also suggest increased mortality rates for inpatients on insulin therapy who experienced a blood glucose of <2.8 mmol/L (50 mg/dL) compared with those with no hypoglycemia (20.3% vs. 4.5%) [111]. However, only 41–51% of these participants had diabetes and subgroup analysis of those with diabetes was not performed.

Evidence for treatment options

There is limited evidence regarding the quantity of quick-acting carbohydrate required to treat an episode of hypoglycemia successfully. The initial quantities chosen were the result of expert consensus subsequently backed up with glucose clamp studies [112, 113]. Subsequent work has shown that ~20 g of rapid-acting carbohydrate is often sufficient, with less than 10 g likely to be inadequate [114, 115]. Chocolate- and sucrose-containing foods should be avoided, because the high fat content in chocolate slows gastric emptying, thus delaying absorption, and sucrose needs to be cleaved by intestinal disaccharidases prior to absorption [116, 117]. Fresh fruit juice or glucose-containing tablets or gel remain the most frequently used treatment for hypoglycemia and are an essential component of "Hypoboxes" [113, 118, 119]. The suggested contents of a Hypobox, which are commercially available, can be found in Box 34.4.

Management of in-hospital hypoglycemia

People experiencing hypoglycemia require quick-acting carbohydrate to return their blood glucose levels to the normal range. The quick-acting carbohydrate should be followed up by giving long-acting carbohydrate either as a snack or as part of a planned meal. All patients experiencing hypoglycemia should be treated without delay. When it is safe to do so, a blood glucose measurement should be taken to confirm hypoglycemia (especially if there is any suspicion that the person may be currently under the influence of alcohol or non-prescription drugs). If measurement is difficult (e.g. in a patient having a seizure), then treatment should not be delayed.

Adults who have poor glycemic control may start to experience symptoms of hypoglycemia at blood glucose levels >4.0 mmol/L (72 mg/dL). There is no evidence that the thresholds for cognitive dysfunction are reset upwards; therefore, the only reason for treatment is symptomatic relief. Hence adults who are experiencing hypoglycemia symptoms but have a blood glucose level >4.0 mmol/L (72 mg/dL) should be treated with a small carbohydrate snack only, e.g. one medium banana, a slice of bread, or normal meal if due. All adults with a blood glucose level <4.0 mmol/L (72 mg/dL) with or without symptoms of hypoglycemia should be treated as shown in Figure 34.2.

Box 34.4 Suggested contents of a Hypobox.

- A copy of the locally agreed hypoglycemia algorithm
  - laminated and attached to inside of lid
- 2× 200-mL cartons fruit juice
- 2× packets of dextrose tablets
- 1× mini-pack of biscuits (source of long-acting carbohydrate)
- 3 × tubes (1 box) Glucogel
- 20% glucose i.v. solution (100-mL vial)
- 1× 18G intravenous cannula
- 1× 16G intravenous cannula
- 1× 10-mL sterile syringe
- 3 × 10-mL 0.9% sodium chloride solution ampoules for flush
- 1× 21G sterile needle
- Chlorhexidine spray/alcohol wipes
- 1× dressing cover for the intravenous cannula
- 10% glucose for intravenous infusion (500-mL bag)
- Audit form
- Instructions on where to send audit form and replenish supplies
- 1× glucagon pack: to be kept in the nearest drug refrigerator or labeled with a reduced expiry date of 18 months if it is stored at room temperature

Source: Stanisstreet et al. 2013 [119].

All hypoglycemic events should be documented in the patient's notes. Regular capillary blood glucose monitoring should be continued for 24–48 h. The patient should be told to continue this at home if they are to be discharged. Hypoglycemia education should be given or a referral made to the DISN/CDE.

Surgery in people with diabetes

There have been several studies showing that hyperglycemia in the postoperative period is associated with harm. These include (but are not limited to) general surgery [31, 32], cardiac surgery [120], vascular surgery [121, 122], neurosurgery [123], orthopedic surgery [124, 125], colorectal surgery [126], trauma [127], breast surgery [128], liver transplantation [129], hepatobiliary and pancreatic surgery [130], cholecystectomy [131], and foot and ankle surgery [132]. These harms include wound infection, length of time in hospital, acute kidney injury, myocardial infarction, time spent in an ICU or on a ventilator, and death. The perioperative mortality rate is up to 50% higher than in people without diabetes [32]. Because of these factors, and the data showing that people with diabetes are less likely to be offered day-case surgery and are more likely to have emergency surgery, have longer lengths of stay following admission, and have a higher rate of 28-day readmissions following surgery [133], it would seem sensible to optimize glycemic control prior to surgery and around the time of the operation. However, this optimization would require a great deal of coordination between all the people involved in the care of the person with diabetes.

Primary care

The patient journey for elective surgical patients usually starts with a primary care assessment and referral to the surgeons [33]. It is important that primary care physicians communicate to the surgeons that the person has diabetes when they are referred, ideally indicating the type of diabetes, the duration of diabetes, the most recent HbA_{1c} (ideally taken within the previous 3 months), current treatment, any comorbidities, and who is the usual diabetes care provider. A recent meta-analysis suggested that there was no relationship between HbA_{1c} and outcomes in surgical patients [48]. The current guidelines are effectively pragmatic because it is well recognized that the high-risk surgical patient is often elderly, with multiple coexisting medical conditions, and therefore attempting to attain more aggressive glycemic control may be associated with harm in the form of hypoglycemia. In addition, there has previously been evidence to show that an HbA_{1c} of >64 mmol/mol (8%) has been associated with poor outcomes [67] and the UK National Guidelines suggest that HbA_{1c} should be <69 mmol/mol (8.5%) [33]. Hence it would be incumbent on the primary care provider to optimize glycemic control prior to referral, if possible, or after referral is made, to reduce the risk of (a) the procedure being cancelled or postponed owing to poor glycemic control or (b) the risk of harm postoperatively. The information provided by the primary care team should help the surgeon when they are seen in the surgical outpatient clinic. If the decision is made to operate, then the surgeon should communicate the presence of diabetes to the preoperative assessment team, the anesthetists, and the operating list planners, so that the patient may be placed early on a theater list to minimize starvation time and subsequent metabolic disturbance.

Preoperative assessment

At this stage, the opportunity should be taken to optimize preoperative glycemic control, either by referring back to the primary healthcare team responsible for their diabetes or using a DSN or CDE as necessary [134]. The management of other comorbidities should also be optimized.

There should be good lines of communication between the preassessment team and the surgical team, such that the patient is aware of when they are due to come in, where they are due to go, and what time their surgery is. They should also have very explicitly written instructions on how to manage their diabetes medication. These are shown in Tables 34.4 and Table 34.5. It is important that the preoperative assessment team ensure that the person with diabetes is put first on the morning list to avoid prolonged starvation time and avoid the inappropriate use of a variable-rate intravenous insulin infusion. This would result in the increasing likelihood that they could be same-day admissions. In addition,

Figure 34.2 Algorithm for the treatment of hypoglycemia in adults with diabetes in hospital. Hypoglycemia is defined as a blood glucose level of <4.0 mmol/L (72 mg/dL). If the patient is symptomatic but the blood glucose is >4.0 mmol/L (72 mg/dL) then a small carbohydrate snack should be given for symptom relief. ABC, airway, breathing, circulation; NBM, nil by mouth. Source: [119].

Table 34.4 Guidelines for perioperative adjustment of insulin.

Insulin	Day prior to admission	Day of surgery/while on a VRIII		
		Patient for a.m. surgery	Patient for p.m. surgery	If a VRIII is being used[a]
Once daily (evening) (e.g. Lantus or Levemir, Tresiba, Insulatard, Humulin I, Insuman)	Reduce dose by 20%	Check blood glucose on admission	Check blood glucose on admission	Continue at 80% of the usual dose
Once daily (morning) (Lantus or Levemir, Tresiba Insulatard, Humulin I, Insuman)	Reduce dose by 20%	Reduce dose by 20% Check blood glucose on admission	Reduce dose by 20% Check blood glucose on admission	Continue at 80% of the usual dose
Twice daily (e.g. Novomix 30, Humulin M3, Humalog Mix 25, Humalog Mix 50, Insuman Comb 25, Insuman Comb 50, twice daily Levemir or Lantus)	No dose change	Halve the usual morning dose Check blood glucose on admission Leave the evening meal dose unchanged	Halve the usual morning dose Check blood glucose on admission Leave the evening meal dose unchanged	Stop until eating and drinking normally
Twice daily: separate injections of short acting (e.g. animal neutral, NovoRapid, Humulin S, Apidra) *and intermediate acting* (e.g. animal isophane Insulatard, Humulin I, Insuman)	No dose change	Calculate the total dose of both morning insulins and give half as intermediate acting only in the morning Check blood glucose on admission Leave the evening meal dose unchanged	Calculate the total dose of both morning insulins and give half as intermediate acting only in the morning Check blood glucose on admission Leave the evening meal dose unchanged	Stop until eating and drinking normally
3, 4 or 5 injections daily	No dose change	Basal bolus regimens: omit the morning and lunchtime short-acting insulins. If the dose of long-acting basal insulin is usually taken in the morning then the dose should be reduced by 20%. Keep the basal unchanged[a]. Premixed a.m. insulin: halve the morning dose and omit lunchtime dose Check blood glucose on admission	Take usual morning insulin dose(s). Omit lunchtime dose Check blood glucose on admission	Stop until eating and drinking normally

At the preoperative assessment clinic, all patients should have emergency treatment for hypoglycemia written on their drug chart, i.e. Glucogel, and 20% dextrose. Rapid-acting insulin should also be prescribed.
[a]If the patient requires and ongoing VRIII then the long-acting background insulin should be continued but at 80% of the dose that the patient usually takes when they are well. Normal insulin doses should be recommenced when the patient is eating and drinking normally.
VRIII, variable-rate intravenous insulin infusion.
Source: Dhatariya et al. 2015 [148].

the provision should be made for postoperative admission to critical care, if this is indicated, especially with people who are at high risk and with poor glycemic control.

There are data from the UK to show that many people with diabetes are being inappropriately denied day-case surgery [6]. This means that a large number of people are being unnecessarily admitted to hospital for overnight hospital stay, adding to the cost burden, in the belief that being in hospital will lead to "glycemic optimization." However, this is likely to mean that the patient is admitted to a ward the evening prior to surgery, when there are fewer nursing staff available, and put on a variable-rate intravenous insulin infusion and looked after by one of the most junior members of the medical team, who are known to have poor levels of knowledge of diabetes management [47].

Hospital admission

During the hospital admission, it is important that the individualized care plan is communicated to all staff involved in the care of the patient and that all efforts are made to minimize the metabolic consequences of starvation and surgical stress. At the same time, optimal glycemic control should be achieved using the standard of care for that institution, such as a basal bolus insulin regimen [97, 135].

The principles of the enhanced recovery after surgery program should be put into place, including, for people with type 2 diabetes, the administration of a preoperative carbohydrate load [136].

When the starvation time is short, i.e. less than one missed meal, there would be no need for a variable-rate intravenous insulin infusion; however, if the starvation period is likely to be longer,

Table 34.5 Guidelines for perioperative adjustment of non-insulin medication.

Tablets	Day prior to admission	Day of surgery/while on a VRIII		
		Patient for a.m. surgery	Patient for p.m. surgery	If a VRIII is being used[a]
Acarbose	Take as normal	Omit morning dose if NBM	Give morning dose if eating	Stop until eating and drinking normally
Meglitinide (repaglinide or nateglinide)	Take as normal	Omit morning dose if NBM	Give morning dose if eating	Stop until eating and drinking normally
Metformin (procedure not requiring use of contrast media[b])	Take as normal	If taken once or twice a day take as normal. If taken three times per day, omit lunchtime dose	If taken once or twice a day take as normal. If taken three times per day, omit lunchtime dose	Stop until eating and drinking normally
Sulfonylurea (e.g. glibenclamide, gliclazide, glipizide)	Take as normal	Once daily, omit a.m. Twice daily, omit a.m.	Once daily, omit a.m. Twice daily, omit a.m. and p.m.	Stop until eating and drinking normally
Pioglitazone	Take as normal	Take as normal	Take as normal	Stop until eating and drinking normally
DPP-4 inhibitor (e.g. sitagliptin, vildagliptin, saxagliptin, alogliptin, linagliptin)	Take as normal	Take as normal	Take as normal	Stop until eating and drinking normally
GLP-1 receptor agonist (e.g. exenatide, liraglutide, lixisenatide)	Take as normal	Take as normal	Take as normal	Take as normal
SGLT-2 inhibitor (e.g. dapagliflozin, canagliflozin)	Take as normal	Omit on day of surgery	Omit on day of surgery	Stop until eating and drinking normally

Warn the patient that their blood glucose control may be erratic for a few days after the procedure.
[a]If the patient requires an ongoing VRIII then any long-acting background insulin should be continued but at 80% of the dose that the patient usually takes when they are well. Normal insulin doses should be recommenced when the patient is eating and drinking normally.
[b]If contrast medium is to be used and eGFR <60 mL/min/1.73 m^2, metformin should be omitted on the day of the procedure and for the following 48 h.
eGFR, estimated glomerular filtration rate; NBM, nil by mouth; VRIII, variable-rate intravenous insulin infusion.
Source: Dhatariya et al. 2015 [148].

then one should be *in situ* and the use of long-acting insulin should be continued to prevent rebound hyperglycemia when the intravenous insulin regimen is taken down [106]. During the entire inpatient admission, the patient's pressure areas, including their heels and feet, should be regularly inspected.

While in the operating theater and recovery

While the patient is in theater and in recovery, good glycemic control should be monitored and maintained and normal electrolyte concentration should also be maintained.

The use of multimodal analgesia with an appropriate antiemetic to permit an early return to a normal diet and the usual diabetes regimen is paramount, although the use of dexamethasone in this situation remains a matter for debate [137].

Postoperative period

There are several factors that influence glycemic control in the postoperative period, including a variation in nutritional intake, the discontinuation of the usual blood glucose-lowering medication, the decrease in physical activity, the increase in stress hormones, and the presence of infection or pain. It is therefore important that glycemic control is maintained in addition to fluid and electrolyte balance and that pain and postoperative nausea and vomiting are controlled.

Hospital discharge

Prior to hospital discharge, factors that are likely to delay discharge from hospital should have been identified in the preoperative stage and necessary arrangements should have been made to allow the patient to go back to their usual place of care when they are medically fit. The patient should be made aware that the metabolic and endocrine effects of surgery may last for several days because of ongoing changes in the amount that they eat, their activity levels, and the levels of stress hormones. The patient should be advised that their blood glucose management may need to change for some time postoperatively. The diabetes specialist team or the patient's usual provider of diabetes care should be involved in this discussion.

Emergency surgery

For patients requiring emergency surgery where preoperative glycemic optimization is not possible, then the use of a variable-rate intravenous insulin infusion is likely to be necessary, trying to maintain a blood glucose level between 6.0 and 10.0 mmol/L (108 and 180 mg/dL). This should be continued until the patient is eating and drinking normally. Some patients who are not known to have diabetes may develop transient hyperglycemia (so-called stress hyperglycemia) [8, 9]. These individuals should be treated just as aggressively as people known to have diabetes because

their risk of postoperative complications is far higher than in those who were previously known to have diabetes [31, 32].

Continuous subcutaneous insulin infusions (CSIIs; "pumps")

Manipulation of CSIIs depends on the length of surgery and the length of starvation. If the length of starvation is short, i.e. less and one missed meal, the pump therapy can usually be continued and the patient should remain on their basal rate until they are eating and drinking normally without giving themselves a bolus dose. Regular blood glucose testing is necessary. If, however, the starvation period is likely to be prolonged, then the pump should be discontinued and a variable-rate intravenous insulin infusion started.

If there is a period of post- or perioperative hypotension, then peripheral skin perfusion may be compromised, thus reducing the absorption of insulin given subcutaneously and may necessitate treatment with a variable-rate intravenous insulin infusion, especially if the patient is unable to self-manage.

If the insulin pump has been discontinued and replaced with a variable-rate intravenous insulin infusion, the insulin pump should be restarted once the patient is eating and drinking normally and the variable-rate intravenous insulin infusion should be discontinued 30 min after the first mealtime bolus.

Glucocorticoid use

The prevalence of steroid use in hospital inpatients may be in excess of 10% [138]. The use of steroid treatment in people with pre-existing diabetes is very likely to result in worsening glucose control, which may be termed steroid-induced hyperglycemia. This will warrant temporary additional, and more active, glycemic management. A rise in glucose level may occur in people without a known diagnosis of diabetes, and this may be termed steroid-induced diabetes. It may or may not resolve when the steroids are withdrawn. Short courses of steroids resulting in minimal periods of hyperglycemia may not warrant intervention, although higher dose steroids, for longer periods, may result in significant symptomatic hyperglycemia with the potential for acute complications [139]. Hence addressing the hyperglycemia may reduce these risks.

Steroid therapy: impact on blood glucose

Steroids may be administered by various regimens and at variable doses. A single daily dose of steroid (e.g. prednisolone/prednisone) in the morning is the commonest mode of administration. In susceptible patients, this will often result in a rise in blood glucose by late morning that continues through to the evening. Overnight, the blood glucose generally often falls back to baseline levels by the next morning. Therefore, treatment should be tailored to treating the hyperglycemia, while avoiding nocturnal and early morning hypoglycemia.

Multiple daily doses of steroid, be it intravenous hydrocortisone or oral dexamethasone, can cause a hyperglycemic effect throughout the 24-h period. It may be, however, that a twice-daily premixed or basal bolus regimen may need to be started if oral medication or once-daily insulin proves insufficient to control hyperglycemia. Close attention will therefore need to be paid to blood glucose monitoring and early intervention may be necessary.

Glucose levels in most individuals can be predicted to rise ~4–8 h following the administration of oral steroids, and sooner following the administration of intravenous steroids. Again, capillary blood glucose monitoring is paramount to guide appropriate therapeutic interventions. Conversely, glucose levels may improve to presteroid levels 24 h after intravenous steroids have been discontinued. If oral steroids are weaned down over several weeks, the glucose levels may decline in a dose-dependent fashion, but this may not occur, particularly in those with pre-existing undiagnosed diabetes.

Monitoring

At the commencement of steroid therapy, or for those already on a supraphysiological dose of corticosteroid, capillary blood glucose (CBG) testing should be initiated once daily, perhaps most appropriately prior to or following lunch or the evening meal, when the hyperglycemic effects of a morning dose of steroid is likely to be greatest.

Medication options for people taking once-daily steroid therapy

Non-insulin therapies

Given their mode of action, a short-acting sulfonylurea taken once daily may best manage the glucose excursion associated with a once-daily oral steroid. While monitoring for hypoglycemia, the dose of sulfonylurea may be maximally titrated in the morning. Intuitively, pioglitazone may seem an appropriate choice for the management of steroid-induced hyperglycemia; however, the evidence base for its use is weak [140]. There is currently no evidence to support the use of GLP-1 receptor agonists, DPP-4 inhibitors, or SGLT-2 inhibitors; however, their mode of action may suggest that they would be beneficial in this circumstance.

Insulin therapies

Morning administration of basal human insulin may closely fit the glucose excursion induced by a single morning dose of oral steroid. Basal insulin analogs may be appropriate if hyperglycemia is present for more prolonged periods. However, care should be taken to identify and protect against hypoglycemia overnight and in the early morning if long-acting insulin analogs are used in this context.

Medication options for people taking multiple daily doses of steroid

Non-insulin therapies

Multiple doses of oral or intravenous steroid in at-risk individuals will most likely result in hyperglycemia throughout the day and

night. Administrations of oral hypoglycemic agents are unlikely to be effective in controlling the resultant hyperglycemia. A trial of twice-daily low-dose, short-acting sulfonylurea may be indicated, then with titration as needed. Metformin and pioglitazone are unlikely to be of significant benefit and there is currently no evidence to support the use of other classes of agent.

Insulin therapies

It is likely that subcutaneous insulin using a basal or multiple daily injection regimen will be the most appropriate choice to achieve glycemic control in the event of hyperglycemia for the majority of patients.

Hospital discharge

When a patient is discharged from hospital on steroid therapy, a clear strategy for the management of hyperglycemia or potential hyperglycemia, and the titration of therapy to address the hyperglycemia, should be communicated to the community diabetes team and primary care team. Patients commenced on steroids as an inpatient and discharged after a short stay with the intention of continuing high-dose steroids should receive standard education with regard to diabetes, encompassing the risks associated with hyper- and hypoglycemia.

If steroids are discontinued prior to discharge, and hyperglycemia persists, then CBG testing should be continued on discharge until normoglycemia returns or until a definitive test for diabetes is undertaken (fasting glucose, oral glucose tolerance test, or HbA_{1c}).

If steroid treatment is ceased in hospital and CBG tests are in the normal range, then post-discharge testing is not recommended. A definitive test for diabetes should still be undertaken.

Steroid treatment in end-of-life care

People with diabetes at the end stages of life have a unique set of clinical needs (Chapter 63). Steroid therapy is frequently used in palliative care for symptom control, usually as dexamethasone or prednisolone/prednisone. The hyperglycemia associated with once-daily steroid therapy can often be managed by morning administration of a long-acting sulfonylurea, or morning isophane insulin. However, if steroids are to be given twice daily, it is probable that an alternative approach will be needed. Twice-daily short-acting sulfonylurea or isophane insulin can be effective, but there is a risk of early morning hypoglycemia.

If hypoglycemia is a concern, a once-daily long-acting insulin analog given in the morning may be a safer, less complex regimen, especially for those new to insulin.

Short-term courses (<3 days) of steroids may only require closer CBG testing, but longer courses will require a review of glucose-lowering therapy and may result in a switch from oral agents to insulin. In the latter situation, an isophane insulin given once daily could be considered. In those without a diagnosis of diabetes prior to the commencement of steroids, then CBG testing and patient and carer education should be undertaken.

Blood glucose targets at the end of life may differ from those traditionally given. Glucose levels should be targeted between 6.0 and 15.0 mmol/L (108 and 270 mg/dL), although targets should be individualized.

Foot care

The "diabetic foot" remains the commonest cause for a diabetes-specific acute hospital admission [141], and it has been estimated that that ~£1 in every £150 spent by the NHS in England each year is on diabetes-related foot disease [142], and much of this on in-hospital care (Chapter 48).

It has been well recognized that the presence of a multidisciplinary foot team leads to better outcomes [143]. This should include a specialist podiatrist, diabetologist, vascular and orthopedic surgeon, interventional radiologist, tissue viability nurse, microbiologist, DSN/CDE, and orthotist [144, 145]. Specialist diabetes podiatrists provide the best value when considering admission avoidance, reducing length of hospital stay, and reducing amputation rates [146, 147].

The general principles for foot care in people with diabetes should apply to all admissions, not just those with active foot disease. These measures include taking a specific foot history and an inspection of the feet, looking for evidence of neuropathy, ischemia, ulceration, inflammation, and/or infection, deformity, or Charcot neuroarthropathy. It is important to take the shoes, socks, and any dressings off the feet to inspect any underlying wounds, ensuring that pressure areas are healthy. The feet should be inspected daily during the inpatient stay and new problems that are identified should be managed in conjunction with the specialist diabetic foot multidisciplinary team.

Conclusions

People with diabetes are twice as likely to be admitted to hospital and stay twice as long as those without diabetes. They have worse outcomes and a poorer patient experience than those without diabetes. Given the large numbers of inpatients with diabetes, and the considerable excess costs associated with their care, diabetes inpatient care is now being taken more seriously. However, although there is now a wealth of evidence that specialist inpatient diabetes teams reduce length of stay, reduce errors in prescribing, and improve the patient experience and clinical outcomes, many institutions across the world still lack inpatient specialist teams.

There are now a large number of national and international guidelines available that should make the care of inpatients with diabetes easier to achieve. There remains a lot of work to be done to provide more evidence to substantiate the consensus opinions in many of the guidelines, but as more evidence accrues to show which interventions work, so the excess morbidity and mortality seen in this cohort of patients should reduce to equal those of individuals without diabetes.

Until more evidence is available, it remains incumbent on those delivering the care to ensure that an attitude of nihilism is avoided—"the absence of evidence does not mean the absence of effect." All attempts should be made to achieve suitable glycemic control, avoiding symptomatic hyperglycemia or debilitating hypoglycemia.

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35 Hypoglycemia in Diabetes

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Key points

- Iatrogenic hypoglycemia is the limiting factor in the glycemic management of diabetes. It occurs during treatment with a sulfonylurea, a glinide, or insulin.
- The key physiological defenses against falling plasma glucose concentrations are decrements in insulin and increments in glucagon and epinephrine. The behavioral defense is carbohydrate ingestion prompted by symptoms that are largely the result of sympathetic neural activation.
- Hypoglycemia in diabetes is the result of therapeutic hyperinsulinemia. As glucose levels fall, decrements in insulin and increments in glucagon are lost, because of β-cell failure, in type 1 diabetes mellitus (T1DM) and advanced type 2 diabetes mellitus (T2DM). In that setting, attenuated increments in epinephrine cause the syndrome of defective glucose counter-regulation. Attenuated increments in sympathetic neural activity largely bring about the syndrome of hypoglycemia unawareness.
- The concept of hypoglycemia-associated autonomic failure (HAAF) in diabetes posits that recent antecedent hypoglycemia, and also prior exercise or sleep, cause both defective glucose counter-regulation and hypoglycemia unawareness by attenuating the sympathoadrenal response to subsequent hypoglycemia.
- Hypoglycemia unawareness and, in part, the reduced epinephrine component of defective glucose counter-regulation are reversible in 2–3 weeks with scrupulous avoidance of hypoglycemia in most affected individuals.
- The risk factors for hypoglycemia, based on this pathophysiology, include both relative and absolute therapeutic insulin excess and factors indicative of HAAF, which include absolute endogenous insulin deficiency, a history of severe hypoglycemia, hypoglycemia unawareness, or both, in addition to prior exercise or sleep, and aggressive glycemic therapy per se.
- This pathophysiology explains why the incidence of iatrogenic hypoglycemia increases over time in T2DM, approaching that in T1DM. Most episodes of hypoglycemia occur in people with T2DM.
- Minimizing the risk of iatrogenic hypoglycemia requires acknowledging the problem, applying the principles of aggressive glycemic therapy, and considering the risk factors for relative and absolute therapeutic insulin excess and for HAAF.
- A reasonable individualized glycemic goal is the lowest HbA_{1c} that does not cause severe hypoglycemia and preserves awareness of hypoglycemia, preferably with little or no symptomatic or even asymptomatic hypoglycemia, at a given stage in the evolution of the individual's diabetes.
- Maintenance of the greatest degree of glycemic control that can be accomplished safely in a given patient at a given stage of that individual's diabetes is in the person's best interest. Concerns about hypoglycemia should not be an excuse for poor glycemic control.

Overview of the clinical problem

Iatrogenic hypoglycemia is the limiting factor in the glycemic management of diabetes [1, 2]. It causes recurrent morbidity in most people with type 1 diabetes mellitus (T1DM) and many with advanced type 2 diabetes mellitus (T2DM), and is sometimes fatal. It compromises physiological and behavioral defenses against subsequent falling plasma glucose concentrations and thus causes a vicious cycle of recurrent hypoglycemia. It precludes maintenance of euglycemia over a lifetime of diabetes and thus full realization of the vascular benefits of glycemic control.

Hypoglycemia in diabetes is fundamentally iatrogenic, the result of pharmacokinetically imperfect treatments with an insulin secretagogue (e.g. a sulfonylurea or a glinide) or with exogenous insulin that results in episodes of hyperinsulinemia. Nonetheless, hypoglycemia is typically the result of the interplay of relative or absolute therapeutic insulin excess and compromised physiological and behavioral defenses against falling plasma glucose concentrations [1, 2].

Textbook of Diabetes, Fifth Edition. Edited by R. Holt, C. Cockram, A. Flyvbjerg and B. Goldstein.

The problem of hypoglycemia in diabetes has been summarized [1] and reviewed in detail [2]. Our premise is that understanding of the pathophysiology of glucose counter-regulation, the mechanisms that normally prevent or rapidly correct hypoglycemia, leads to insight into the frequency of, risk factors for, and prevention of iatrogenic hypoglycemia. Therefore, the physiology of glucose counter-regulation and its pathophysiology in diabetes are addressed first, followed by a summary of the magnitude of the clinical problem. With that background, a clinical approach to the prevention of iatrogenic hypoglycemia, and if necessary its treatment, is discussed.

Physiology of glucose counter-regulation

Hypoglycemia and the brain

Glucose is an obligate oxidative fuel for the brain under physiological conditions [1–4]. The brain accounts for 20% of whole-body glucose utilization. Because it cannot synthesize glucose, utilize physiological concentrations of circulating non-glucose fuels effectively, or store more than a few minutes' supply as glycogen [1, 2], the brain requires a virtually continuous supply of glucose from the circulation. Because facilitated blood–brain glucose transport is a direct function of the arterial plasma glucose concentration, that requires maintenance of the physiological plasma glucose concentration. Hypoglycemia causes functional brain failure, which is typically reversed after the plasma glucose concentration is raised [4]. Rarely, hypoglycemia causes death [4].

Responses to hypoglycemia

Falling plasma glucose concentrations cause a sequence of responses in individuals without diabetes (Table 35.1) [1, 5–8]. The first physiological response, which occurs as plasma glucose concentrations decline within the postabsorptive plasma glucose concentration range, is a decrease in insulin secretion. The secretion of glucose counter-regulatory (plasma glucose-raising) hormones, including glucagon and epinephrine, increases as plasma glucose concentrations fall just below the physiological range. Lower plasma glucose levels cause a more intense sympathoadrenal, both sympathetic neural and adrenomedullary, response and symptoms. Even lower plasma glucose concentrations cause functional brain failure [4].

Clinical manifestations of hypoglycemia

The symptoms and signs of hypoglycemia are not specific [8, 9]. Thus, clinical hypoglycemia is most convincingly documented by Whipple's triad: symptoms, signs, or both, consistent with hypoglycemia; a low reliably measured plasma glucose concentration; and resolution of those symptoms and signs after the plasma glucose concentration is raised.

Neuroglycopenic symptoms, which are the result of brain glucose deprivation per se, include cognitive impairments, behavioral changes, and psychomotor abnormalities and, at lower plasma glucose concentrations, seizure and coma [1, 2, 4, 8, 9]. Neurogenic (or autonomic) symptoms, which are largely the result of the perception of physiological changes caused by the sympathoadrenal—particularly the sympathetic neural [9]—discharge triggered by hypoglycemia, include both adrenergic (e.g. palpitations, tremulousness, and anxiety/arousal) and cholinergic (e.g. sweating, hunger, and paresthesias) symptoms [8]. Central mechanisms may also be involved in some of the latter symptoms, such as hunger [10]. Awareness of hypoglycemia is largely the result of the perception of neurogenic symptoms [8].

Signs of hypoglycemia include pallor and diaphoresis, the result of adrenergic cutaneous vasoconstriction and cholinergic activation of sweat glands, respectively [1, 2]. Neuroglycopenic manifestations are often observable.

Table 35.1 Physiological responses to decreasing plasma glucose concentrations.

Response	Glycemic threshold[a] (mg/dL) [mmol/L])	Physiological effects	Role in prevention or correction of hypoglycemia (glucose counter-regulation)
↓ Insulin	80–85 [4.4–4.7]	↑ R_a (↓ R_d)	Primary glucose regulatory factor, first defense against hypoglycemia
↑ Glucagon	65–70 [3.6–3.9]	↑ R_a	Primary glucose counter-regulatory factor, second defense against hypoglycemia
↑ Epinephrine	65–70 [3.6–3.9]	↑ R_a, ↓ R_d	Involved, critical when glucagon is deficient, third defense against hypoglycemia
↑ Cortisol and growth hormone	65–70 [3.6–3.9]	↑ R_a, ↓ R_d	Involved but not critical
Symptoms	50–55 [2.8–3.1]	↑ Exogenous glucose	Prompt behavioral defense (food ingestion)
↓ Cognition	<50 [<2.8]	–	Compromises behavioral defense

[a] Arterialized venous, not venous, plasma glucose concentrations.
R_a, rate of glucose appearance, glucose production by the liver and kidneys; R_d, rate of glucose disappearance, glucose utilization by insulin-sensitive tissues such as skeletal muscle (no direct effect on central nervous system glucose utilization).
Source: Cryer PE. Glucose homeostasis and hypoglycemia. In: Kronenberg HM, Melmed S, Polonsky KS, Larsen PR, eds. *Williams Textbook of Endocrinology*, 11th edn. Philadelphia: Saunders, 2008; 1503–1533. Reproduced with permission.

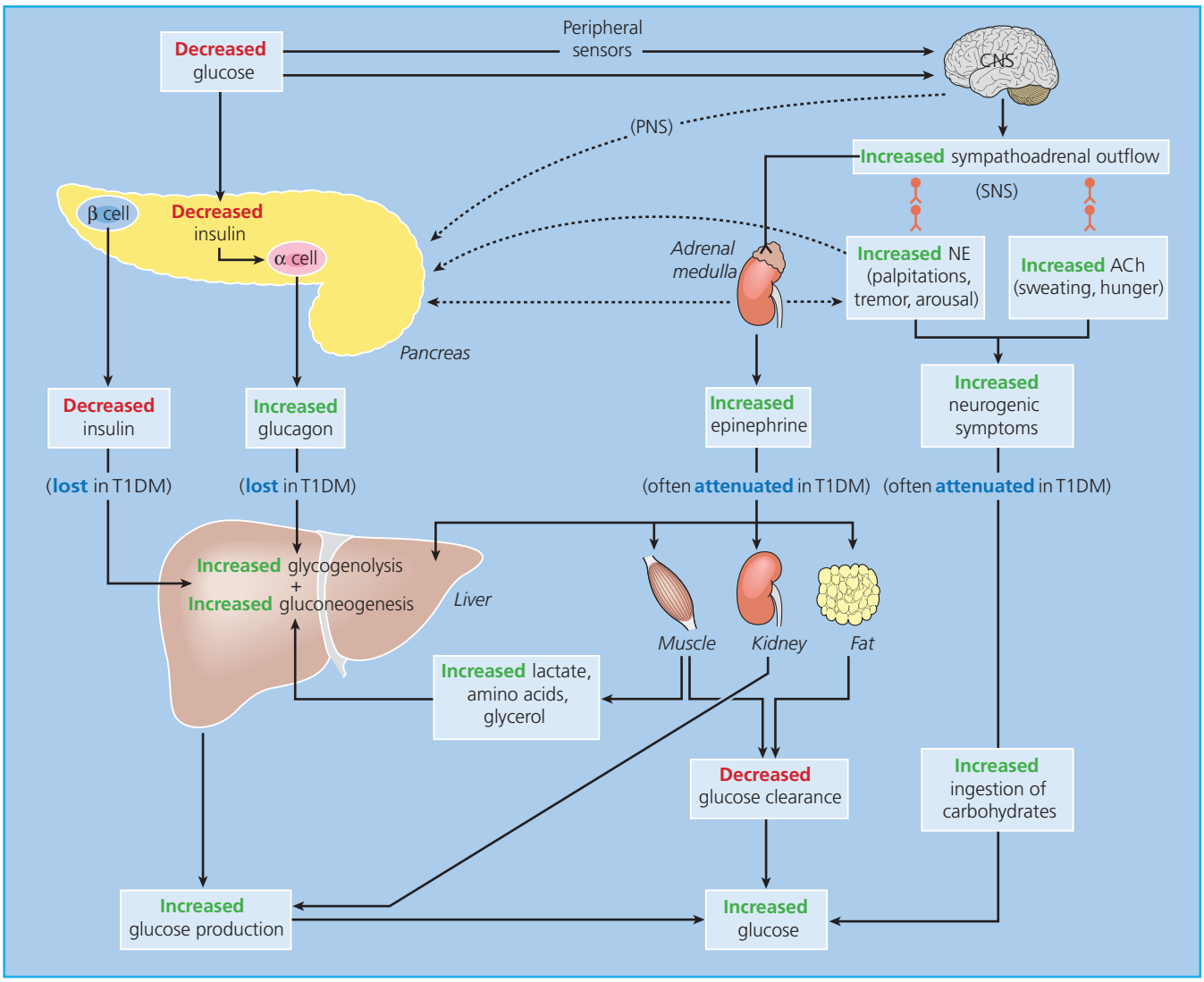

Figure 35.1 Physiological and behavioral defenses against hypoglycemia in humans. ACh, acetylcholine; α cell, pancreatic islet α cell; β cell, pancreatic islet β cell; NE, norepinephrine; PNS, parasympathetic nervous system; SNS, sympathetic nervous system; T1DM, type 1 diabetes mellitus. Source: Cryer PE. Mechanisms of sympathoadrenal failure and hypoglycemia in diabetes. *J Clin Invest* 2006; **116**:1470–1473. Reproduced with permission from the American Society for Clinical Investigation.

Maintenance of systemic glucose balance

Because obligatory glucose utilization, largely by the brain, is fixed and exogenous glucose delivery from ingested carbohydrates is intermittent, systemic glucose balance is maintained, and hypoglycemia (and also hyperglycemia) is prevented, by dynamic regulation of endogenous glucose production from the liver (and the kidneys) and of glucose utilization by non-neural tissues such as muscle [1, 11]. Although an array of hormones, neurotransmitters, and metabolic substrates are involved, endogenous glucose production and glucose utilization by non-neural tissues are regulated primarily by insulin (Figure 35.1; Table 35.1) [11].

The first physiological defense against hypoglycemia is a decrease in pancreatic islet β-cell insulin secretion. That occurs as plasma glucose concentrations decline within the physiological range (Table 35.1) and favors increased hepatic (and renal) glucose production with virtual cessation of glucose utilization by insulin-sensitive tissues such as muscle (Figure 35.1). The second physiological defense is an increase in pancreatic islet α-cell glucagon secretion. That occurs as plasma glucose concentrations fall just below the physiological range (Table 35.1) and stimulates hepatic glucose production (largely by stimulating glycogenolysis) (Figure 35.1). Increased glucagon secretion is signaled primarily by a decrease in intra-islet insulin, perhaps among other β-cell secretory products, in the setting of low glucose concentrations [1, 2, 12] and secondarily by increased autonomic nervous system—sympathetic, parasympathetic, and adrenomedullary—inputs [1, 2, 13]. The third physiological defense, which becomes critical when glucagon is deficient, is an increase in adrenomedullary epinephrine secretion [1, 2, 11]. That, too, occurs as plasma

glucose concentrations fall just below the physiological range (Table 35.1). It raises plasma glucose concentrations largely by β_2-adrenergic stimulation of hepatic (and renal) glucose production (Figure 35.1), but the glucose-raising actions of epinephrine also involve limitation of glucose clearance by insulin-sensitive tissues, mobilization of gluconeogenic substrates such as lactate and amino acids from muscle and glycerol from fat, and α_2-adrenergic limitation of insulin secretion [1, 2, 14]. Sympathoadrenal activity, including epinephrine secretion, is regulated in the brain [1, 2, 11]. Circulating epinephrine is almost exclusively derived from the adrenal medullae [9]; while circulating norepinephrine is largely derived from sympathetic nerves under resting and many stimulated (e.g. exercise) conditions, the plasma norepinephrine response to hypoglycemia is also largely adrenomedullary in origin [9].

If these physiological defenses fail to abort an episode of developing hypoglycemia, lower plasma glucose concentrations cause a more intense sympathoadrenal response that causes neurogenic symptoms (Figure 35.1) [1, 2, 11]. Those symptoms cause awareness of hypoglycemia that prompts the behavioral defense of ingestion of carbohydrates [1, 2, 11].

All of these defenses against hypoglycemia, not just insulin secretion, are typically compromised in people with T1DM and those with advanced (i.e. absolutely endogenous insulin-deficient) T2DM (Figure 35.1) [1, 2].

Pathophysiology of glucose counter-regulation in diabetes

Insulin excess

Although substantial insulin excess alone can cause hypoglycemia, the integrity of the defenses against falling plasma glucose concentrations determines whether a typical episode of therapeutic hyperinsulinemia results in clinical hypoglycemia [1, 2]. Thus, iatrogenic hypoglycemia is typically the result of the interplay of relative or absolute therapeutic hyperinsulinemia and compromised physiological and behavioral defenses against falling plasma glucose concentrations (Figure 35.1; Table 35.2) [1, 2, 15, 16].

Table 35.2 Responses to falling plasma glucose concentrations in humans.

Plasma glucose	Individuals	Plasma		
		Insulin	Glucagon	Epinephrine
↓	Non-diabetic	↓	↑	↑
↓	T1DM[a]	No ↓	No ↑	Attenuated ↑
↓	Early T2DM	↓	↑	↑
↓	Late T2DM[a]	No ↓	No ↑	Attenuated ↑

[a]These alterations account for the appearance of defective glucose counter-regulation and hypoglycemia unawareness in T1DM and late T2DM.

Defective glucose counter-regulation and hypoglycemia unawareness

In fully developed (i.e. C-peptide-negative) T1DM, circulating insulin concentrations cannot decrease as plasma glucose concentrations fall in response to therapeutic (exogenous) hyperinsulinemia (Table 35.2) [1, 2, 15]. That is the result of β-cell failure, which also causes loss of the increase in circulating glucagon concentrations (Figure 35.2; Table 35.2) [1, 2, 12, 15]. The latter conclusion is based on the finding that indirect reciprocal β-cell-mediated signaling normally predominates over direct α-cell signaling in the regulation of glucagon secretion in humans [1, 2, 12]. Thus, the absence of a decrease in intra-islet insulin, perhaps among other β-cell secretory products, in concert with low glucose levels, plausibly explains loss of the glucagon response [1, 2, 12]. Therefore, both the first and second physiological defenses against hypoglycemia are lost. Furthermore, the increase in circulating epinephrine, the third physiological defense, is typically attenuated (Figure 35.2; Table 35.2) [1, 15]. In the setting of absent insulin and glucagon responses, the attenuated epinephrine response causes the clinical syndrome of defective glucose counter-regulation (Table 35.2) [1, 2, 15–18], which is associated with a 25-fold [18] or greater [17] increased risk of severe iatrogenic hypoglycemia in T1DM. In addition, the attenuated epinephrine response is a marker for an attenuated sympathoadrenal, including sympathetic neural, response (Table 35.2), which is largely responsible for reduced neurogenic symptom responses and therefore the clinical syndrome of hypoglycemia unawareness [1, 2, 9] which is associated with a sixfold increased risk of severe iatrogenic hypoglycemia in T1DM [19]. Attenuated sympathoadrenal responses to falling plasma glucose concentrations can be caused by recent antecedent hypoglycemia (Figures 35.3 and 35.4) [1, 2, 15, 16, 20], prior exercise [1, 2, 21–23], or sleep [1, 2, 24–26].

Although hypoglycemia unawareness is largely the result of reduced release of the neurotransmitters norepinephrine and acetylcholine [1, 9], there is evidence of decreased β-adrenergic sensitivity, specifically reduced cardiac chronotropic sensitivity to isoproterenol, in affected individuals [27, 28]. However, vascular sensitivity to β_2-adrenergic agonism was not found to be reduced in people with unawareness [29]; reduced sensitivity to β-adrenergic signaling of neurogenic symptoms remains to be demonstrated in those with unawareness, and it would be necessary to postulate decreased cholinergic sensitivity to explain reduced cholinergic symptoms such as sweating.

The pathophysiology of glucose counter-regulation is the same in T1DM and advanced (i.e. absolutely endogenous insulin-deficient) T2DM, albeit with different time courses (Table 35.2) [1, 2, 15, 16]. The pathogenesis of an episode of iatrogenic hypoglycemia involves therapeutic hyperinsulinemia resulting in falling plasma glucose concentrations and loss of the appropriate decrements in insulin and increments in glucagon. The hypoglycemia, in turn, reduces the sympathoadrenal responses to subsequent hypoglycemia. Because β-cell failure, which causes loss of both the insulin and glucagon responses [1, 2, 15, 16], occurs rapidly in T1DM but slowly in T2DM, the syndromes

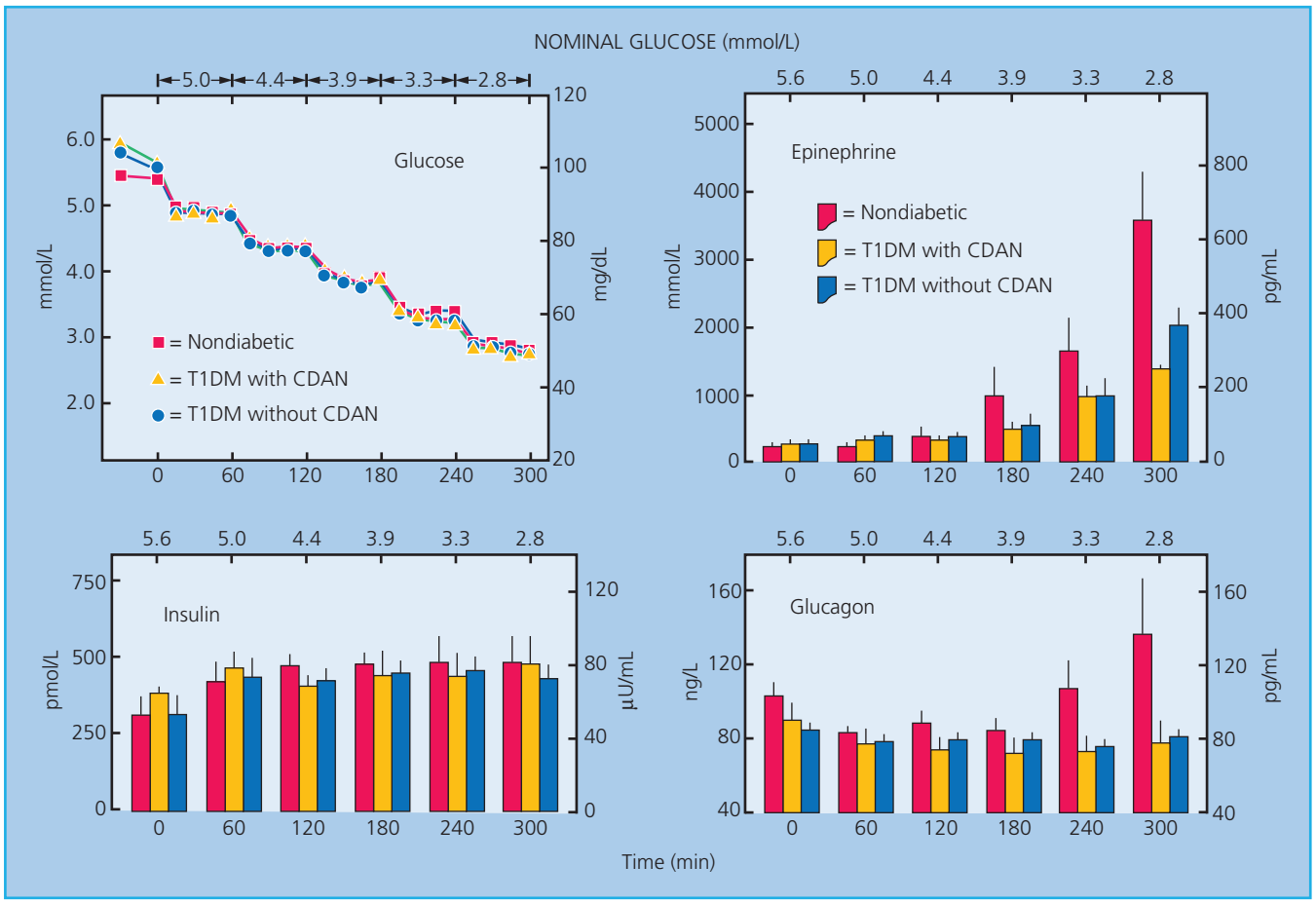

Figure 35.2 Mean (± SE) plasma glucose, insulin, epinephrine, and glucagon concentrations during hyperinsulinemic stepped hypoglycemic glucose clamps in individuals without diabetes (red squares and columns), people with type 1 diabetes (T1DM) with classic diabetic autonomic neuropathy (CDAN) (yellow triangles and columns), and people with type 1 diabetes without CDAN (blue circles and columns). Source: Dagogo-Jack et al. 1993 [15]. Reproduced with permission from the American Society for Clinical Investigation.

of defective glucose counter-regulation and hypoglycemia unawareness develop early in T1DM but later in T2DM. This temporal pattern of compromised glycemic defenses explains why iatrogenic hypoglycemia becomes progressively more frequent as individuals approach the insulin-deficient end of the spectrum of T2DM, as discussed later.

Hypoglycemia-associated autonomic failure

The concept of hypoglycemia-associated autonomic failure (HAAF) in diabetes posits that recent antecedent hypoglycemia (Figures 35.3 and 35.4) [1, 2, 15, 16, 20]—and also prior exercise [1, 2, 21–23] or sleep [1, 2, 24–26]—causes both defective glucose counter-regulation (by attenuating the epinephrine responses to subsequent hypoglycemia in the setting of absent decrements in insulin and absent increments in glucagon) and hypoglycemia unawareness (by attenuating the sympathoadrenal, including the sympathetic neural, and resulting neurogenic symptom responses to subsequent hypoglycemia). It therefore leads to a vicious cycle of recurrent iatrogenic hypoglycemia (Figure 35.5). Thus, HAAF is, at least in large part, a dynamic functional disorder that is distinct from classic diabetic autonomic neuropathy [1, 2]. Nonetheless, the key feature of HAAF, an attenuated sympathoadrenal response to a given level of hypoglycemia, is more prominent in people with diabetic autonomic neuropathy (Figure 35.2) [30, 31].

The clinical impact of HAAF is well established in T1DM [1, 2, 15, 32–37]. Recent antecedent hypoglycemia, even asymptomatic nocturnal hypoglycemia, reduces epinephrine, symptomatic, and cognitive dysfunction responses to a given level of subsequent hypoglycemia [36], reduces detection of hypoglycemia in the clinical setting [37], and reduces defense against hyperinsulinemia [15] in T1DM. Perhaps the most compelling support for the concept of HAAF is the finding, initially by three independent research teams [32–35], that as little as 2–3 weeks of scrupulous avoidance of hypoglycemia reverses hypoglycemia unawareness (Figure 35.6) and improves the attenuated epinephrine component of defective glucose counter-regulation in most affected individuals.

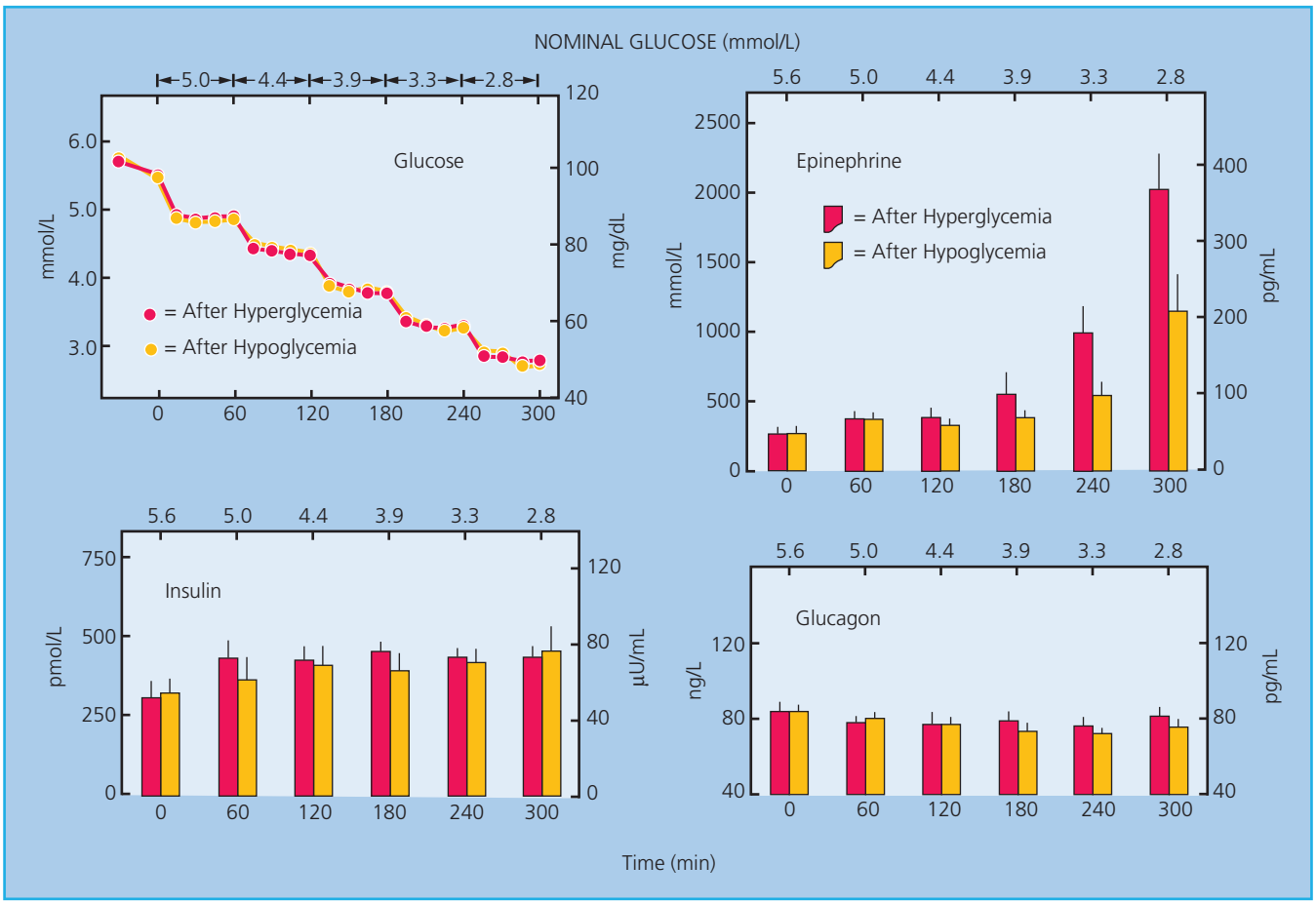

Figure 35.3 Mean (± SE) plasma glucose, insulin, epinephrine, and glucagon concentrations during hyperinsulinemic stepped hypoglycemic glucose clamps in people with type 1 diabetes without classic diabetic autonomic neuropathy on mornings following afternoon hyperglycemia (red circles and columns) and on mornings following afternoon hypoglycemia (yellow circles and columns). Source: Dagogo-Jack, et al. 1993 [15]. Reproduced with permission from the American Society for Clinical Investigation.

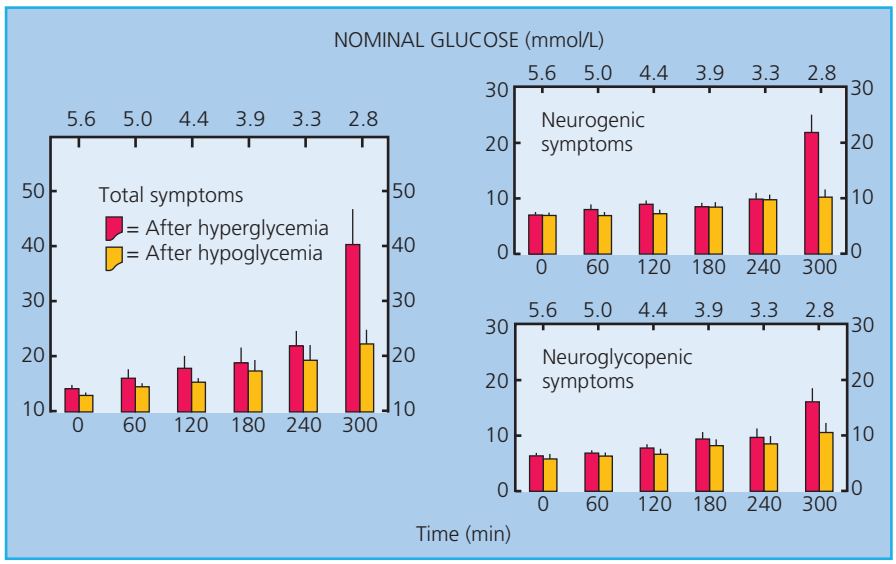

Figure 35.4 Mean (± SE) total, neurogenic, and neuroglycopenic symptom scores during hyperinsulinemic stepped hypoglycemic clamps in people with type 1 diabetes without classic diabetic autonomic neuropathy on mornings following afternoon hyperglycemia (red columns) and on mornings following afternoon hypoglycemia (yellow columns). Source: Dagogo-Jack et al. 1993 [15]. Reproduced with permission from the American Society for Clinical Investigation.

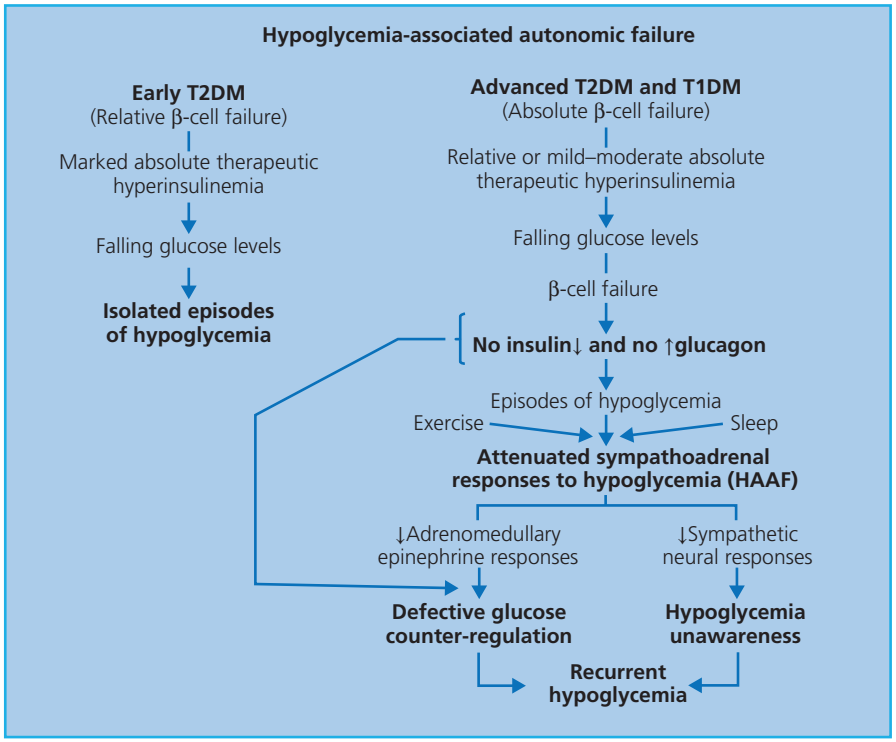

Figure 35.5 Hypoglycemia-associated autonomic failure (HAAF) in the pathogenesis of iatrogenic hypoglycemia in diabetes.

People with advanced T2DM are also at risk for HAAF [1, 2, 16]. Glucagon responses to hypoglycemia are lost [16], as they are in T1DM. Furthermore, the glycemic thresholds for sympathoadrenal and symptomatic (among other) responses to hypoglycemia are shifted to lower plasma glucose concentrations by recent antecedent hypoglycemia [16], as they are in T1DM.

The three recognized causes of HAAF each lead to attenuated sympathoadrenal and symptomatic (among other) responses to a given level of hypoglycemia [1, 2]. Antecedent hypoglycemia-related HAAF [1, 2, 15, 16, 20] led to the concept. Exercise-related HAAF [1, 2, 21–23] is exemplified by late post-exercise hypoglycemia, which typically occurs 6–15 h after strenuous exercise and is often nocturnal [38, 39]. Sleep-related HAAF [1, 2, 24–26] is the result of further attenuation of the sympathoadrenal response to hypoglycemia during sleep. Sleeping patients are therefore much less likely to be awakened by hypoglycemia than individuals without diabetes [24, 26]. There may well be additional, as yet unrecognized, functional, and therefore potentially reversible, causes of HAAF [1, 2]. In addition, there may be a structural component [1, 2].

The mechanisms of HAAF are summarized in Figure 35.7 [1, 2]. Loss of the insulin and glucagon responses to falling plasma glucose concentrations caused by therapeutic hyperinsulinemia is the result of β-cell failure in T1DM and advanced T2DM. Because normal insulin and glucagon responses to low glucose concentrations occur in people with a transplanted (i.e. denervated) pancreas [40] and in dogs with a denervated pancreas [41], and also from the perfused pancreas and perifused pancreatic islets innervation is not required [12].

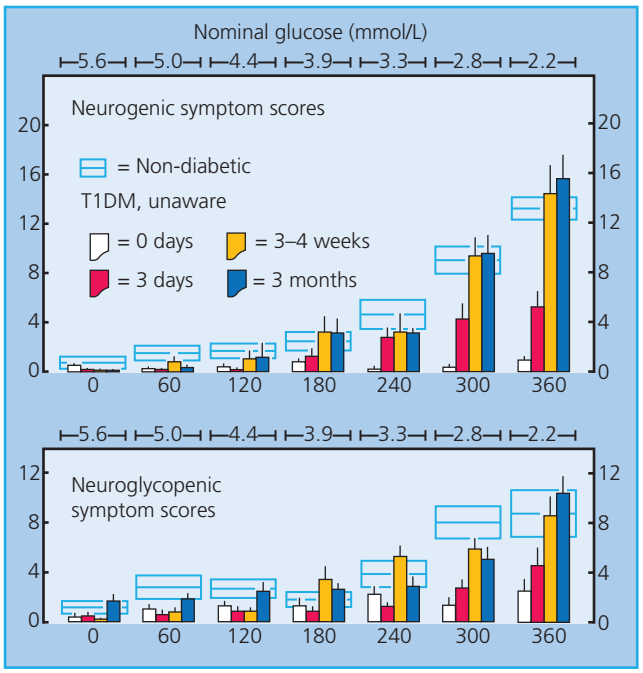

Figure 35.6 Mean (± SE) neurogenic and neuroglycopenic symptom scores during hyperinsulinemic stepped hypoglycemic clamps in individuals without diabetes (open rectangles) and in people with T1DM (columns) at baseline (0 days), after 3 days of inpatient strict avoidance of hypoglycemia, and after 3–4 weeks and 3 months of outpatient scrupulous avoidance of hypoglycemia. Source: Dagogo-Jack et al. 1994 [33]. Reproduced with permission from the American Diabetes Association.

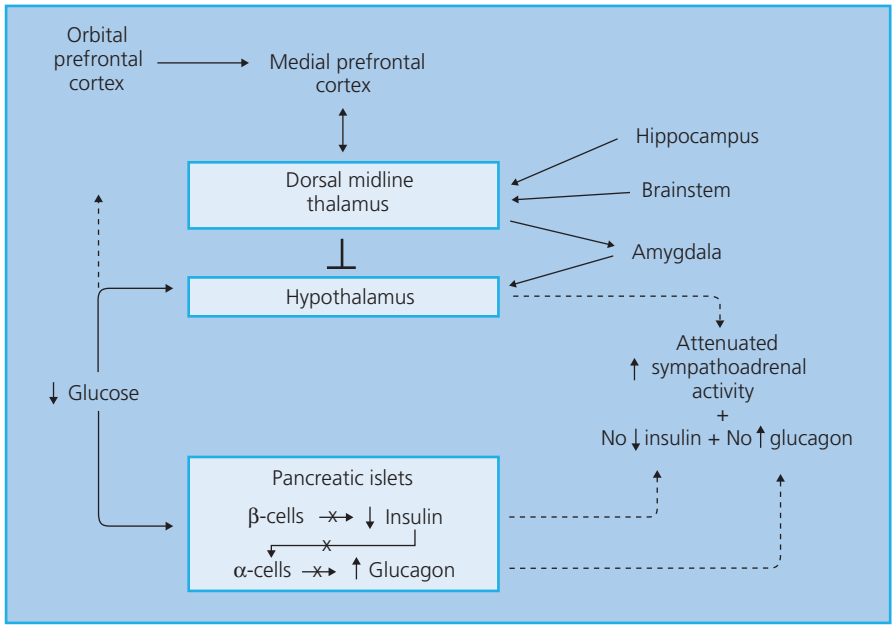

Figure 35.7 Pancreatic islet, hypothalamic and cerebral network mechanisms of hypoglycemia-associated autonomic failure (HAAF) in diabetes. Source: Cryer 2008 [1]. Reproduced with permission from the American Diabetes Association.

In the setting of absent insulin and glucagon responses to falling plasma glucose concentrations, attenuated sympathoadrenal responses cause both defective glucose counter-regulation and hypoglycemia unawareness, the two components of HAAF [1, 2]. The mechanism of the attenuated sympathoadrenal response is not known, but it must be at the level of the brain (or the afferent or efferent components of the sympathoadrenal system) (Figure 35.7). The proposed mechanisms include the systemic mediator, brain fuel transport, and brain metabolism hypotheses, all of which have been reviewed [1, 2, 12, 42, 43].

Much of the research into the pathogenesis of HAAF has focused on the hypothalamus, the central integrator of the sympathoadrenal responses to hypoglycemia [43]. While the primary alteration could reside in the hypothalamus, the changes in hypothalamic function could be secondary to those in other brain regions. For example, measurements of regional cerebral blood flow with [^{15}O]water and positron emission tomography (PET) [44] indicate that hypoglycemia activates widespread but interconnected brain regions, including the medial prefrontal cortex, the lateral orbitofrontal cortex, the thalamus, the globus pallidus, and the periaqueductal gray. These studies also show that recent antecedent hypoglycemia both reduces the sympathoadrenal and symptomatic responses (a model of HAAF) and causes a greater increase in synaptic activity in the dorsal midline thalamus during subsequent hypoglycemia [45]. Hence it has been suggested that there may be a cerebral network that results in thalamic inhibition of hypothalamic activity in HAAF (Figure 35.7) [45]. That suggestion is generically consistent with the findings of various patterns of [^{18}F]deoxyglucose uptake in people with T1DM with and without hypoglycemia unawareness [46].

Risk factors for hypoglycemia in diabetes

The risk factors for hypoglycemia in diabetes follow directly from the pathophysiology of glucose counter-regulation and are based on the principle that iatrogenic hypoglycemia is typically the result of the interplay of relative or absolute therapeutic insulin excess and compromised physiological and behavioral defenses against falling plasma glucose concentrations (i.e. HAAF) in T1DM and advanced T2DM [1, 2, 47].

Absolute or relative insulin excess

The conventional risk factors for hypoglycemia in diabetes are based on the premise that absolute or relative therapeutic insulin excess is the sole determinant of risk (Table 35.3) [1, 2, 47]. Absolute therapeutic insulin excess occurs when insulin secretagogue or insulin doses are excessive, ill-timed, or of the wrong type, or when insulin clearance is reduced as in renal failure. Relative therapeutic insulin excess occurs under a variety of conditions. It occurs when exogenous glucose delivery is decreased (as following missed or low-carbohydrate meals and during the overnight fast), when glucose utilization is increased (as during and shortly after exercise), when endogenous glucose production is decreased (as following alcohol ingestion), and when sensitivity to insulin is increased (as following weight loss or improved glycemic control and in the middle of the night). People with diabetes and their caregivers must consider each of these risk factors when the problem of iatrogenic hypoglycemia is recognized. Overall, however, they explain only a minority of episodes of hypoglycemia [48].

Table 35.3 Risk factors for hypoglycemia in diabetes.

Relative or absolute insulin excess

1. Insulin or insulin secretagogue doses are excessive, ill-timed, or of the wrong type
2. Exogenous glucose delivery is decreased (e.g. following missed meals and during the overnight fast)
3. Glucose utilization is increased (e.g. during and shortly after exercise)
4. Endogenous glucose production is decreased (e.g. following alcohol ingestion)
5. Sensitivity to insulin is increased (e.g. in the middle of the night and following weight loss or improved glycemic control)
6. Insulin clearance is decreased (e.g. with renal failure)

Hypoglycemia-associated autonomic failure

1. Absolute endogenous insulin deficiency
2. A history of severe hypoglycemia, hypoglycemia unawareness, or both, and also recent antecedent hypoglycemia, prior exercise, and sleep
3. Aggressive glycemic therapy per se (lower HbA_{1c} levels, lower glycemic goals)

Compromised defenses against hypoglycemia

The risk factors indicative of HAAF (Table 35.3) [1, 2, 47, 49–55] include absolute endogenous insulin deficiency [1, 2, 47, 49–51, 53, 54], a history of severe iatrogenic hypoglycemia, hypoglycemia unawareness, or both, and also recent antecedent hypoglycemia, prior exercise or sleep [1, 2, 47, 49, 50, 53, 55], and aggressive glycemic therapy per se (i.e. lower HbA_{1c} levels, lower glycemic goals, or both) [1, 2, 47, 49, 50, 52–55]. The degree of endogenous insulin deficiency (i.e. β-cell failure) determines the extent to which insulin levels will not decrease and glucagon levels will not increase as plasma glucose concentrations fall in response to therapeutic hyperinsulinemia. A history of severe hypoglycemia indicates, and that of hypoglycemia unawareness implies, recent antecedent hypoglycemia. The latter causes attenuated sympathoadrenal and symptomatic responses to subsequent hypoglycemia, the key feature of HAAF. In addition, prior exercise and sleep cause that feature of HAAF. Studies of intensive glycemic therapy with a control group treated to a higher HbA_{1c} level consistently report higher rates of hypoglycemia in the group treated to lower HbA_{1c} levels in T1DM [56–58] and T2DM [55, 59, 60]. That does not mean that one cannot both improve glycemic control and minimize the risk of hypoglycemia [1, 2, 47], as discussed below.

Magnitude of the clinical problem of hypoglycemia in diabetes

Diabetes is an increasingly common disease. It has been estimated that its prevalence will rise from 415 million people worldwide in 2015 to 642 million people by 2040 [61]. Iatrogenic hypoglycemia affects most of the minority with T1DM and many of the majority with T2DM [1, 2]. Indeed, because it precludes maintenance of euglycemia over a lifetime of diabetes, the barrier of hypoglycemia ultimately affects virtually all people with diabetes [1, 2].

Frequency of hypoglycemia

Hypoglycemia is a fact of life for people with T1DM (Table 35.4) [1, 2, 49, 52, 62]. The average person has untold numbers of episodes of asymptomatic hypoglycemia and experiences two episodes of symptomatic hypoglycemia per week—thousands of such episodes over a lifetime of diabetes—and one or more episodes of severe, temporarily disabling hypoglycemia, often with seizure or coma, per year. There is little evidence that this problem has abated since it was highlighted by the report of the Diabetes Control and Complications Trial (DCCT) in 1993 [56]. For example, in 2007 the UK Hypoglycaemia Study Group [62] reported an incidence of severe hypoglycemia that was twice that in the DCCT in people with T1DM for <5 years and an incidence fivefold higher than that in the DCCT in those with T1DM for >15 years (Table 35.4). An incidence comparable to the latter was also found in a large observational study [52].

Overall, hypoglycemia is less frequent in T2DM (Table 35.4) [1, 2, 52, 55, 58, 62–77], but for the pathophysiological reasons discussed, hypoglycemia becomes progressively more frequent as people approach the insulin-deficient end of the spectrum of T2DM [1, 2, 62, 70]. Indeed, its frequency has been reported to be similar in those with T2DM and T1DM matched for duration of insulin therapy [70]. When the UK Hypoglycaemia Study Group [62] contrasted people with T2DM treated with insulin for <2 years with those treated with insulin for >5 years, they found severe hypoglycemia prevalences of 7% and 25% and incidences of 10 and 70 episodes per 100 patient-years, respectively. The pattern for self-treated hypoglycemia was similar [62]. Thus, although the incidence of iatrogenic hypoglycemia is relatively low (with current less than euglycemic goals) in the first few years of insulin treatment of T2DM, the risk increases substantially, approaching that in T1DM, in advanced of T2DM.

Because asymptomatic episodes will almost invariably be missed, and symptomatic episodes may not be recognized as the result of hypoglycemia [78] and, even if they are, they are not long remembered [79, 80], estimates of the frequency of iatrogenic hypoglycemia are underestimates. Although they represent only a small fraction of the total hypoglycemic experience, because they are dramatic events that are more likely to be reported (by the patient or an associate) [79, 80], estimates of the frequency of severe hypoglycemia, requiring the assistance of another person, are more reliable, particularly if they are determined in population-based prospective studies that include a focus on hypoglycemia [1, 2].

The prospective population-based data of Donnelly et al. [67] indicate that the overall incidence of hypoglycemia in insulin treated T2DM is approximately one-third of that in T1DM (Table 35.4). The incidence of any and of severe hypoglycemia was ~4300 and 115 episodes per 100 patient-years, respectively, in

Table 35.4 Event rates for severe hypoglycemia (that requiring the assistance of another person), expressed as episodes per 100 patient-years, in insulin-treated diabetes.

Study	*n*	Event rate	Comment
Type 1 diabetes			
UK Hypoglycaemia Study Group [62]	57[a]	320	Prospective multicenter study
	50[b]	110	
MacLeod et al. [73]	544	170	Retrospective clinic survey, randomly selected sample
Donnelly et al. [67]	94	115	Prospective study, population-based random sample
Reichard and Pihl [58]	48	110	Clinical trial, intensive insulin group
DCCT Research Group [56]	711	62	Clinical trial, intensive insulin group
Type 2 diabetes			
MacLeod et al. [73]	56	73	Retrospective clinic survey, randomly selected sample
UK Hypoglycaemia Study Group [62]	77[c]	70	Prospective multicenter study
	89[d]	10	
Akram et al. [66]	401	44	Retrospective clinic survey
Donnelly et al. [67]	173	35	Prospective study, population-based random sample
Henderson et al. [69]	215	28	Retrospective clinic survey, randomly selected sample
Murata et al. [74]	344	21	Prospective study, random Veterans Affairs sample
Saudek et al. [76]	62[e]	18	Clinical trial, multiple insulin injection group
Gürlek et al. [68]	114	15	Retrospective clinic survey
Abraira et al. [65]	75	3	Clinical trial, intensive insulin group
Yki-Järvinen et al. [77]	88	0	Clinical trial, initial insulin therapy
Ohkubo et al. [75]	52	0	Clinical trial, initial insulin therapy

[a] Insulin treatment for >15 years.
[b] Insulin treatment for <5 years.
[c] Insulin treatment for >5 years.
[§] Insulin treatment for <2 years.
[e] Definite (8 per 100 patient-years) plus suspected (10 per 100 patient-years).
Source: Republished with permission of the Endocrine Society, from Cryer et al. *J Clin Endocrinol Metab* 2009; **94**(3):709–728; permission conveyed through Copyright Clearance Center, Inc.

T1DM and ~1600 and 35 episodes per 100 patient-years, respectively, in insulin-treated T2DM. In addition, in population-based studies, the incidence of severe hypoglycemia requiring emergency treatment in insulin-treated T2DM was ~40% [71] and ~100% [72] of that in T1DM. Because the prevalence of T2DM is ~20-fold greater than that of T1DM, and most people with T2DM ultimately require treatment with insulin, these data suggest that most episodes of iatrogenic hypoglycemia, including severe hypoglycemia, occur in people with T2DM.

Impact of hypoglycemia

Iatrogenic hypoglycemia causes recurrent physical and psychological morbidity, and some mortality, impairs defenses against subsequent hypoglycemia, and precludes maintenance of euglycemia over a lifetime of diabetes [1, 2]. In the short term, it causes brain fuel deprivation that, if unchecked, results in functional brain failure that is typically corrected after the plasma glucose concentration is raised [4]. Rarely, it causes sudden, presumably cardiac arrhythmic [81, 82], death or, if it is profound and prolonged, brain death [4].

The physical morbidity of an episode of hypoglycemia ranges from unpleasant symptoms to seizure and coma [1, 2, 4]. It can impair judgment, behavior, and performance of physical tasks. Permanent neurological damage is rare. Although there is concern that recurrent hypoglycemia might cause chronic cognitive impairment, long-term follow-up of the participants in the DCCT is reassuring in that regard [83]. Nonetheless, the possibility that it does so in young children remains [84, 85], and there are few corresponding data in the elderly [83]. The psychological morbidity includes fear of hypoglycemia [86], which can be a barrier to glycemic control.

Three early reports indicated that 2–4% of people with diabetes die from hypoglycemia [87–89]. More recent reports indicated that 6% [83], 7% [90], and 10% [91] of deaths of people with T1DM were the result of hypoglycemia. In T2DM, mortality rates of up to 10% during episodes of severe sulfonylurea-induced hypoglycemia have been reported [92]. In one trial of T2DM, between 1 and 9% of evaluable deaths were attributed to hypoglycemia [93].

Excessive mortality during intensive glycemic therapy with increased rates of hypoglycemia was found in randomized controlled trials in patients in the intensive care unit (ICU) [94] and in people with T2DM [59]. Although that might have been the result of some non-glycemic effect of the intensive therapy regimens in the people with T2DM, none was found and the regimens themselves (in contrast to the glycemic targets) were

Table 35.5 American Diabetes Association Workgroup on Hypoglycemia classification of hypoglycemia in people with diabetes [98].

Classification	Definition
Severe hypoglycemia	An event requiring the assistance of another person to administer actively carbohydrate, glucagon, or other resuscitative actions. Plasma glucose measurements may not be available during such an event, but neurological recovery attributable to the restoration of plasma glucose to normal is considered sufficient evidence that the event was induced by a low plasma glucose concentration
Documented symptomatic hypoglycemia	An event during which typical symptoms of hypoglycemia are accompanied by a measured plasma glucose concentrations ≤70 mg/dL (3.9 mmol/L)
Asymptomatic hypoglycemia	An event not accompanied by typical symptoms of hypoglycemia but with a measured plasma glucose concentration ≤70 mg/dL (3.9 mmol/L)
Probable symptomatic hypoglycemia	An event during which symptoms typical of hypoglycemia are not accompanied by a plasma glucose determination but that was presumably caused by a plasma glucose concentration ≤70 mg/dL (3.9 mmol/L)
Relative hypoglycemia	An event during which the person with diabetes reports any of the typical symptoms of hypoglycemia, and interprets those as indicative of hypoglycemia, with a measured plasma glucose concentration >70 mg/dL (3.9 mmol/L) but approaching that level

the same in the intensive and the standard care groups in the patients in the ICU. The fact that increased mortality was consistently associated with severe hypoglycemia in six randomized controlled trials, two in patients in the ICU [94, 95] and four in people with T2DM [59, 60, 96, 97], reduces the probability that these associations were the result of chance.

Clinical definition and classification of hypoglycemia

The American Diabetes Association (ADA) and ADA/Endocrine Society Workgroups on Hypoglycemia [98, 99] defined hypoglycemia in diabetes as "all episodes of abnormally low plasma glucose concentration that expose the individual to potential harm." It is not possible to state a specific plasma glucose concentration that defines clinical hypoglycemia. Although symptoms typically develop at plasma glucose concentrations of ~50–55 mg/dL (2.8–3.1 mmol/L) (Table 35.1) [11] in individuals without diabetes, the glycemic threshold for symptoms (and also those for glucose counter-regulatory and cognitive dysfunction responses) shift to lower plasma glucose concentrations in people with tightly controlled diabetes and recurrent hypoglycemia [100, 101] and to higher plasma glucose concentrations in those with poorly controlled diabetes [100–102].

The Workgroups recommended that people with drug-treated diabetes (implicitly those treated with an insulin secretagogue or insulin) become concerned about the possibility of developing hypoglycemia at a plasma glucose concentration of ≤70 mg/dL (3.9 mmol/L) [98, 99]. Within the error of self-monitoring of blood glucose (or continuous glucose sensing), that conservative alert value approximates the lower limit of the non-diabetic post-absorptive plasma glucose concentration range [11] and the normal glycemic thresholds for activation of physiological glucose counter-regulatory systems [11], and is low enough to reduce glycemic defenses against subsequent hypoglycemia [103] in individuals without diabetes. Indeed, impairment of a complex function, driving, has been demonstrated at plasma glucose levels in this general range in T1DM [104]. It also generally provides some margin for the relative inaccuracy of glucose monitors at low plasma glucose concentrations. The ADA/Endocrine Society Workgroup also recommended a clinical classification of hypoglycemia (Table 35.5) [98, 99].

Prevention and treatment of hypoglycemia in diabetes

Prevention of hypoglycemia: hypoglycemia risk factor reduction

Iatrogenic hypoglycemia is a barrier to glycemic control in people with diabetes [1, 2], but that barrier can be lowered in individuals with diabetes by the practice of hypoglycemia risk factor reduction (Table 35.6) [1, 2, 47]. That involves four steps:

1 Acknowledge the problem.

2 Apply the principles of aggressive glycemic therapy [1, 2, 47, 105–109].

3 Consider the conventional risk factors for hypoglycemia (Table 35.3).

4 Consider the risk factors for hypoglycemia-associated autonomic failure (HAAF) in diabetes (Table 35.3).

Table 35.6 Hypoglycemic risk factor reduction.

1 Acknowledge the problem
2 Apply the principles of aggressive glycemic therapy
- Diabetes self-management (patient education and empowerment)
- Frequent self-monitoring of blood glucose (and in some instances continuous glucose sensing)
- Flexible and appropriate insulin (and other drug) regimens
- Individualized glycemic goals
- Ongoing professional guidance and support

3 Consider the conventional risk factors for hypoglycemia (Table 35.3)
4 Consider the risk factors indicative of hypoglycemia-associated autonomic failure (Table 35.3)

The issue of hypoglycemia should be addressed in every contact with people with diabetes, at least those treated with a sulfonylurea, a glinide, or insulin [1, 2, 47]. Acknowledging the problem allows the caregiver either to move on if hypoglycemia is not an issue or to address it, and keep it in perspective, if hypoglycemia is an issue. Patient concerns about the reality, or even the possibility, of hypoglycemia can be a barrier to glycemic control [110, 111]. It is often helpful also to question close associates of the patient because they may have observed clues to episodes of hypoglycemia not recognized by the person with diabetes. Even if no concerns are expressed, examination of the self-monitoring of blood glucose records (or continuous glucose monitoring data) will often disclose that hypoglycemia is a problem.

If hypoglycemia is an issue, the principles of aggressive glycemic therapy in diabetes [1, 2, 47, 105–109] should be reviewed and applied. These include diabetes self-management based on patient education and empowerment, frequent self-monitoring of blood glucose (and in some instances continuous glucose monitoring), flexible and appropriate insulin (and other drug) regimens, individualized glycemic goals, and ongoing professional guidance and support (Table 35.6).

Patient education and empowerment are fundamentally important. As the therapeutic regimen becomes progressively more complex—early in T1DM and later in T2DM—the success of glycemic management becomes progressively more dependent on the many management decisions and skills of the well-informed person with diabetes. In addition to basic training about diabetes, people with insulin secretagogue or insulin-treated diabetes need to be taught about hypoglycemia [112]. They need to know the common symptoms of hypoglycemia, and their individual most meaningful symptoms, and how to treat (and not overtreat) an episode. Close associates also need to be taught the symptoms and signs of hypoglycemia, and when and how to administer glucagon. Patients need to understand the relevant conventional risk factors for hypoglycemia (Table 35.3), including the effects of the dose and timing of their individual secretagogue or insulin preparation(s) and also the effects of missed meals and the overnight fast, exercise, and alcohol ingestion. They also need to know that episodes of hypoglycemia signal an increased likelihood of future, often more severe, hypoglycemia [49, 50, 53, 55, 112–115]. Finally, patients using an online glucose monitor need to apply those data critically to their attempts to minimize both hypoglycemia and hyperglycemia.

The core approach to virtually all patients in whom iatrogenic hypoglycemia becomes a problem is structured patient education (or often re-education), which has been shown to reduce rates of severe hypoglycemia [116–120], typically coupled with short-term scrupulous avoidance of hypoglycemia, which has been shown to reverse hypoglycemia unawareness in most affected patients [32–35]. The therapeutic objective is to minimize the number and the magnitude of episodes of hypoglycemia, not to promote hyperglycemia. Indeed, it is often possible to lower HbA_{1c} levels.

In people treated with an insulin secretagogue, and particularly those treated with insulin, frequent self-monitoring of blood glucose becomes progressively more key to diabetes self-management as the therapeutic regimen becomes more complex, early in T1DM and later in T2DM. Ideally, patients should estimate their glucose levels whenever they suspect hypoglycemia. That would not only confirm or deny an episode of hypoglycemia, it would also help the individual learn the key symptoms of their hypoglycemic episodes and might lead to regimen adjustments. It is particularly important for people with hypoglycemia unawareness to monitor their glucose level before performing a critical task such as driving. Self-monitoring of blood glucose provides a glucose estimate only at one point in time; it does not indicate whether glucose levels are falling, stable, or rising. That limitation is addressed by evolving technologies for real-time continuous glucose monitoring (CGM) [121–123]. Subcutaneous glucose concentrations lag changes in plasma glucose by 10–15 min and their measurement suffers from some inaccuracy. Nonetheless, CGM has been found to be associated with an HbA_{1c} reduction of 0.4–0.6% in adults with T1DM who generally actually used the device without an increase in detected hypoglycemia [121]. However, in one study, the sensitivity and specificity for the detection of low glucose levels were only 65% and 80%, respectively, and both false-negative and false-positive results were common [123].

Flexible and appropriate drug regimens are key components of hypoglycemia risk factor reduction [1, 2, 47]. Hypoglycemia is typically the result of relative or absolute therapeutic (endogenous or exogenous) insulin excess and compromised defenses against falling plasma glucose concentrations. The relevant treatments include insulin or an insulin secretagogue such as a sulfonylurea (e.g. glibenclamide [glyburide], glipizide, glimepiride, and gliclazide) or a glinide (e.g. repaglinide and nateglinide). Early in the course of T2DM, people may respond to drugs that do not raise insulin levels at low or normal plasma glucose concentrations and therefore should not, and probably do not, cause hypoglycemia [1, 2]. Those include the biguanide metformin, which nonetheless has been reported to cause self-reported hypoglycemia [55], thiazolidinediones, α-glucosidase inhibitors, glucagon-like peptide 1 (GLP-1) receptor agonists, dipeptidyl peptidase 4 (DPP-4) inhibitors, and sodium–glucose co-transporter 2 inhibitors. All of these drugs require endogenous insulin secretion to lower plasma glucose concentrations, and insulin secretion declines appropriately as glucose levels fall into the normal range. That is true even for the GLP-1 receptor agonists and the DPP-4 inhibitors, which enhance glucose-stimulated insulin secretion (among other actions). They do not stimulate insulin secretion at normal or low plasma glucose concentrations (i.e. they increase insulin secretion in a glucose-dependent fashion). However, all five categories of drugs can increase the risk of hypoglycemia if used with an insulin secretagogue or insulin.

Among the commonly used sulfonylureas, the longer acting glibenclamide (glyburide) is more often associated with hypoglycemia than the shorter acting glimepiride [92, 124]. The use of long-acting insulin analogs (e.g. glargine or detemir), rather than

neutral protamine Hagedorn (NPH) insulin, as the basal insulin in a multiple daily injection (MDI) insulin regimen reduces at least the incidence of nocturnal hypoglycemia, and perhaps also that of total, symptomatic, and nocturnal hypoglycemia, in T1DM and T2DM [124–126]. The use of a rapid-acting analog (e.g. lispro, aspart, or glulisine) as the prandial insulin in an MDI regimen reduces the incidence of nocturnal hypoglycemia, at least in T1DM [125–128]. Longer acting basal insulins such as degludec and glargine U300 reduce nocturnal hypoglycemia further.

Because one can vary the basal insulin infusion rate across the day, continuous subcutaneous insulin infusion (CSII) should be superior to MDI, although this has been difficult to establish convincingly [129]. It may reduce HbA_{1c}, the frequency of hypoglycemia, or both, in selected capable and motivated individuals. However, in the HypoCOMPaSS trial [120], neither CSII (compared with MDI) nor CGM (compared with SMPG) reduced severe hypoglycemia or improved awareness of hypoglycemia to a greater extent.

The combination of real-time CGM with CSII—sensor-augmented pump therapy—has been reported to achieve an ~0.5% greater decrease in HbA_{1c} than MDI alone without an increase in hypoglycemia [130, 131]. A sensor-augmented CSII pump that temporarily suspends insulin infusion for up to 2 h when the CGM value falls below a preselected level (a low glucose suspend [LGS] feature) has been reported to reduce the frequency of severe hypoglycemia [132, 133].

Additional approaches to the prevention of nocturnal hypoglycemia include attempts to produce sustained delivery of exogenous carbohydrate or sustained endogenous glucose production throughout the night [134].

Closed-loop insulin replacement (e.g. [135]) or closed-loop insulin and glucagon replacement (e.g. [136]) and also pancreas or islet transplantation (e.g. [137]), when these are shown to be consistently successful, will eliminate hypoglycemia.

Given the evidence that glycemic control partially prevents or delays microvascular complications of diabetes, and may partially prevent or delay macrovascular complications, it follows that a lower HbA_{1c} is in the best interest of people with diabetes if that can be achieved and maintained safely [81]. Thus, a reasonable individualized glycemic goal is the lowest HbA_{1c} that does not cause severe hypoglycemia, preferably with little or no symptomatic or even asymptomatic hypoglycemia, at a given stage in the evolution of the individual's diabetes [81]. That links the selection of a glycemic goal to the risk of hypoglycemia, specifically the use of drugs that can cause hypoglycemia and the type and duration of diabetes, a surrogate for endogenous insulin deficiency. If the therapeutic regimen produces severe hypoglycemia or hypoglycemia unawareness, or an unacceptable number of symptomatic or asymptomatic episodes, hypoglycemia has become a problem that needs to be addressed.

Because the glycemic management of diabetes is empirical, caregivers should work with each individual over time to find the most effective and safest method of glycemic control at a given point in the course of that person's diabetes. Care is best accomplished by a team that includes, in addition to a physician, professionals trained in, and dedicated to, translating the standards of care into the care of individual and making full use of modern communication and computing technologies.

Another step is to consider the conventional risk factors for hypoglycemia, those that result in both relative and absolute therapeutic insulin excess. In addition to insulin secretagogue or insulin doses, timing and type, these include conditions in which exogenous glucose delivery or endogenous glucose production is decreased, glucose utilization or sensitivity to insulin is increased, or insulin clearance is reduced (Table 35.3).

Finally, the risk factors for HAAF need to be considered. Those include the degree of endogenous insulin deficiency, a history of severe hypoglycemia, hypoglycemia unawareness, or both, and also any relationship between hypoglycemic episodes and recent antecedent hypoglycemia, prior exercise or sleep, and lower HbA_{1c} levels (Table 35.3). Unless the cause is easily remediable, a history of severe hypoglycemia should prompt consideration of a fundamental regimen adjustment. Without that, the risk of a subsequent episode of severe hypoglycemia is high [49, 50, 53, 55, 112–115]. Given a history of hypoglycemia unawareness, a 2–3-week period of scrupulous avoidance of hypoglycemia, which may require acceptance of somewhat higher glycemic goals in the short term, is advisable because that can be expected to restore awareness [32–35]. A history of late post-exercise hypoglycemia, nocturnal hypoglycemia, or both, should prompt appropriately timed regimen adjustments (generically, less insulin action, more carbohydrate ingestion, or both) (see Chapter 26).

When prevention fails, treatment of hypoglycemia becomes necessary. Most episodes of asymptomatic hypoglycemia (detected by self-monitoring of blood glucose or continuous glucose sensing) and of mild–moderate symptomatic hypoglycemia are effectively self-treated by ingestion of glucose tablets or carbohydrate-containing juice, soft drinks, candy, other snacks, or a meal [138, 139] A reasonable dose is 20 g of glucose [139]. Clinical improvement should occur in 15–20 min; however, in the setting of ongoing hyperinsulinemia, the glycemic response to oral glucose is transient, typically less than 2 h [139]. Thus, ingestion of a more substantial snack or meal shortly after the plasma glucose concentration is raised is generally advisable.

Parenteral treatment is required when a hypoglycemic patient is unwilling (because of neuroglycopenia) or unable to take carbohydrate orally. Glucagon, injected subcutaneously or intramuscularly (in a usual dose of 1.0 mg in adults) by an associate of the patient, is often used. That can be life-saving, but it often causes substantial, albeit transient, hyperglycemia and it can cause nausea or even vomiting. Smaller doses of glucagon (e.g. 150 mg), repeated if necessary, have been found to be effective without side effects [140]. Because it acts by stimulating hepatic glycogenolysis, glucagon is ineffective in glycogen-depleted individuals (e.g. following a binge of alcohol ingestion).

Although glucagon can be administered intravenously by medical personnel, intravenous glucose is the standard parenteral therapy. A common initial dose is 25 g [138]. The glycemic response to intravenous glucose is, of course, transient in the setting of ongoing hyperinsulinemia.

The duration of an episode of iatrogenic hypoglycemia is a function of its cause. An episode caused by a rapid-acting insulin secretagogue or insulin analog will be relatively brief, that caused by a long-acting sulfonylurea or insulin analog substantially longer. The latter can result in prolonged hypoglycemia requiring hospitalization.

The clinical problem of hypoglycemia in children

Diabetes is one of the most common chronic diseases in childhood, affecting more than 190,000 (1 in 433) youth aged less than 20 years in the United States [141] and its incidence has been increasing worldwide [142, 143]. The ultimate goal of diabetes management is to achieve good glycemic control while avoiding hypoglycemia. However, in this effort, iatrogenic hypoglycemia has become the most common complication of youth living with diabetes [144–146]. It occurs more frequently in children and adolescents with T1DM owing to the inadequacies of insulin replacement therapy and the unique challenges for this group of patients. This somewhat unavoidable complication can result in morbidity and sometimes in death. Moreover, given that these hypoglycemic events are occurring at a time of dynamic changes in brain structure and metabolic demand, it has been hypothesized that exposure to this glycemic extreme during childhood could alter normal brain developmental trajectories depending on the age and severity at which these extremes are experienced [147]. Despite the use of insulin analogs, insulin pumps, and continuous glucose sensors, the problem of hypoglycemia has not been solved. Therefore, it is important that hypoglycemia be recognized as a key component of pediatric diabetes care.

Definition of hypoglycemia in youth

As in adults, hypoglycemia in youth is most convincingly documented by the presence of the Whipple's triad [148]: (1) symptoms consistent with hypoglycemia, (2) a low plasma glucose concentration, and (3) relief of those symptoms when the plasma glucose concentration is raised. Symptoms of hypoglycemia may be unique to each individual, and are likely to be diminished or absent by prior hypoglycemia. They are conventionally attributed either to autonomic nervous system activation (autonomic or neurogenic symptoms), which include, but are not limited to, palpitations, tremor, hunger, and sweating, or to glucose deprivation in the central nervous system (neuroglycopenic symptoms), which include behavioral changes, fatigue, headaches, difficulty thinking, confusion, poor feeding, hypotonia or lethargy in infants, seizure, coma, and even death [8]. However, data suggest that symptoms in children differ from those in adults. Behavioral changes such as irritability, stubbornness, quietness, and tantrums may be their primary features of low blood glucose [149].

The ADA and the Endocrine Society define iatrogenic hypoglycemia in people with diabetes as "all episodes of an abnormally low plasma glucose concentration that expose the individual to potential harm" [98, 99]. According to the International Society for Pediatric and Adolescent Diabetes (ISPAD) Consensus Guidelines, a blood glucose level of <65 mg/dL (3.6 mmol/L) has been often accepted in clinical practice as a level for defining hypoglycemia in children with T1DM. However, a glucose value of ≤70 mg/dL (3.9 mmol/L) is conventionally used as the threshold value for recognizing and initiating treatment for hypoglycemia [98, 99, 144] in diabetes in adults and children, since glucose levels can potentially fall further and cause a life-threatening event. In adults, a severe hypoglycemic episode is defined as an event requiring assistance of another person actively to administer carbohydrates or glucagon or take other corrective actions to allow neurological recovery. However, this definition is problematic in children, as most young children require the assistance of another person to correct even mild hypoglycemia. Hence, in the pediatric population, severe hypoglycemia is generally defined as an event associated with severe neuroglycopenia usually resulting in coma or seizure and requiring parenteral therapy (glucagon or intravenous glucose) [150, 151].

Prevalence and incidence of hypoglycemia in youth

The average person with diabetes has an uncountable number of episodes of asymptomatic and symptomatic hypoglycemia in their lifetime; hypoglycemia is therefore a "fact of life" for people with T1DM [152–154], and more so in children than adults [155]. Changes in clinical practice (e.g. new insulin regimens, more intense glucose monitoring and delivery) have reduced the rates of hypoglycemia over the last 15 years [155–160], but the problem of hypoglycemia has not disappeared. Even though the rates of hypoglycemia can vary between clinical studies around the world, it is estimated that the incidence of hypoglycemia in children ranges between 5 and 60 episodes per 100 patient-years [155, 159, 161–167] and is more common in infants [168, 169]. Nocturnal hypoglycemia is common in childhood, with reported incidences on any given night of between 10 and 55% [170–172]. Symptoms can be subtle and may include nightmares, restless sleep, and behavior changes upon awakening. There is a lack of specific mortality data attributed to severe hypoglycemia in the pediatric population.

Risk factors for hypoglycemia in the pediatric population

Undoubtedly, the most important risk factor for hypoglycemia lies within insulin therapy itself, but managing type 1 diabetes in young children and youth presents unique challenges owing to the young child's developmental level, unpredictability of an infant or toddler's dietary intake, the child's irregular activity level, and the child's emotional maturity (see Chapter 59). These variables may explain why hypoglycemic events are less predictable and occur

without a clear cause in younger children [169]. Perhaps the second most important risk factor for severe hypoglycemia is hypoglycemia unawareness. In the pediatric population, this occurs due to recurrent hypoglycemia, which causes blunting of the autonomic responses, which, together with the child's developmental level, impedes their ability to feel and communicate symptoms of hypoglycemia. Therefore, at times, these patients depend on adults for most, if not all, aspects of their care.

Since publication of the DCCT results in the 1990s [56], diabetes management changed, aiming for tighter glycemic control to minimize vascular complications. However, it was soon noticed that the risk of hypoglycemia increased as HbA_{1c} decreased, particularly in younger children (<6 years old) [158, 159, 173]. Therefore, the ADA cautiously set higher targets for glycated hemoglobin (HbA_{1c}) for young children compared with adolescents and adults. However, recent population-based studies of children with T1DM suggest that there is no longer a significant risk of severe hypoglycemia associated with age <6 years, irrespective of treatment modality [155, 174, 175]. In addition, even though elevated HbA_{1c} levels in those with poorly controlled diabetes, per se, do not seem to protect against severe hypoglycemia [158], the previously close relationship between tight glycemic control [158] and the risk of severe events is now weaker [155, 174, 176]. This change in severe hypoglycemic rates has been attributed to the improvements in intensive treatment regimens over the past 20 years. Therefore, the ADA and ISPAD now recommend a general target HbA_{1c} of <7.5% for all pediatric age groups, while also recognizing that targets should be tailored to the individual child [177, 178].

The non-physiological nature of current insulin replacement regimens makes people with diabetes vulnerable to hypoglycemic events. In youth, conventional (split-mixed) insulin regimens with a fixed daily two-shot insulin schedule, have been shown to denote a higher rate of severe hypoglycemic episodes than intensive (basal bolus) insulin regimens with either MDI or pumps [49]. Intermediate and long-acting insulins used in these conventional insulin regimens peak several hours after administration and, given the erratic eating patterns and usual delay in carbohydrate intake in children, puts them at higher risk for hypoglycemia owing to inadequate carbohydrate availability at the time of peak insulin effect. The incidence of hypoglycemia in children treated with a conventional regimen ranges between 20 and 60 episodes per 100 patient-years [162, 163]. Although some controlled trials of insulin pump therapy in children suggest that it is similar to MDI in achieving glycemic control and avoiding hypoglycemic episodes [179, 180], others suggest that pump therapy significantly reduced the risk of severe hypoglycemia [129, 155, 181–184] compared with MDI therapy.

Exercise-induced hypoglycemia is a major limiting factor in establishing optimal glycemic control in children and adolescents with T1DM [185]. Glucose utilization and insulin sensitivity are increased during physical activity. Thus, when energy supply is inadequate in relation to high ambient insulinemia, hypoglycemia ensues [186]. Frequent bouts of hypoglycemia impair counter-regulatory responses to hypoglycemia in people with insulin-deficient diabetes [1, 2]; therefore, episodes of hypoglycemia during and following exercise in people with diabetes [38], particularly children [187, 188], become frequent clinical complaints and may result in seizures, coma, or death [1, 2]. The Diabetes Research in Children Network (DirecNet) Study Group showed that during moderate-intensity treadmill exercise, more than two-thirds of the children studied decreased their plasma glucose concentrations by >25%, and 30% of those children required treatment for hypoglycemia [39, 189]. Moreover, this group and others have shown that following afternoon exercise, hypoglycemia can occur hours after, or at night [186, 189, 190].

Other modifiable risk factors in youth include sleep [25, 191–193], missed snacks or meals, malabsorption attributable to celiac disease [194], alcohol intake in teens, and acute illnesses altering the timing, frequency, and carbohydrate intake [195]. Non-modifiable risk factors of severe hypoglycemia include, but are not limited to, coexisting autoimmune disorders such as adrenal insufficiency, celiac disease, and thyroiditis; hence these disorders should be excluded in children with recurrent unexplained hypoglycemia. Other non-modifiable risk factors include being a minority [158, 196], being male, having longer duration of diabetes [197], having a lower socioeconomic status [158, 161], having an ACE DD genotype, and C-peptide negativity.

Physiology of counter-regulation in youth with T1DM

Although hypoglycemia in diabetes is typically the result of therapeutic hyperinsulinemia, compromised symptoms and physiological glucose counter-regulatory defenses to hypoglycemia are what leads to the cycle of recurrent hypoglycemia [2]. As blood glucose falls just below the post-absorptive physiological range (~70–110 mg/dL), signals to and from the hypothalamus and other brain regions lead to a cascade of hierarchical physiological (counter-regulatory hormone) and behavioral (hypoglycemic symptoms) responses to maintain euglycemia [2] (previously explained in section Physiology of glucose counter-regulation). These responses are normally so effective that hypoglycemia is an uncommon clinical event in individuals without diabetes. Data suggest that some of the counter-regulatory responses in children are initiated at plasma glucose levels higher than in adults [164]. However, in people with diabetes, the normal physiological counter-regulatory responses are disrupted because exogenously administered insulin cannot be suppressed and the glucagon response to hypoglycemia is blunted [2, 198–201]. The loss of the glucagon response to hypoglycemia is not the result of loss of α cells since the glucagon response to arginine [198, 201] or to a meal is not lost, and indeed may be exaggerated [202]. These alterations in glucose counter-regulation occur early in the course of the disease and are present shortly after diagnosis in children [200, 203–205] and adults [198, 199], even when there is some residual endogenous insulin secretion [200, 204]. In contrast to glucagon, epinephrine responses to acute hypoglycemia in youth [203, 204] and adults [2] are not blunted early in the absence of prior hypoglycemia. This suggests that the mechanisms of attenuation of the glucagon

and epinephrine responses to acute hypoglycemia are different, and more so, that an intact plasma epinephrine response is critical early in the course of T1DM.

Antecedent hypoglycemia in people with T1DM causes both defective glucose counter-regulation (by attenuating the adrenomedullary epinephrine response in the setting of absent insulin and glucagon responses) and hypoglycemia unawareness (by attenuating the sympathoadrenal, largely the sympathetic neural, response) to subsequent hypoglycemia [2, 15, 206]. In addition, a prior episode of hypoglycemia can lower the glucose threshold at which sympathoadrenal responses and symptoms occur, increasing the risk for subsequent severe hypoglycemia. Studies have shown that children with T1DM younger than 8 years old with good glycemic control have lower catecholamine, cortisol, and blunted glucagon responses to hypoglycemia (∼<60 mg/dL) compared with adolescents [207]. In addition, the glycemic threshold for release of epinephrine in youth with T1DM was higher than that in adults with T1DM [164] and more so in those with poorly controlled T1DM (mean HbA_{1c} 15.1%) than in those without diabetes [164]. Moreover, in children with T1DM, as in adults, sleep markedly impairs counter-regulatory responses to hypoglycemia [25, 187]. Further studies in children are needed to clarify the mechanisms that cause the attenuation of these responses and to determine whether these abnormalities can be reversed with intensive diabetes management using continuous glucose monitoring and closed-loop insulin delivery systems.

Effects and consequences of hypoglycemia in youth

Severe hypoglycemia is acutely associated with significant morbidity and mortality, including cardiac arrhythmias, seizures, and, rarely, permanent neurological impairment and death. Owing to these potentially devastating consequences, it frequently frightens not only the person with diabetes but also their relatives and parents, leading to the phenomenon known as "fear of hypoglycemia." In this setting, parents and children tend to keep blood glucose values above recommended targets in an effort to avoid hypoglycemic episodes, which results in poor glycemic control [208–214].

In the long term, T1DM and its associated glycemic extremes (severe hypoglycemia and chronic hyperglycemia) can affect multiple organ systems, including the retina, cardiovascular system, kidneys, the peripheral nervous system and, more recently noted, the central nervous system. The brain derives its energy almost exclusively from glucose and is largely driven by neuronal signaling, biosynthesis, and neuroprotection. The developing human brain has unique nutritional requirements and undergoes maturational changes, including synaptogenesis and synaptic remodeling, throughout childhood [215, 216], with the brain continuing to account for as much as 20% of total body glucose consumption through early adulthood [217]. When faced with fluctuations in glucose supply, the metabolism of the body and brain changes dramatically, largely to conserve resources and, at a cost to other organs, to preserve brain function [147, 218]. However, if the normal physiological mechanisms that prevent these severe glucose fluctuations and maintain homeostasis are impaired during childhood, normal brain developmental trajectories and neuronal function can be affected [8, 148, 149, 219–221].

The effects of long-duration T1DM and its associated glycemic extremes (severe hypoglycemia and chronic hyperglycemia) on brain structure and function have been examined in multiple adult [83, 222–235] and a handful of child cohorts [84, 236–253]. Even though the DCCT [83, 254] and others [255, 256] have reported no association between the frequency of severe hypoglycemia and cognitive function decline in adults with T1DM, the literature on children with T1DM supports that early exposure (<6 years) to severe hypoglycemia may lead to subtle differences in cognitive and academic function, particularly on declarative memory skills, spatial analysis, verbal function, and psychomotor efficiency [84, 233, 237, 246, 247, 251, 257–266].

Magnetic resonance imaging (MRI) techniques have been used to ascertain the impact of hypoglycemia in T1DM on the developmental trajectory of gray and white matter volumes and structure in children [85, 235, 246, 252, 267]. Case reports and imaging studies in adults and children with T1DM have shown that the regions that appear most susceptible to hypoglycemia include total gray matter, left superior temporal gray matter, thalamus, and hippocampus. Although a prospective study in youth found that exposure to severe hypoglycemia inhibited white matter volume development [236], a retrospective study in youth with T1DM found no significant effects of severe hypoglycemia on white matter integrity across the brain [85, 268]. However this does not rule out the possibility that white matter integrity might be affected over time and be found to be abnormal in a longitudinal study. Despite ample evidence suggesting that children with T1DM have differences in cognitive functioning dependent upon their exposure to glycemic extremes, there have been no studies linking these changes to the observed brain structural or functional differences. Hence further research on the effects of hypoglycemia on the brain is needed to understand better the mechanisms that lead to cognitive outcomes and brain regional vulnerability. Moreover, such studies may allow us a better understanding of the mechanisms involved in the development of recurrent hypoglycemia and HAAF.

Even though rates of severe hypoglycemia may have decreased in the last decade and the ADA and ISPAD have lowered glycemic targets in children with T1DM, hypoglycemia continues to be a fact of life for youth with this disease. Owing to the brain's unique energy demands and key neurodevelopmental processes that occur during childhood, hypoglycemia in children with T1DM may lead to acute and permanent neurological complications. Pending prevention and cure of diabetes or better diabetes regimens providing regulated insulin and glucagon replacement, the management plan of childhood-onset T1DM should be tailored to each child's age, cognitive ability, and emotional maturity to avoid severe and recurrent hypoglycemia while achieving good glycemic control.

Perspective on hypoglycemia in diabetes

Glycemic control, a focus of this chapter, is but one aspect of the management of diabetes. It is now possible to drive plasma low-density lipoprotein (LDL) cholesterol concentrations to subphysiological levels and to normalize blood pressure pharmacologically, usually without major side effects, in most people with diabetes. Weight loss and smoking cessation are more challenging. Although it is not possible to maintain euglycemia over a lifetime of diabetes, because of the barrier of hypoglycemia, maintenance of the lowest mean glycemia that can be accomplished safely is in the best interest of people with diabetes.

Despite the difficulty, people with diabetes and their caregivers should keep the problem of iatrogenic hypoglycemia in perspective. Early in the course of T2DM, by far the most common type of diabetes, hyperglycemia may respond to lifestyle changes, specifically weight loss, or to glucose-lowering drugs that do not raise insulin levels and therefore do not cause hypoglycemia. In theory, when such drugs are effective in the absence of side effects, there is no reason not to accelerate their dosing until euglycemia is achieved. Over time, however, as people with T2DM become progressively more insulin deficient, those drugs, even in combination, fail to maintain glycemic control. Insulin secretagogues are also effective early in the course of T2DM, but they cause hyperinsulinemia and therefore introduce the risk of hypoglycemia. Euglycemia is not an appropriate goal during therapy with an insulin secretagogue or with insulin. Nonetheless, as discussed earlier, the frequency of hypoglycemia is relatively low (with current less than euglycemic goals) during treatment with an insulin secretagogue or even with insulin early in the course of T2DM when glycemic defenses against falling plasma glucose concentrations are still intact. Therefore, over much of the course of the most common type of diabetes, it is possible to maintain a meaningful degree of glycemic control with a relatively low risk of hypoglycemia.

The challenge is greater in people with advanced T2DM and T1DM caused by compromised defenses against falling plasma glucose concentrations and the resulting higher barrier of iatrogenic hypoglycemia. In such individuals, therapy with insulin is demonstrably effective, but it is not demonstrably safe. Nonetheless, concerns about hypoglycemia should not be used as an excuse for poor glycemic control. It should be recalled that the DCCT data [56, 269] document that the relationship between microvascular complications and mean glycemia is curvilinear; some degree of glycemic control puts the person with diabetes at substantially lower risk than little or no glycemic control.

Diabetes will someday be cured and prevented. Pending that, elimination of hypoglycemia from the lives of people with diabetes will likely be accomplished by new treatment methods that provide plasma glucose-regulated insulin replacement or secretion. In the meantime, innovative research is needed if we are to improve the lives of all people affected by diabetes by lowering the barrier of iatrogenic hypoglycemia.

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This chapter was written shortly after completion of the second edition of *Hypoglycemia in Diabetes: Pathophysiology, Prevalence and Prevention* [2]. Therefore, much of the factual and interpretive content here is the same, as is no small part of the phraseology.

Disclosures

Dr. Cryer has served as a consultant to several pharmaceutical firms, including Boehringer-Ingelheim/Lilly, Calibrium, Merck and Co., Novo Nordisk A/S, and Pfizer, in recent years. Dr. Arbeláez has no disclosures.

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36 Acute Metabolic Complications of Diabetes: Diabetic Ketoacidosis and the Hyperosmolar Hyperglycemic State

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Key points

Diabetic ketoacidosis

- Lack of insulin is the culprit in diabetic ketoacidosis.
- The most common precipitating cause is infection.
- The classic signs include polyuria and polydipsia, rapid weight loss, weakness, Kussmaul respiration, drowsiness, and, rarely, coma.
- The cornerstones of treatment are rehydration, intravenous insulin, and potassium supplementation.
- Intravenous insulin administration should continue until the acidosis is normalized (i.e. not merely until euglycemia is achieved).

Hyperosmolar non-ketotic hyperglycemia

- This is characterized by hyperosmolality with progressive hyperglycemia of >35–40 mmol/L and an effective serum osmolality of >320 mOsm/kg.
- It typically affects older people with type 2 diabetes.
- The most common precipitating causes are infection and cardiovascular disease.
- Treatment involves aggressive rehydration and intravenous insulin.

Introduction

Both diabetic ketoacidosis (DKA) and the hyperosmolar non-ketotic hyperglycemic state (HHS) are caused by a lack of insulin, leading to unrestricted flux of stored lipid, carbohydrate, and amino acid nutrients into the blood. These conditions are both acute and life-threatening, and represent the ultimate metabolic consequences of deranged type 1 (T1DM) and type 2 diabetes mellitus (T2DM), respectively [1–3]. The hallmark of DKA is a high-anion-gap metabolic acidosis caused by a rapidly progressive excess of keto acids (3-hydroxybutyrate and acetoacetate—"ketone bodies") whereas severe hyperosmolality caused by hyperglycemia is the most notable feature of HHS. The distinction is not always obvious on clinical grounds; patients with DKA may be very hyperosmolar and ketone body levels are in general somewhat elevated in HHS. Although the clinical picture may vary considerably depending on comorbidities, differential diagnosis seldom poses any major problem and, in the rare cases in which distinction remains difficult, treatment generally follows the same principles, regardless of whether ketosis or hyperglycemia is the most urgent clinical challenge.

Mortality rates have been steadily declining over the past few years [4], but remain close to around 1% for DKA and 10–15% for HHS [2, 5, 6]. The decline in mortality may be a consequence of lower incidence of DKA and HHS, earlier diagnosis, improved treatment, or, more plausibly, all of these effects combined. Improved education schedules and self-monitoring (e.g. blood ketone testing), organization of specialized diabetes clinics, and the use of standardized low-dose insulin regimens have also contributed to this favorable trend [2, 7].

Diabetic ketoacidosis

Definitions

Diabetic ketoacidosis is one of the most common, serious, and demanding medical emergencies within the fields of diabetes and endocrinology. There is no generally accepted definition of DKA and, in particular, very mild cases may be difficult to diagnose. At a minimum, it is reasonable to require that the pH is below the normal range and that the levels of keto acids (ketone bodies) in the blood or urine are markedly elevated. As outlined in

Textbook of Diabetes, Fifth Edition. Edited by R. Holt, C. Cockram, A. Flyvbjerg and B. Goldstein.

Table 36.1 Classification of clinical pictures and diagnostic criteria.

Property	Stress ketosis	Compensated DKA	Diabetic ketoacidosis			Hyperosmolar hyperglycemia
			Mild	Moderate	Severe	
Plasma glucose	Variable	Generally increased	Generally increased	Generally increased	Generally increased	>35–40 mmol/L
Arterial pH	Normal	Normal	Decreased >7.25	7.0–7.25	<7.0	Generally normal
Serum bicarbonate	Normal	Marginally decreased	15–18 mmol/L	10–15 mmol/L	<10 mmol/L	>15 mmol/L
Urine ketones	Increased	Increased	Increased	Increased	Increased	Normal/marginally increased
Blood ketones	Increased	Increased	Increased	Increased	Increased	Normal/marginally increased
Anion gap[a]	Normal/marginally increased	Marginally increased	>10	>12	>12	Variable
Mental status	Normal	Normal	Normal	Normal/drowsy	Drowsy–coma	Drowsy–coma

[a] Anion gap can be calculated as $[Na^+] - ([Cl^-] + [HCO_3^-])$.
DKA, diabetic ketoacidosis.
Source: Adapted from American Diabetes Association. Standards of Medical Care in Diabetes – 2004/2006 position statement. *Diabetes Care* 2004; **27**:S94–S101.

Table 36.1, there is a continuous deterioration from clinically insignificant "stress" ketosis to full-blown severe ketoacidosis. In the US population, it has been estimated that 2–8% of hospital admissions in children with diabetes are a result of DKA and that the annual incidence rate of DKA in children is around 5 per 1000 patients [1].

Pathogenesis and pathophysiology

Insulin deficiency

DKA is caused by insulin deficiency. Insulin deficiency may be relative (e.g. in the setting of severe infection) where normal amounts of insulin are insufficient, or absolute when insulin therapy is neglected. Lack of insulin leads to uncontrolled lipolysis and ketogenesis and increased plasma glucose. Although often disregarded, it should also be borne in mind that insulin deficiency, most particularly when long-standing, causes increased breakdown of body protein, as evidenced by the extreme sarcopenia and cachexia of people with T1DM prior to the insulin era. Excessive protein breakdown and ensuing release of ketogenic and gluconeogenic amino acids may contribute to ketosis and hyperglycemia.

Stress hormones and cytokines

At some stage, insulin deficiency becomes coupled with excess "counter-regulatory" or "stress" hormones and cytokines [8, 9]. Release of stress hormones may in part be triggered by cytokines and in part by general stress, such as dehydration, hypotension, and hypoperfusion. It has been shown that both endotoxin and tumor necrosis factor (TNF) mimic all metabolic responses to infection, including hyperthermia and stress hormone release [10, 11]. The traditional stress hormones include glucagon, epinephrine, growth hormone (GH), and cortisol, all of which have well-described metabolic actions. Glucagon and epinephrine have a rapid onset of action, whereas GH and cortisol act with a latency of hours.

Cytokine levels are elevated in DKA, even in the absence of infection. The metabolic actions of cytokines are in general not so well understood and it is plausible that many of these actions are mediated by hypothalamo-pituitary activation and subsequent stress hormone release. Certain cytokines, such as TNF-α, may impair insulin sensitivity in peripheral tissues [12, 13] and a vicious circle may thus be initiated with self-perpetual increments in blood glucose and cytokine levels. Insulin has anti-inflammatory properties in critically ill patients [14], and administration of exogenous insulin may in itself increase insulin sensitivity [15], conceivably to some extent by breaking this vicious circle but also because glucotoxicity and lipotoxicity wane.

Lipid metabolism

Contrary to popular belief, deranged lipid—not carbohydrate—metabolism is the main cause of DKA. In essence, DKA is brought about by uncontrolled lipolysis in adipose tissue and uncontrolled ketogenesis in liver.

Adipose tissue is present in regional depots such as subcutaneous upper and lower body and visceral fat [16]. Apart from these classic depots, fat is present in most other tissues (e.g. connective tissue, bone marrow, liver, and muscle). The picture is further complicated by the fact that within each tissue, fat is distributed in compartments. In muscle, for instance, fat is present intramyocellularly, intermyocellularly, and intermuscularly. Under physiological conditions, lipolysis is tightly controlled by lipases. Hormone-sensitive lipase and probably also adipose triglyceride lipase stimulate the release of free fatty acids and glycerol into the circulation. This process is inhibited by insulin, and low insulin levels increase lipolysis swiftly. The stress hormones, such as epinephrine, growth hormone, and cortisol, stimulate lipolysis. It

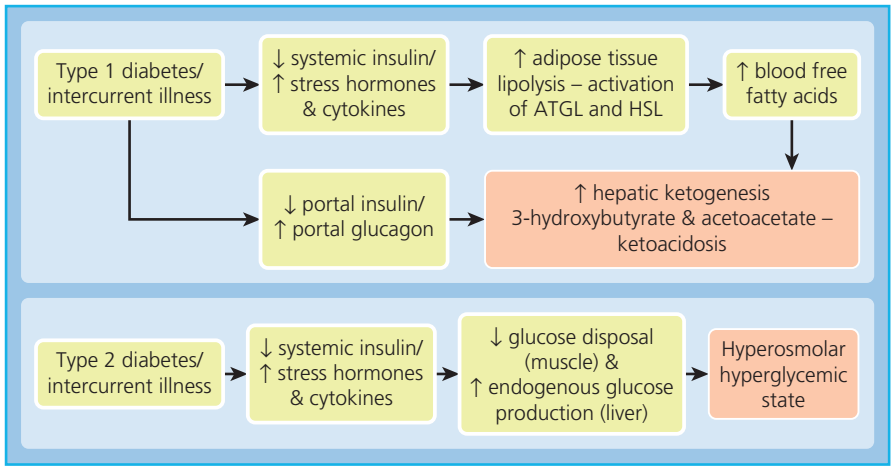

Figure 36.1 Simplistic diagram of the pathogenesis of diabetic ketoacidosis and hyperosmolar non-ketotic hyperglycemic state ATGL: adipose triglyceride lipase, HSL: hormone sensitive lipase.

is plausible that dehydration per se also participates in the stimulation of lipolysis [17]. These events take place in the course of hours and may rapidly triple or quadruple blood concentrations of free fatty acids.

Ketogenesis occurs in the liver by oxidation of free fatty acids to keto acids or ketone bodies (Figure 36.1). Ketone bodies, in particular 3-hydroxybutyrate, are phylogenetically ancient fuel compounds, which are present and prominent in very primitive species [18], suggesting that they have had an important role throughout evolution for the past 2–3 billion years. Physiologically, ketone bodies provide important fuel energy for the brain and other tissues under fasting, prolonged exercise, and other conditions of fuel shortage. In DKA, ketogenesis becomes uncontrolled and circulating levels of ketone bodies rise rapidly and excessively. This occurs because of both an increased supply of fatty acids to the liver and because low levels of insulin and high levels of glucagon in the liver promote ketogenesis [19]. In normal individuals, this unrestrained process is prevented by compensatory rises in insulin secretion, but this does not occur in those with T1DM.

Glucose metabolism

Hyperglycemia is usually present in DKA, but it is important to stress that DKA not infrequently presents with normal or modestly elevated glucose concentrations [20]. This may particularly be the case during caloric deprivation caused by gastrointestinal disease, for example. Recently, euglycemic DKA has been reported during treatment with SGLT-2 inhibitiors. Hyperglycemia is caused by a combination of lack of insulin and an excess of stress hormones, leading to insulin resistance. In the liver, this increases gluconeogenesis and hepatic glucose production. The kidney is unlikely to have any significant role in the initial stages of DKA [21]. The ensuing high glucose levels generate a high flux state with increased peripheral glucose disposal, but the increased mass action of glucose is generally insufficient to compensate fully. Muscle glucose metabolism is characterized by insulin resistance because of high levels of stress hormones, high levels of free fatty acids, and varying degrees of dehydration.

Precipitating factors

In people with known diabetes, DKA is usually precipitated by a coexisting illness or by omission of insulin therapy. The most common factor is infection, ranging from trivial viral infections to full-blown septicemia. Other precipitating factors include cardiovascular events (myocardial infarction, stroke), gastrointestinal disease, inflammatory diseases, pancreatitis, trauma and major surgery, alcohol abuse, and drugs, especially glucocorticoids. All of these factors induce insulin resistance because of the stress hormone responses. Furthermore, poor appetite and food deprivation will often lead the patient to take less insulin. In this context, gastrointestinal disease with nausea and vomiting pose a specific problem and it may be necessary to admit such patients to hospital for intravenous glucose and insulin therapy. Diabetes ketoacidosis may be a presenting feature of new onset T1DM (see Chapter 22).

Psychological factors also play an important part. Poor adherence is commonly seen in younger people with T1DM, those with psychiatric illnesses, and in minority groups who unfortunately may have a poor understanding of diabetes care principles for linguistic or cultural reasons.

Diagnosis and clinical presentation

DKA usually develops over a short period of time, generally in less than 24 h. There may have been some antecedent days with general malaise and poor metabolic control. Depending on the degree of hyperglycemia, the history will include symptoms of polydipsia and polyuria (Box 36.1). Specific symptoms depend on the precipitating factors and other comorbidities that might be present. Physical examination may reveal poor skin turgor, hyperventilation (Kussmaul respirations), hypotension, tachycardia, and impairment of mental state. Many patients have infections but often with normothermia or even hypothermia, caused by peripheral vasodilatation brought about by the acidemia.

Box 36.1 Common clinical features of diabetic ketoacidosis.

Polyuria, polydipsia
Rapid weight loss
Muscular weakness
Visual disturbance
Air hunger with Kussmaul respiration, dry lips
Abdominal pain, leg cramps
Nausea, vomiting
Confusion, drowsiness, coma

Prompt diagnosis and initial treatment rests on:

1 careful clinical examination;
2 determination of plasma glucose;
3 measurement of ketones in blood or urine;
4 measurement of plasma potassium and other electrolytes; and
5 assessment of acidemia.

If glucose is high and blood or urine ketones are markedly elevated, DKA is likely and fluid and insulin therapy should usually be initiated, unless the patient is severely hypokalemic (<3.5 mmol/L). If potassium is very low, supplementation must be given prior to insulin therapy; however, rehydration should not be delayed while waiting for a potassium measurement.

The next diagnostic steps usually include arterial blood gas analysis, blood electrolytes (including anion gap), serum lactate (if there is doubt about the cause of the acidemia), complete blood cell count, biochemical assessment of liver and renal function, blood and urine cultures, myocardial biomarkers (if there is suspicion of a myocardial infarction), electrocardiogram (ECG) and chest X-ray. In this context, it is advantageous that most modern gas analyzers also readily provide potassium concentrations. Another recent advantage is the advent of bedside ketone body monitors. Hence it is now possible to have a quick and reliable measure of 3-hydroxybutyrate concentrations in blood, as opposed to unreliable measurements of acetoacetate in urine or the time-consuming conventional laboratory methods used in the past [22]. The diagnostic criteria are given in Table 36.1.

Despite total body potassium depletion, serum potassium is typically either normal or elevated because of water deficiency and an intracellular to extracellular shift caused by insulin deficiency and acidemia. Patients with potassium in the low range have a severe total body potassium deficiency and should receive vigorous replacement therapy together with cardiac monitoring. Sodium concentrations can be normal or low, as a result of osmotic shifts. It can be calculated that for every 3 mmol/L rise in plasma glucose, the plasma sodium falls by 1 mmol/L. Hence there is often a real hypernatremia with sodium levels rising as the glucose is brought under control. A majority of patients will have a leukocytosis, which correlates with ketone body levels rather than with the presence of infection. There is also a water deficit of around 10% of body weight. Non-specific elevations of amylase and liver enzymes are also common.

Differential diagnoses include all other causes of acidosis. Note that many acute medical conditions induce a stress ketosis and may be associated with acidosis. DKA is a metabolic acidosis characterized by a high anion gap and varying degrees of respiratory compensation. Hence it is crucial to obtain measures of ketone body concentrations and perform an arterial gas analysis. If there is a major discrepancy between the extent of the ketonemia and the acidemia, then lactate measurements are warranted. Starvation ketosis and alcoholic ketoacidosis can usually be identified by clinical history. Other conditions causing metabolic acidosis include lactic acidosis and intoxication with salicylate, methanol, ethylene glycol (antifreeze), and paraldehyde. The clinical picture may be blurred whenever the acidosis is aggravated by renal failure or respiratory failure. In addition, DKA may imitate other diseases. High levels of potassium may also cause ECG changes suggestive of myocardial infarction and elevation of myocardial enzymes and biomarkers may occur in the absence of a clinical myocardial infarction [23]. DKA may also mimic an acute abdomen, particularly in younger patients.

Management

Management and treatment of DKA rests on four pillars:

1 fluid and electrolyte therapy;
2 intravenous (i.v.) insulin therapy;
3 treatment of comorbidities; and
4 careful monitoring of the clinical course.

It is particularly important that treatment is initiated without delay and that the patient is monitored frequently and carefully, preferably in a highly specialized unit. Severe cases should be treated and monitored in an intensive care unit where possible. Useful algorithms for treatment are available from many sources, including the American Diabetes Association. In general, the overall goal is a controlled, gradual correction of metabolic abnormalities and fluid and electrolyte deficiencies in the course of ~24 h.

Treatment of DKA in children and young adolescents follows slightly different guidelines than those presented below (see Chapter 59) [24]. It is recommended that in children insulin is given continuously intravenously (0.1 IU/kg body weight/h) after initiation of fluid and electrolyte therapy in order to minimize the risk of cerebral edema. Otherwise, children are in general treated with weight-reduced doses as indicated below.

Fluid/saline therapy

The first priority is to start to replace fluids. Water and sodium deficits typically are ~10% of body weight and 10 mmol/kg and isotonic saline (0.154 mmol/L; 0.9% NaCl) is given at a rate of ~15–20 mL/kg/h or 1 L/h initially, followed by 250 mL/h after the first 2–3 h depending on the state of dehydration. Depending on prevailing sodium concentrations and hydration, hypotonic saline may also be used, but this is rarely necessary. Urine production and also cardiovascular, renal, and mental performance should be monitored frequently.

Insulin

Lack of insulin is the culprit in DKA and insulin treatment is mandatory. Insulin therapy in adults is given by infusion of 0.1 IU/kg body weight/h or more simply as 6–8 units/h. An i.v. bolus of 0.15 IU/kg body weight (or 10 IU) of regular insulin can be given initially but is not really required, as most of the initial improvement in metabolic status is brought about by rehydration. Alternatively, a bolus of 0.15 IU/kg body weight (or 10 IU) may be given every hour or a 20-unit bolus i.m. followed by 6 units every hour. If the patient is very insulin resistant, as assessed by daily insulin requirements, dosage can be increased, and vice versa if the patient is insulin sensitive. Considering the short half-life of i.v.-administered insulin, it is imperative that insulin is given at least every hour, regardless of the prevailing blood glucose.

Insulin therapy may be adjusted based on hourly measurements of blood glucose and, if possible, blood ketones, with the overall aim being a gradual decline in both. However, recent guidelines now advocate a fixed rate intravenous infusion as being safer and more effective in normalizing the ketonemia. The initial decline is to a large extent caused by rehydration and expansion of the extracellular volume. Repeated analysis of arterial blood gases may be indicated but only in those patients with very low pH values and/or poor clinical condition. Measurement of ketone levels in urine is in general unreliable in this phase; these methods measure acetoacetate, which is quantitatively of minor importance compared with 3-hydroxybutyrate, and acetoacetate in urine may exhibit a paradoxical initial increase because of increasing blood concentrations (and low urine production), despite successful treatment. In particular, acetone is also measured by standard urine dipstick methods and may continue to be excreted for up to 48 h after the onset of treatment as it is fat soluble and leaches out slowly during treatment.

When glucose concentrations are 10–15 mmol/L, glucose is given i.v. and/or orally to avoid hypoglycemia. It may be possible to taper i.v. insulin treatment when 3-hydroxybutyrate concentrations are well below 3 mmol/L. For i.v. replacement 10% glucose should be used as this provides some extra anabolic substrate. If the patient is still dehydrated, then the saline infusion should be continued.

Potassium, bicarbonate, and phosphate

Potassium

Even though the body is potassium depleted, with a typical deficit of around 5 mmol/kg, initial potassium values are usually normal or elevated. Insulin therapy, rehydration, and correction of acidosis all cause a rapid decrease in serum potassium and 20–30 mmol potassium/h should be administered once potassium levels are below 5.0 mmol/L, provided that renal function is intact. Subsequent potassium administration is guided by frequent concentration measurements; adjuvant oral administration may be used in very mild cases of DKA. It is a frequent practical problem that there may be some delay before values are available from the laboratory; gas analyzers that provide instant bedside potassium concentrations greatly facilitate this process.

Bicarbonate

Bicarbonate use in DKA is a matter of controversy [25], but it is empirically recommended that 25–50 mmol sodium bicarbonate is given hourly for 1–2 h if the pH is below 7.0.

Phosphate

Phosphate deficiency of around 1 mmol/kg is typically present in DKA, but there is no evidence that phosphate supplementation should be given routinely. In patients with severe hypophosphatemia and/or cardiac and skeletal or respiratory muscle weakness, 20–30 mmol potassium phosphate can be given hourly for 1–2 h.

Comorbidity

Coexisting diseases precipitate DKA and DKA precipitates coexisting disease. Most often, people with DKA have infectious disease, and signs of infection should be vigorously sought and treatment should be instituted as appropriate. Other prominent comorbidities include cardiovascular events (myocardial infarction, stroke, thrombophlebitis, pulmonary embolism), acute gastrointestinal disorders, and a variety of intoxications.

Complications

Iatrogenic hypoglycemia and hypokalemia are common and preventable, provided that there is access to rapid analysis of glucose and potassium and—not less important—a competent and experienced medical team. Another frequent complication is recurrence of DKA or unnecessary protraction of the course, typically caused by insufficient insulin therapy. Thrombotic events are also not uncommon, although more often in HHS than DKA.

Cerebral edema is a rare, but often fatal, complication preponderant in children and adolescents. The pathophysiology is poorly understood, but may relate to overly aggressive therapy, the use of hypotonic replacement fluids, local cerebral overhydration, and abnormalities of vasogenic function [24]. Symptoms frequently develop 4–12 h after initiation of therapy and include headache, altered mental status, specific neurological deficits, and signs of increased intracranial pressure. Treatment with mannitol or hypertonic saline may be beneficial in this condition.

In some patients, the high anion-gap ketoacidosis may be further complicated by the appearance of a non-anion-gap hyperchloremic acidosis during treatment with insulin and saline infusions [26]. This is because of loss of alkali in the form of ketoanions with sodium or potassium in the urine. This component often results in protracted acidosis, which can confuse clinical assessment. Some of these patients may benefit from bicarbonate therapy.

Prevention

Implementation of self-care and shared-care principles is crucial. People with T1DM should learn about the symptoms of DKA and be able to measure ketones in blood or urine when they feel ill or if their blood glucose is high. A common lapse is the omission or reduction of insulin during episodes with impaired well-being and poor appetite. Persistent ketosis should be treated with extra insulin, fluid, and carbohydrate, when necessary. Furthermore, it is very important that the individual patient has ready, 24 h/day access to diabetological expertise, preferably in a specialized diabetes center.

Hyperosmolar hyperglycemic state

The HHS is generally the fulminant result of poorly treated T2DM or delayed diagnosis of previously unknown T2DM. HHS is less frequent than DKA, but mortality is higher and remains close to 15% in many centers [2, 27]. As implied, hyperosmolality is the primary clinical problem accompanied by hyperglycemia of >35–40 mmol/L and an effective serum osmolality of >320 mOsm/kg (Table 36.1). HHS most often occurs in frail patients in combination with other potentially fatal conditions. Strict differentiation between DKA and HHS can be difficult, because some degree of ketosis may be present in HHS and because lactic acidosis and respiratory and renal failure may also be present. In practice, this dilemma is mainly ornamental, because diagnostic and therapeutic efforts follow the same principles.

In line with DKA, HHS is most often precipitated by infectious diseases or cardiovascular events and symptoms of hyperglycemia usually have been present for some days. Hyperglycemia is caused by a vicious cycle, in which relative insulin deficiency and high levels of stress hormones lead to increased endogenous glucose production and decreased peripheral glucose utilization; hyperglycemia in turn induces hyperosmolality and dehydration, which amplifies the stress hormone response and further impairs insulin secretion, and vice versa.

At presentation, the patient's clinical condition is poor, with severe dehydration, poor skin turgor, and often an altered level of consciousness (ranging from drowsiness to coma) and signs of hypovolemic shock. In general, the diagnostic procedures are similar to those for DKA. Typically, there will be a water deficit of 10–20% of body weight together with sodium, chloride, and potassium deficits of 5–10 mmol/kg body weight.

Treatment of HHS in general follows the same guidelines as for DKA, the main aim being a controlled correction of hyperglycemia, hyperosmolality, and water and electrolyte deficits over 24 h. Patients are generally more sensitive to insulin and an infusion of 0.1 IU/kg body weight/h is more than adequate in most cases. Repeated hourly boluses of 0.15 IU/kg body weight (or 10 IU) may also be used. As with DKA, the dosage should be adjusted according to normal daily insulin needs and depending on the therapeutic response. Usually 1 L of isotonic saline is infused in the first hour but after that slower rehydration is advisable. Hemodynamic performance should be monitored carefully and it should be borne in mind that many of the patients have pre- or coexisting cardiac disease. The use of a central venous pressure line is helpful. It should be noted that a significant proportion of HHS patients are hypernatremic. In this case, hypotonic saline can be used, but more slowly. Potassium is administered along the same lines as with DKA and it is often prudent to monitor the patient in the intensive care unit.

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7 Microvascular Complications in Diabetes

37 Pathogenesis of Microvascular Complications

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Key points

- Microvascular complications affect the capillaries and arterioles in the retina (retinopathy), the kidney (nephropathy), and nerves (neuropathy).
- Microvascular complications are caused by prolonged exposure to hyperglycemia.
- Microvascular complications are best prevented by strict metabolic control.
- Hyperglycemia damages cell types that cannot downregulate glucose uptake, causing intracellular hyperglycemia.
- Persistent consequences of hyperglycemia-induced mitochondrial superoxide production may also explain the continuing progression of tissue damage after improvement of glycemic levels ("hyperglycemic memory" or "legacy effect").
- Different individual susceptibilities to microvascular complications have been linked to genetic polymorphisms.
- A number of proven and potential pathogenic factors linking hyperglycemia to the development of microvascular complications may be categorized into five groups: metabolic factors, hemodynamic factors, growth factors/cytokines, intracellular factors, and the complement system.

Diabetic angiopathy: definition and clinical features

Diabetic angiopathy is characterized by functional and structural organ damage as a result of changes in the vascular system. Diabetic angiopathy is divided into *microangiopathy*, which affects the capillaries and arterioles in the retina (retinopathy), the kidney (nephropathy), and nerves (neuropathy), and *macroangiopathy*, which affects arteries in the brain (cerebrovascular disease), heart (ischemic heart disease and congestive heart failure), and the lower extremities (peripheral arterial disease) (Figure 37.1). The consequences of diabetic angiopathy are late diabetic complications, which have a significant impact on the prognosis, life expectancy, and quality of life of people with diabetes. Late diabetic complications may occur both in type 1 diabetes mellitus (T1DM) and type 2 diabetes mellitus (T2DM), which is the reason why all people with diabetes should be examined regularly in an appropriate screening program. Microvascular complications are quantitatively dominant in T1DM, whereas macroangiopathy dominates the clinical appearance in T2DM. In the treatment priorities in the prevention of diabetic angiopathy, microvascular complications are best avoided by strict metabolic control of blood glucose, whereas macrovascular complications are best avoided by strict treatment of dyslipidemia, hypertension, and other risk factors for cardiovascular disease (CVD) (Figure 37.2).

The pathogenesis of macrovascular complications, including atherosclerosis in diabetes, is described in Chapter 41, cardiovascular risk factors in diabetes in Chapters 42 and 43, ischemic heart disease in Chapter 44, congestive heart failure in Chapter 45, cerebrovascular disease in Chapter 46, and peripheral arterial disease in Chapter 47. The pathogenesis of microvascular complications is described in this chapter, followed by a description of diabetic retinopathy in Chapter 38, diabetic nephropathy in Chapter 39 and diabetic peripheral neuropathy in Chapter 40.

A classical morphological feature of diabetic microvascular complications (i.e. microangiopathy) is a thickening of the basement membrane in the capillaries and arterioles in the retina, kidney, and nerves. The magnitude of the thickening increases with the duration of diabetes. The thickening of the basement membrane is seen in virtually all people with diabetes, but clinically symptomatic organ damage is far less frequent. However, much of the impact of chronic diabetes falls on the microcirculation [1, 2]. With long-standing disease, there is progressive narrowing and eventual occlusion of vascular lumina, resulting in impaired perfusion, ischemia, and dysfunction of the affected tissues. Several processes contribute to microvascular occlusion. One of the earliest is increased vascular permeability, allowing extravasation of plasma proteins that accumulate as periodic acid–Schiff

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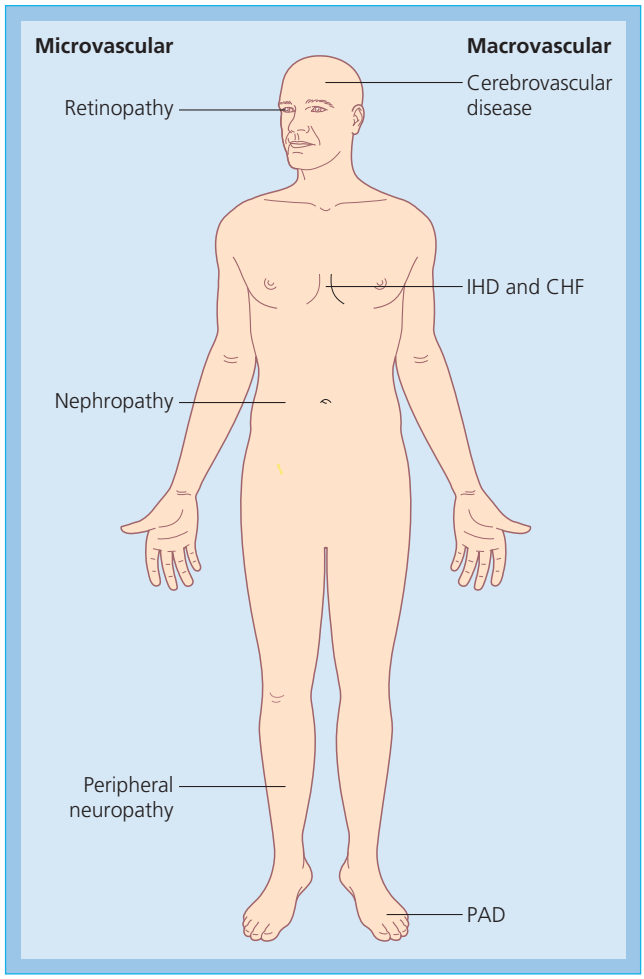

Figure 37.1 Diabetic angiopathy. Diabetic angiopathy is divided into *microangiopathy*, which affects the capillaries and arterioles in the retina (retinopathy), the kidney (nephropathy), and nerves (neuropathy), and *macroangiopathy*, which affects arteries in the brain (cerebrovascular disease), heart (ischemic heart disease [IHD] and congestive heart failure [CHF]), and the lower extremities (peripheral artery disease [PAD]).

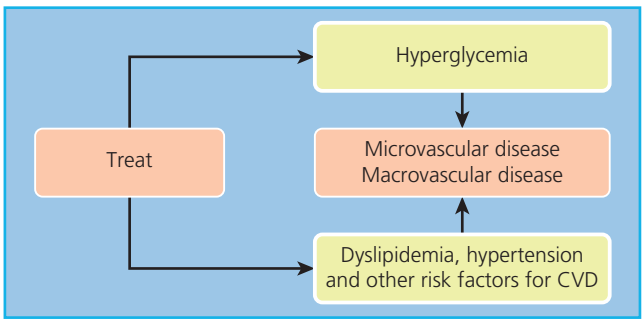

Figure 37.2 Primary priorities in the prevention of diabetic angiopathy. *Microvascular complications* are best prevented by strict metabolic control of glucose, whereas *macrovascular complications* are best avoided by strict treatment of dyslipidemia, hypertension, and other risk factors for cardiovascular disease (CVD).

(PAS)-positive deposits in the vessel walls. In addition, extracellular matrix production by perivascular cells such as pericytes (retina) and mesangial cells (glomerulus) is increased, brought about by changes in synthesis and turnover of its component proteins and glycosaminoglycans. As a result, the basement membrane is thickened in many tissues, including retinal capillaries and the vasa nervorum, along with mesangial matrix in the renal glomerulus. Hypertrophy and hyperplasia of endothelial, mesangial, and arteriolar smooth muscle cells also contribute to vessel wall thickening. Finally, increased coagulability and adhesion of platelets and leukocytes to the endothelial surface lead to microthrombus formation and luminal occlusion.

The progressive narrowing and blockage of diabetic microvascular lumina are accompanied by loss of microvascular cells. In the retina, diabetes induces apoptosis of Müller cells and ganglion cells [3], pericytes, and endothelial cells [4]. In the glomerulus, widespread capillary occlusion and declining renal function are associated with podocyte loss. In the vasa nervorum of diabetic nerves, endothelial cell and pericyte degeneration occur [5] and appear to precede functional abnormalities of peripheral nerves [6]. Increased apoptosis of cells in the retina, renal glomerulus, and peripheral neurons is a prominent feature of diabetic microvascular tissue damage [7–11] and may also damage adjacent cells.

Pathogenesis of microvascular complication: the role of hyperglycemia

Overall, diabetic microvascular complications are caused by prolonged exposure to high glucose levels. This has been established by large-scale prospective studies for both T1DM by the Diabetes Control and Complications Trial/Epidemiology of Diabetes Interventions and Complications Study (DCCT/EDIC) [12] and for T2DM by the UK Prospective Diabetes Study (UKPDS) [13]. Similar T2DM data have been reported by the Steno-2 study [14].

In this section, the potential mechanisms of differences in cell response to hyperglycemia, the phenomenon of glycemic memory, and determinants of individual susceptibility to hyperglycemia-induced damage are described.

Differences in cell response to hyperglycemia

As every cell in the body of individuals with diabetes is exposed to abnormally high glucose concentrations, it may be asked why hyperglycemia selectively damages some cell types whereas others are unaffected. The targeting of specific cell types by generalized hyperglycemia reflects the failure of those cells to downregulate their uptake of glucose when extracellular glucose concentrations are elevated. Cells that are not directly susceptible to direct hyperglycemic damage, such as vascular smooth muscle, show an inverse relationship between extracellular glucose concentrations and glucose transport. In contrast, vascular endothelial cells, a major target of hyperglycemic damage, show no significant change in glucose transport rate when the glucose

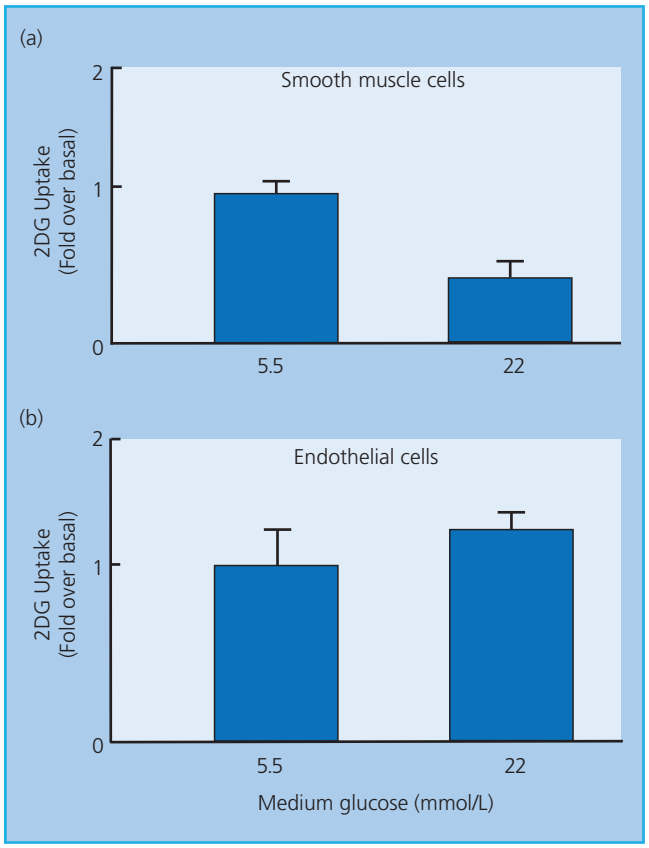

Figure 37.3 Lack of downregulation of glucose transport by hyperglycemia in cells affected by diabetic complications. (a) 2-Deoxyglucose uptake in vascular smooth muscle cells pre-exposed to 5.5 or 22 mmol/L glucose; (b) 2-deoxyglucose uptake in aortic endothelial cells pre-exposed to 5.5 or 22 mmol/L glucose. Source: Data adapted from Kaiser et al. 1993 [15].

concentration is elevated, resulting in intracellular hyperglycemia (Figure 37.3) [15]. These differences are caused in part by tissue-specific differences in expression and function of different glucose transporter (GLUT) proteins [16].

Glycemic memory or legacy effect

In 1993, the results of the landmark DCCT study showed that, in people with short-duration T1DM, intensive glycemic control dramatically reduced the occurrence and severity of diabetic microvascular complications. After the announcement of the DCCT results, many participants who had been in the standard therapy group adopted more intensive therapeutic regimens, and their level of glycemic control improved, as measured by HbA_{1c}. At the same time, the mean level of HbA_{1c} worsened for those who had been in the intensive therapy group. The post-DCCT HbA_{1c} values for both groups became statistically identical for the following 14 years of the EDIC Study.

Surprisingly, however, the effects of a 6.5-year difference in HbA_{1c} during the DCCT on the incidence of retinopathy and nephropathy persisted and became greater over the subsequent 14 years of follow-up. People in the standard therapy group continued to have a higher incidence of complications, even with an improvement in glycemic control during the 14 years of EDIC, whereas people in the intensive therapy group continued to have a lower incidence of complications, even with deterioration in glycemic control during the EDIC years. This phenomenon has been given the name *glycemic memory* or *legacy effect* (Figure 37.4). More recent data indicate that glycemic memory also occurs in people with T2DM. The tight glucose control group from the UKPDS demonstrated a continued reduction in microvascular risk and emergent risk reductions for acute myocardial infarction and death from any cause, despite an early loss of glycemic differences. A continued benefit was evident during the 10-year post-trial follow-up among overweight participants [17–19]. Glycemic memory has several important clinical implications and recommendations:

1 Early and tight metabolic control is very important.

2 Tight metabolic control after long-term metabolic dysregulation may not prevent subsequent development of diabetic microvascular complications.

3 There is a need for the development of novel therapies that reverse hyperglycemic memory.

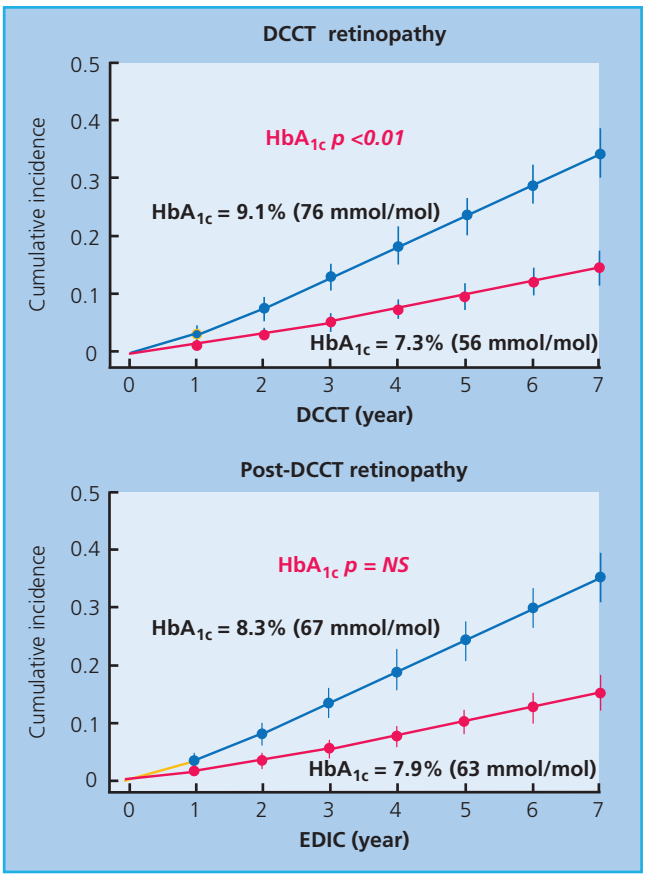

Figure 37.4 Hyperglycemic memory. Previous higher blood glucose levels make people with diabetes more susceptible to damage despite subsequent lower blood glucose exposure. After the end of the Diabetes Control and Complications Trial (DCCT) study, the group who had been poorly controlled on conventional insulin therapy continued to have a higher incidence of diabetic retinopathy than the tightly controlled group given intensive therapy, even though post-trial HbA_{1c} levels were comparable in the two groups. Reported HbA_{1c} is the mean in each group. EDIC, Epidemiology of Diabetes Interventions and Complications Study.

Hyperglycemia-induced mitochondrial superoxide production may provide an explanation for the continuing progression of tissue damage after the correction of hyperglycemia (*hyperglycemic memory*). Post-translational modifications of histones cause chromatin remodeling and changes in levels of gene expression [20–22]. Because these modifications do not involve differences in DNA sequence, they are called *epigenetic* (Figure 37.5a). Transient hyperglycemia has been shown to induce long-lasting activating epigenetic changes in the promoter of the Fib-subunit p65 in human aortic endothelial cells (16 h exposure) and in aortic cells *in vivo* in non-diabetic mice (6 h exposure), which cause sustained increases in p65 gene expression (Figure 37.5b) and in the expression of p65-dependent pro-inflammatory genes. Both the epigenetic changes and the gene expression changes persist for at least 6 days of subsequent normal glycemia. Hyperglycemia-induced epigenetic changes and increased p65 expression are prevented by normalizing mitochondrial superoxide production or superoxide-induced methylglyoxal (Figure 37.5b and c) [23]. These results highlight the dramatic and long-lasting effects that short-term hyperglycemic spikes can have on vascular cells and suggest that transient spikes of hyperglycemia may be an HbA_{1c}-independent risk factor for diabetic complications. Demethylation of another histone lysine residue, H3K9, is also induced by hyperglycemia-induced overproduction of reactive oxygen species (ROS). This reduces inhibition of p65 gene expression, and thus acts synergistically with the activating methylation of histone 3 lysine 4 [24]. Consistent with these observations, others have shown similar epigenetic changes in lymphocytes

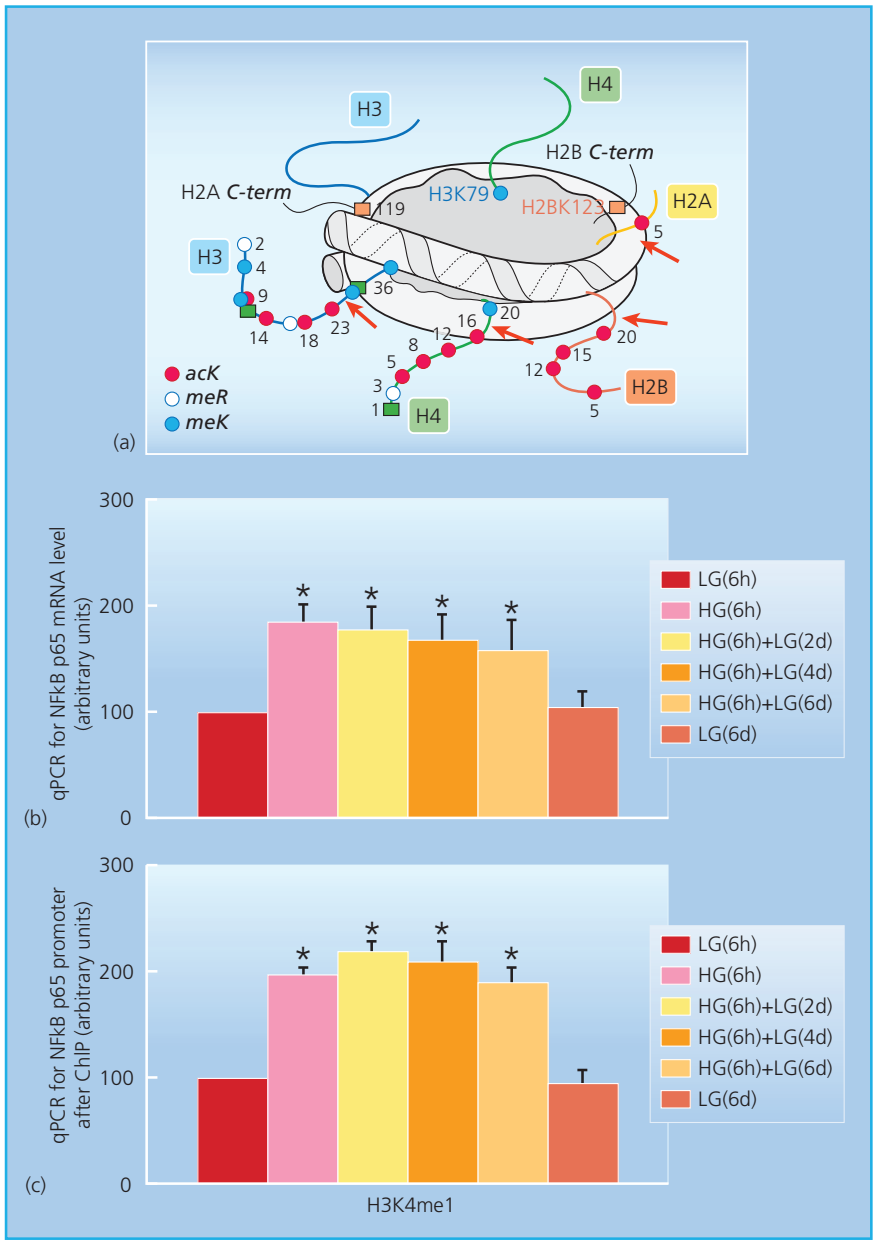

Figure 37.5 Transient hyperglycemia causes persistent epigenetic changes and altered gene expression during subsequent normoglycemia. (a) Schematic representation of several histone modifications (acK, acetylated lysine; meK, methylated lysine; meR, methylated arginine). (b), (c) Transient hyperglycemia induces persistent increased expression of the NFκB p65 subunit, caused by persistent epigenetic changes, including histone 3 lysine 4 monomethylation (H3K4me1) in the proximal promoter of the NFκB p65 subunit. HG, high glucose; LG, low glucose. Source: Data adapted from El-Osta et al. 2008 [23].

from people with T1DM [25] and in vascular smooth muscle cells derived from an experimental mouse model of T2DM [26].

Determinants of individual susceptibility to hyperglycemia-induced damage

As with all complex diseases, the occurrence and progression of diabetic complications vary markedly among people with diabetes. Some have T1DM for over 50 years with minimal complications, whereas others manifest severe disease or death within 15 years after diagnosis. The control of blood glucose, and also blood pressure and blood lipid profiles, are important factors in predicting the risk of complications, but they only partially explain the risk of complications for an individual. Therefore, genetic factors have been investigated for their influence on the risk of developing complications. An understanding of the genes involved in the susceptibility to or protection from diabetic complications can lead both to a better understanding of the pathophysiological mechanisms and to new biomarkers and molecular targets for drug development. Familial clustering studies strongly support a role for genetic determinants of susceptibility to hyperglycemic damage.

In two studies of families that have two or more siblings with T1DM, if one sibling had advanced diabetic nephropathy, the other sibling with diabetes had a nephropathy risk of 72–83%. By contrast, the risk was only 17–22% if the index sibling did not have diabetic nephropathy [27, 28]. Numerous associations have been made between various genetic polymorphisms and the risk of various diabetic complications. These include the HLA-DQB10201/0302 alleles [29], polymorphisms of the aldose reductase gene [30], the sorbitol dehydrogenase gene [31], and the promoter of erythropoietin gene [32]. A positive linkage and association with diabetic nephropathy of simple tandem repeat polymorphisms and single nucleotide polymorphisms in 20 genes have been demonstrated in families of people with T1DM of white European descent [33]. Three genes code for growth factors or growth factor receptors, five genes code for intracellular factors, three genes code for components of the extracellular matrix, and two genes are involved in its degradation. The remaining genes are likely to be important in kidney function [33]. The DCCT/EDIC trial also reported familial clustering and association with gene polymorphisms. In those with diabetes, the odds ratio for risk of severe retinopathy was 5.4-fold higher in family members of participants with retinopathy than in those without; coronary artery calcification also showed familial clustering [34]. In the same cohort, an association of multiple superoxide dismutase 1 variants was associated with the development and progression of diabetic nephropathy [35].

In the future, the challenge will be to identify specific genes involved in the varying clinical severity of diabetic complications. Recent emphasis in human disease genetics has been on so-called modifying genes, i.e. genetic variants that are distinct from disease susceptibility genes but modify the phenotypic and clinical expression of the disease genes. Studies show that genetic modifiers can be *tipping point* genes. This means that one gene changes the whole phenotype in an all-or-nothing fashion, in contrast with the incremental effects seen with changes in a large number of non-modifier genes. Many examples of modifier genes are known in model organisms, and several have been identified in humans [36, 37].

Pathogenesis of microvascular complication: beyond hyperglycemia

During recent decades, it has become increasingly evident that a number of different pathways may play a role as mediators between elevated and fluctuating blood glucose levels, thereby leading to the development of diabetic microvascular complications. The number of systems and interactions between these factors are complex, but as described in a review article dealing with the pathogenesis of diabetic kidney disease, four important groups of mediators are metabolic factors, hemodynamic factors, growth factors/cytokines, and intracellular factors [38]. Further, an increasing amount of evidence for an important role of the innate immune system has been published in recent years. In Figure 37.6, a schematic depiction of the potential hierarchy and interactions between metabolic, hemodynamic, growth factors/cytokines, intracellular factors, and the innate immune system in the pathogenesis of diabetic microvascular complications is proposed. In the following section, the five systems and the evidence for their role are described in more detail.

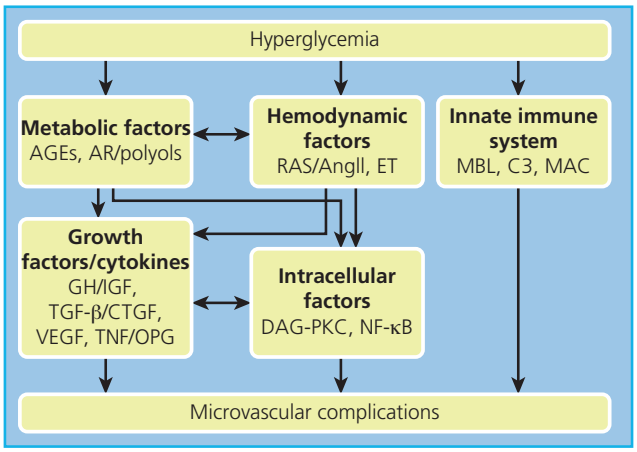

Figure 37.6 Schematic depiction of pathogenetic factors in diabetic microvascular complications. The potential hierarchy and interactions between metabolic, hemodynamic, growth factors/cytokines, intracellular factors, and the innate immune system in the pathogenesis of diabetic microvascular complications. AGEs, advanced glycation end-products; AR/polyols, aldose reductase/polyols; RAS, renin–angiotensin system; AngII, angiotensin II; ET, endothelin; GH, growth hormone; IGF, insulin-like growth factor; TGF-β, transforming growth factor β; CTGF, connective tissue growth factor; VEGF, vascular endothelial growth factor; TNF, tumor necrosis factor; OPG, osteoprotegerin; DAG–PKC, diacylglycerol–protein kinase C; NFκB, nuclear factor κB; MBL, mannose binding lectin; C3, complement C3; MAC, membrane attack complex.

Metabolic factors

Among the different metabolic pathways that impact the development of diabetic microvascular complications, the role of advanced glycation end-products (AGEs) and the aldose reductase (AR)/polyol pathway have been studied in detail.

Advanced glycation end-products (AGEs)

Amadori products are formed when glucose and other reactive carbonyl compounds react non-enzymatically with proteins, lipids, or nucleic acids and Schiff bases. Additional rearrangements and modifications lead to the generation of various forms of AGEs, such as carboxymethyllysine (CML), pentosidine, imidazolone, and pyrraline [39, 40]. AGEs interact with specific receptors [39–41]. p60 (OST-48, AGE-R1), p90 (80K-H, AGE-R2), galectin-3 (AGE-R3), the macrophage scavenger receptor type II (ScR-II), and CD36 all regulate the uptake and clearance of AGEs [39, 41]. The best-characterized receptor is receptor for AGEs (RAGE) [39]. AGEs can also act in a receptor-independent way by cross-linking proteins [39, 40]. AGEs alter the structure and function of intra- and extracellular molecules, increase oxidative stress, and modulate cell activation, signal transduction, and the expression of cytokines and growth factors through receptor-dependent and -independent pathways [39–41].

Preclinical data in support of a role for AGEs in diabetic microvascular complications come from studies in diabetic animal models [38, 42]. Renal AGE levels are increased in long-term experimental diabetes [43, 44]. Furthermore, in models of T1DM and T2DM, the intake of food-derived AGEs accelerates renal changes whereas a low-AGE diet provides protection against kidney damage [45]. In diabetic animal models of both T1DM [46, 47] and T2DM, elevated RAGE glomerular podocyte staining has been reported, compared with non-diabetic controls [48]. Finally, diabetic transgenic mice overexpressing human RAGE present with kidney and glomerular hypertrophy, increased albuminuria, mesangial expansion, advanced glomerulosclerosis, and increased impaired kidney function, compared with controls [49]. In clinical studies, AGEs have been shown to be elevated in both T1DM and T2DM [50, 51]. It is important to note, however, that studies indicate that AGEs at the concentrations found in diabetic sera are not the major ligand for RAGE. Rather, several pro-inflammatory protein ligands have been identified that activate RAGE at low concentrations. These include several members of the S100 calgranulin family and high-mobility group box 1 (HMGB1), all of which are increased by diabetic hyperglycemia. Binding of these ligands with RAGE causes cooperative interaction with the innate immune system signaling molecule toll-like receptor 4 (TLR-4) [52, 53].

During the last two decades, various agents have been examined in attempts to interfere with AGE formation or the cross-linking of proteins by AGEs. Agents that block AGE formation by scavenging reactive carbonyl intermediates include aminoguanidine, pyridoxamine, 2,3-diaminophenazine, OPB-9195, and tenilsetam. ALT-711 is an example of an AGE cross-link breaker. Further, ways to block the signal transduction through the RAGE can be achieved by the use of RAGE antibodies, antisense oligodeoxynucleotides (AS-ODNs), or soluble RAGE [38, 42]. A number of clinical trials have been performed aimed at exploring the clinical effects of pyridoxamine in both T1DM and T2DM [54, 55]. In one study, of mild to moderate renal impairment, the intervention reduced the slope of creatinine change without having an influence on urinary albumin excretion (UAE) [54]. In another study of more severe diabetic renal impairment, there was no effect of the treatment, indicating that treatment should be administered before the onset of significant pathological organ changes [55].

Aldose reductase/polyol pathway

The polyol pathway is based on a family of aldoketoreductase enzymes, which can utilize a wide variety of sugar-derived carbonyl compounds as substrates and reduce these by nicotinamide adenine dinucleotide phosphate (NADPH) to their respective sugar alcohols (polyols). The classic representation holds that glucose is converted to sorbitol, and galactose to galactitol. Sorbitol is then oxidized to fructose by the enzyme sorbitol dehydrogenase (SDH), with NAD^+ being reduced to NADH. The first and rate-limiting step of the polyol pathway is regulated by aldose reductase, which is found in tissues such as nerve, retina, lens, glomerulus, and blood vessel wall. In these tissues, glucose uptake is mediated by GLUT proteins other than GLUT-4 and so does not require insulin; intracellular glucose concentrations therefore rise in parallel with hyperglycemia. Several mechanisms have been proposed to explain how hyperglycemia-induced increases in polyol pathway flux could damage the tissues involved. These include sorbitol-induced osmotic stress, decreased cytosolic Na/K^+-ATPase activity, increased cytosolic $NADH/NAD^+$, and decreased cytosolic NADPH. It was originally suggested that intracellular accumulation of sorbitol, which does not diffuse easily across cell membranes, could result in osmotic damage, but it is now clear that sorbitol levels in diabetic vessels and nerves are far too low to do this. Another early suggestion was that increased flux through the polyol pathway led to decreased phosphatidylinositol synthesis, and that this inhibited Na/K^+-ATPase activity. The latter abnormality occurs in diabetes, but has subsequently been shown to result from hyperglycemia-induced activation of protein kinase C (PKC), which increases the production of two inhibitors of Na/K^+-ATPase, arachidonate and prostaglandin E2 [56].

It has also been suggested that the reduction of glucose to sorbitol by NADPH consumes the latter. NADPH is a cofactor required to regenerate reduced glutathione (GSH); as GSH is an important scavenger of ROS, this could induce or exacerbate intracellular oxidative stress. Indeed, overexpression of human AR increased atherosclerosis in diabetic mice and reduced the expression of genes that regulate regeneration of GSH [57]. Reduced GSH is depleted in the lens of transgenic mice that overexpress AR and in diabetic rat lens compared with non-diabetic lens [58, 59]. It has also been demonstrated that decreased glutathiolation of

cellular proteins is related to decreased nitric oxide (NO) availability in diabetic rats, which would decrease *S*-nitrosoglutathione. Restoring the NO levels in experimental animal models of diabetes increases glutathiolation of cellular proteins, inhibits AR activity, and prevents sorbitol accumulation. Moreover, hyperglycemia can also inhibit glucose-6-phosphate dehydrogenase, the major source of NADPH regeneration, which may further reduce the NADPH concentration in some vascular cells and neurons [60]. In diabetic vascular cells, however, glucose does not appear to be the substrate for AR, because the Michaelis constant (K_m) of aldose reductase for glucose is 100 mmol/L, whereas the intracellular concentration of glucose in the diabetic retina is 0.15 mmol/L [61, 62]. Glycolytic metabolites of glucose such as glyceraldehyde-3-phosphate, for which AR has much higher affinity, may be the physiologically relevant substrate.

In recent decades, a number of AR inhibitors have been developed and studied in experimental and clinical studies for their potential effect on diabetic microvascular complications [63]. Unfortunately, these drugs have not so far shown convincing clinical effects [63].

Hemodynamic factors

Tight control of blood pressure delays the progression of retinopathy and nephropathy, whereas elevated blood pressure accelerates the onset of nephropathy and its progression [64–66]. Blockade of the renin–angiotensin system (RAS), and thereby the effects of the vasoconstrictor angiotensin II (AngII), is gold-standard treatment and a cornerstone in the secondary and tertiary treatment of incipient or overt diabetic microvascular complications, in particular diabetic retinopathy (see Chapter 38) and diabetic nephropathy (see Chapter 39). In addition to the well-known systemic and locally hemodynamic effects, RAS and the endothelin (ET) system may exert non-hemodynamic effects through autocrine and paracrine actions. In the following section, the ET system and its role in diabetic microvascular complications are addressed.

Endothelin

The ET system embraces ET-1–3 and two receptors. ET-1 is the most potent vasoconstrictor of the three [67, 68]. In mammals, two receptors, ET_A and ET_B, exert their signal mainly through activation of G-proteins. The ET_A receptor is mainly involved in vasoconstriction and cell proliferation, whereas the ET_B receptor induces NO release and vasodilation [67, 68]. ETs acts through paracrine and autocrine actions.

The effects of ETs can be blocked by the administration of non-selective ET receptor antagonists (e.g. bosentan), selective ET_A antagonists (e.g. avosentan, atrasentan), or ET_B antagonists. As summarized in a recent review [69], ET receptor blockade, in particular by the use of selective ET_A blockers, has shown renal protective effects in experimental animal models of diabetes, by lowering UAE, podocyte loss, and inflammation. In human diabetes, some renoprotective effects have been reported with bosentan treatment [70] or treatment with selective ET_A blockers [71, 72]. However, fluid retention has been a challenge in most studies, which may reduce the future potential for this class of drugs in the treatment of diabetic microvascular complications [69].

Growth factors/cytokines

Of the many known growth factors and cytokines, growth hormone (GH) and insulin-like growth factor I (IGF-I) were the first to be implicated in the development of diabetic microangiopathy [73–75]. The evidence for a role of GH/IGF-I in the pathogenesis is reviewed elsewhere [38]. So far, no drugs with regulatory effects on this axis have yet made it to a clinical use. Transforming growth factor β (TGF-β), connective tissue growth factor (CTGF), and vascular endothelial growth factor (VEGF) have been studied intensively over several decades as significant pathogenic factors for diabetic microangiopathy. In recent years, the role of the tumor necrosis factor (TNF) superfamily has been increasingly associated with a pathogenic role in diabetic microvascular complications.

Transforming growth factor/connective tissue growth factor

The TGF-β superfamily consists of multifunctional cytokines, where TGF-β1, TGF-β2, and TGF-β3 are involved in ECM synthesis [76]. The biologically active isoforms are generated after proteolytic activation [76]. Three TGF-β receptors have been identified and TGF-β signal transduction involves at least three subclasses of SMAD proteins [76–78]. CTGF has been identified as a downstream mediator of TGF-β [38]. There is a huge amount of preclinical and clinical evidence that the TGF-β superfamily, including CTGF, may be involved in the pathogenesis of particular diabetic nephropathy and retinopathy [38, 79, 80].

Accordingly, a number of clinical studies have been conducted in recent years in order to examine the effects of TGF-β or CTGF blockade. A phase II clinical study has been performed with the application of a TGF-β antibody in people with T1DM and diabetic nephropathy, showing a minor effect on the rise in serum creatinine [81]. Pirfenidone, a compound that blocks TGF-β promoter activity, has been trialed in people with T1DM and T2DM and diabetic kidney disease, already on RAS blockade, and demonstrated a beneficial effect on estimated glomerular filtration rate (eGFR) compared with placebo; however, there was a high dropout rate in the pirfenidone-treated participants [82]. In addition to a series of preclinical diabetic studies showing positive results on kidney variables by blocking the CTGF axis, a single clinical trial has been performed with the application of a human monoclonal antibody to CTGF (FG-3019) in people with diabetic nephropathy [83]. The treatment was generally well tolerated and reduced UAE [83].

Although the promising renoprotective results from preclinical studies have facilitated the first clinical studies in people with diabetic renal impairment, the safety and efficacy of using TGF-β and CTGF blockers in the clinical management of diabetic microvascular complications are still uncertain.

VEGF

The VEGF family embraces a number of different isoforms and exists in a number of homodimeric glycoproteins [84, 85]. VEGF increases vascular permeability and has a stimulatory effect on endothelial cell differentiation and proliferation [85]. The two well-described VEGF receptors (VEGFR-1 and VEGFR-2) are high-affinity transmembrane tyrosine kinase receptors [85]. The production of VEGF is regulated by a number of other growth factors and cytokines, including IGF-I [84, 85].

Numerous preclinical and clinical studies have been published in the last two decades, indication a pathogenic role of VEGF in both diabetic nephropathy [38, 86] and diabetic retinopathy [87]. Further, several VEGF/VEGFR antagonists have been developed, including agents that directly block the VEGF peptide, such as an anti-VEGF aptamer (pegaptanib), a monoclonal antibody fragment (ranibizumab), and a full-length VEGF antibody (bevacizumab). Other agents include a soluble VEGF receptor analog (VEGF-Trap) and small interfering RNA drugs (bevasiranib and rapamycin). Although anti-VEGF treatment has been shown to halt the development of diabetic renal changes in experimental models of T1DM and T2DM [38], anti-VEGF treatment have not yet been introduced in the clinic. By contrast, local application of anti-VEGF agents in the eye is a widely used procedure in the management of proliferative diabetic retinopathy (PDR), macular edema, and their associated complications [86, 87]. See also Chapter 38.

The TNF superfamily

The TNF superfamily and its relation to diabetic microvascular complications have been described in detail [88]. In brief, the TNF superfamily consists of structurally related proteins involved in processes such as regulation of immune response, inflammation, and cell death. TNF-related apoptosis-inducing ligand (TRAIL; also called TNF ligand superfamily member 10) was initially identified as a third member of the TNF superfamily to induce apoptosis [89, 89]. In contrast to other members of the TNF superfamily, TRAIL binds to a complex system of TRAIL receptors. Different TRAIL receptors have been described in humans, four of which are membrane bound, that is, TRAIL receptor 1 (TRAIL-R1) to TRAIL-R4 [88, 89]. A fifth receptor is osteoprotegerin (OPG). In addition to being a stimulator of the various TRAIL receptors, TRAIL is also an inhibitor of OPG. OPG was originally known as an inhibitor of bone resorption binding to RANKL (the receptor activator of nuclear factor κB ligand) [89–91]. OPG acts as a soluble inhibitor of the interaction between RANKL and RANK and also of osteoclastogenesis. Therefore, OPG acts as an inhibitor of both TRAIL and RANKL, and the delicate balance between these three components is important both in normal physiology and in pathophysiology [92].

Research on the role of TRAIL in diabetic microvascular complications is in its initial phase [88], while an increasing number of studies have been carried out on the role of OPG. It has become increasingly clear that OPG may play an important role in vascular dysfunction in diabetes, although it was originally identified as a bone molecule, with a inhibitory effect on osteoclast formation [89, 90]. Some studies, on the one hand, indicate that OPG may be involved in the development of vascular calcifications [93–95]. Thus, OPG has also been suggested to be a survival factor for endothelial cells [96]. In addition, OPG knockout (KO) mice develop vascular calcifications [97]. However, most studies are in support of a pro-atherosclerotic role for OPG in the vasculature, which may be particularly pronounced in diabetes. Accordingly, increased circulating levels of OPG have been demonstrated in a studies of experimental diabetes [98, 99] and microarray studies in human diabetes specimens have shown upregulation of OPG mRNA levels in kidney samples [100, 101]. Plasma OPG levels have been shown to correlate with the presence of renal dysfunction or CVD in T1DM and T2DM [88], and further plasma OPG levels are associated with vascular endothelial dysfunction [102]. A number of prospective studies have focused on circulating OPG levels as a putative predictor of progression of end-stage renal disease. Accordingly, in people with T1DM and nephropathy, plasma OPG is a powerful and independent predictor of progression to end-stage renal disease, cardiovascular, and all-cause mortality [103].

Intracellular factors

Among many different intracellular factors, there has been particular focus on the potential role of the activation of the diacylglycerol–protein kinase C (DAG–PKC) pathway in the development of diabetic microvascular complications.

DAG–PKC

PKC is an important intracellular pathway that can be activated by many upstream factors in the development of diabetic microvascular lesions, including metabolic, hemodynamic, and growth factor/cytokine factors. PKC can then be a stimulus for the initiation of several growth factors and cytokines. The group of PKCs comprises at least 11 isoforms that are widely distributed in mammalian tissues. The activity of the classic isoforms is dependent on both Ca^{2+} ions and phosphatidylserine and is greatly enhanced by DAG. Persistent and excessive activation of several PKC isoforms might also operate as a third common pathway mediating tissue injury induced by hyperglycemia and associated biochemical and metabolic abnormalities. This results primarily from enhanced *de novo* synthesis of DAG from glucose via triose phosphates, whose availability is increased because raised intracellular glucose levels enhance glucose flux through the glycolytic pathway [104–107]. Finally, evidence suggests that the enhanced activity of PKC isoforms could also result from the interaction between AGEs and their cell-surface receptors [108]. Hyperglycemia primarily activates the β and δ isoforms of PKC, both in cultured vascular cells [109–111] and in the retina and glomeruli of diabetic animals [106–108], but increases in other isoforms have also been found, such as PKC-α and PKC-ε isoforms in the retina [104] and PKC-α and PKC-δ in the glomerulus of diabetic rats [112, 113].

In early experimental diabetes, activation of PKC-β isoforms was shown to mediate the diabetes-related decreases in retinal

and renal blood flow [114], perhaps by depressing the production of the vasodilator NO and/or increasing ET-1, a potent vasoconstrictor. Overactivity of PKC has been implicated in the decreased NO production by the glomerulus in experimental diabetes [115] and by smooth muscle cells in the presence of high glucose levels [116], and inhibits insulin-stimulated expression of endothelial NO synthase (eNOS) in cultured endothelial cells [102]. Hyperglycemia increases the ability of endothelin-1 to stimulate mitogen-activated protein kinase (MAPK) activity in glomerular mesangial cells, and this occurs by activating PKC isoforms [117]. The increased endothelial cell permeability induced by high glucose levels in cultured cells is mediated by activation of PKC-a [118]; activation of PKC by high glucose also induces expression of the permeability-enhancing factor VEGF in smooth muscle cells [119]. In addition to mediating hyperglycemia-induced abnormalities of blood flow and permeability, activation of PKC may contribute to the accumulation of microvascular matrix protein by inducing expression of TGF-β1, fibronectin and type IV collagen in both cultured mesangial cells [120, 121] and in glomeruli of diabetic rats [112]. This effect also appears to be mediated through the inhibition of NO production by PKC [122]. Hyperglycemia-induced activation of PKC has also been implicated in the overexpression of the fibrinolytic inhibitor plasminogen activator inhibitor 1 (PAI-1) [123], and in the activation of nuclear factor κB (NFκB) in cultured endothelial cells and vascular smooth muscle cells [124].

Over the last few decades, a number of PKC inhibitors have been developed and examined in an attempt to lower PKC activity. Ruboxistaurin mesylate, which is a highly specific blocker of PKCβ isoforms, and the most widely studied specific PKC inhibitor, has been examined in diabetic animal models and a few pilot studies in humans [125]. These studies showed some beneficial effects on the development of diabetic renal changes in animals, but studies in humans have predominantly been inconclusive [125]. Therefore, the clinical effects of lowering PKC activity in the prevention of diabetic microvascular complications remain unclear at present.

The innate immune system

The innate immune or complement system and its relation to diabetic microvascular complications have been described in detail previously [88]. In brief, activation of the complement system takes place through three different pathways: the mannose-binding lectin (MBL), the classical, and the alternative pathways. All three pathways merge to stimulate the formation of a complement C3 convertase. When cleaved by a complement C3 convertase into pro-inflammatory and proteolytic subforms, the zymogens are activated, with subsequent downstream effects that include recruitment of inflammatory cells, tagging and subsequent clearing of immunocomplexes, and the generation of the membrane attack complex (MAC). A number of experimental studies have shown an association between the MBL and diabetic microvascular changes. In a mouse model of T1DM, diabetic MBL KO mice were protected from diabetic kidney damage, as indicated by diminished renal hypertrophy, urinary albumin excretion, and renal collagen IV expression and a tendency to reduced mesangial expansion and basement membrane thickness compared with diabetic wild-type mice [126]. In people with T1DM, high levels of circulating MBL and high MBL genotypes are associated with the development of diabetic nephropathy and increased mortality [127]. In addition, elevated MBL levels were found in people with T1DM with micro- and macroalbuminuria compared with people with normoalbuminuria in the FinnDiane study [128]. Further, serum MBL levels, measured at the onset of diabetes in a cohort of 270 people with T1DM, were predictive for the development of microalbuminuria during an 18-year follow-up period [129]. Finally, serum MBL is a significant predictor of both the development of albuminuria and overall mortality in people with T2DM, as shown in a group without classical risk factors for nephropathy [130]. In this study, the combination of high MBL and high hsCRP (high-sensitivity C-reactive protein) levels at baseline were predicted for an increased risk of developing microalbuminuria or macroalbuminuria compared with those with low levels of both proteins. In addition, high levels of MBL and hsCRP were predictive for mortality in people with T2DM with and without nephropathy [130]. A recent meta-analysis concluded that high expression of MBL is correlated with a significantly increased risk of vascular complications in diabetes and that measurements of MBL levels in diabetes is an effective and feasible method to predict high risk of microvascular complications [131].

In addition to MBL, other studies suggest that downstream complement components may be involved in microvascular complications. Accordingly, the magnitude of renal deposition of C3 has been studied in various preclinical diabetes models. In one study, C3 deposition was localized in glomerular capillaries of mice with T2DM [132]. In an experimental model of T1DM, enhanced glomerular and tubular C3 staining normalized in response to transplantation of pancreatic islets [133, 134]. In addition, renal transplantation from the rats with T1DM into non-diabetic animals normalized the renal C3 staining, whereas transplantation of kidneys from non-diabetic rats to rats with T1DM enhanced kidney C3 staining [135]. Clinical data are also in support of a role of downstream components of the complement system. In people with T1DM and varying degrees of diabetic nephropathy, MAC deposits were found to be localized to the glomerular basement membrane, the tubular basement membrane, and Bowman's capsular membrane. These are locations that correlate with mesangial expansion, which suggests that MAC has a role in the pathogenesis of diabetic nephropathy [136].

Conclusion

Beyond any doubt, hyperglycemia is the main driver in the development of microvascular complications in people with T1DM and T2DM. Accordingly, strict metabolic control is a cornerstone in the primary prevention of the diabetic microvascular complications retinopathy, nephropathy, and neuropathy. Further, a number of effective treatments of manifest microvascular disease have

been developed, in particular against diabetic retinopathy and diabetic nephropathy; see Chapters 38–40 for further descriptions.

Although many pharmaceutical and technical interventions are available today that effectively prevent or delay the development of microvascular complications in diabetes, there is an ongoing need for the development of new biomarkers and new therapeutic treatments for these complications.

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38 Diabetic Retinopathy

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Key points

- Diabetic retinopathy is a frequent cause of blindness in the Western world.
- The pathophysiology of the disease is unknown, but the morphological lesions characterizing the disease indicate that disturbances in retinal vascular function are involved in the disease pathogenesis.
- The early stages of diabetic retinopathy are not accompanied by any subjective symptoms, but the disease can be detected by screening with inspection of the ocular fundus.
- The early changes may develop into one or both of two vision-threatening complications, proliferative diabetic retinopathy and diabetic maculopathy, each with a different epidemiology, clinical appearance, and location in the retina.
- Diabetic retinopathy can be treated by retinal photocoagulation, and recently the advent of intravitreal angiostatic treatment has added to the therapeutic armamentarium for cases where photocoagulation is not suitable or sufficient.
- Countries with effective population screening and timely treatment of diabetic retinopathy have managed to reduce the incidence of low vision and blindness secondary to the disease to a negligible level.

Introduction

Diabetes mellitus is a disease of intermediary metabolism that may lead to complications in all parts of the body, including the eye [1]. The ocular complications include sudden palsies of external eye muscles resulting in diplopia that normally disappears spontaneously within a few weeks. Individuals with diabetes also have reduced motility of the pupil secondary to autonomic neuropathy, and diabetes may lead to the development of cataract at a much earlier age than in the normal population [2]. However, this condition can be treated by surgery with a low complication rate.

The diabetic complication developing in the retina, diabetic retinopathy, is a potentially much more serious condition and constitutes one of the most frequent causes of blindness in the Western world [3]. The disease is characterized by morphological lesions in the retina related to disturbances in retinal blood flow [4]. The initial signs of the disease are microaneurysms and hemorrhages in the macular area (Figure 38.1) that may progress to one or both of the two vision-threatening complications, diabetic maculopathy and proliferative diabetic retinopathy. In diabetic maculopathy, the early changes progress with breakdown of the blood–retina barrier, exudation of plasma proteins, and formation of retinal edema that may expand to include the foveal region with a resulting destructive effect on central vision. Proliferative diabetic retinopathy is initiated by occlusion of capillaries in the retinal periphery. The consequent ischemia and hypoxia stimulate the release of growth factors that diffuse to the nearest venule with an angiogenic potential and initiate a neovascular response.

Nomenclature

The nomenclature of diabetic retinopathy dates back to the initial descriptions of retinopathy in persons with type 1 diabetes mellitus (T1DM), where it was important to distinguish the early changes without visual loss termed simplex, background (inside the retinal background), or non-proliferative diabetic retinopathy from proliferative diabetic retinopathy where neovascularizations grow pre-retinally and lead to vitreous hemorrhage and blindness if untreated [5]. The grading of retinopathy on this scale was supplemented with a notification of whether edema and/or exudates in the macular area (maculopathy) was present or not, since such changes would threaten central vision by mechanisms other than those related to proliferative diabetic retinopathy. However, the comprehension of diabetic retinopathy should reflect the fact that early retinopathy changes can develop into one or both of the two vision-threatening complications, diabetic maculopathy and proliferative diabetic retinopathy, with different sites of development in the retina, different epidemiologies, and different pathophysiologies (Table 38.1).

Textbook of Diabetes, Fifth Edition. Edited by R. Holt, C. Cockram, A. Flyvbjerg and B. Goldstein.

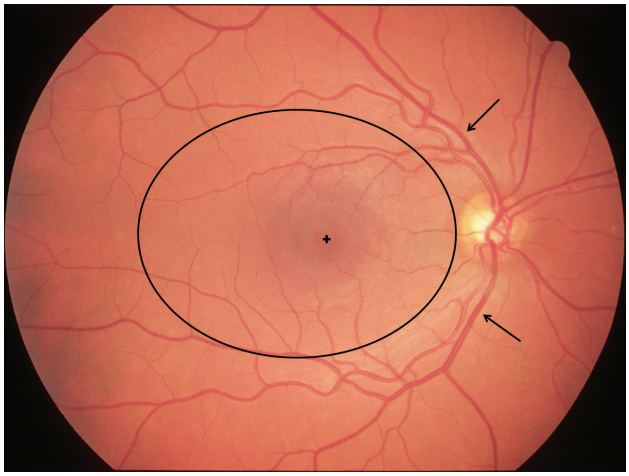

Figure 38.1 Fundus photograph from a normal person. The retinal vascular tree branches from the optic nerve to the right. Arrows indicate the temporal vascular arcades. The ellipse delimits the temporal vascular arcades and the cross in the center indicates the fovea.

Pathophysiology

The coupling between diabetic metabolic disturbances and the development of the morphological changes that characterize diabetic retinopathy is not known in detail [6]. Consequently, diabetic retinopathy has been studied from a number of different perspectives, and over the years a number of different hypotheses have been proposed to explain the development of the disease. One of the most productive hypotheses was the proposal of Michaelson that proliferative diabetic retinopathy is due to the release of growth factors from ischemic and hypoxic areas in the retinal periphery [7], which formed the rational basis for the development of angiostatic treatment for diabetic retinopathy.

Table 38.1 The nomenclature used to describe diabetic retinopathy.

Feature	Nomenclature for diabetic retinopathy	
Early changes without vision loss	• Simplex retinopathy Older notation that has largely been abandoned • Background retinopathy • Non-proliferative diabetic retinopathy Newer notation that is somewhat misleading as it does not indicate that these changes also precede diabetic maculopathy	
Transition towards vision-threatening retinopathy	Preproliferative diabetic retinopathy	Diabetic maculopathy without center involvement
Vision-threatening diabetic retinopathy	Proliferative diabetic retinopathy	Diabetic maculopathy with involvement of the area in and around the fovea

Later hypotheses emphasized metabolic disturbances in the retina, such as hyperglycemia leading to non-enzymatic glycosylation, shunting via aldose reductase, or activation of protein kinase C [8]. Other hypotheses have focused on specific anatomical elements as key factors in the pathogenesis of the disease, such as leukocytes, vascular pericytes, basement membranes, endothelial cells, the blood–retina barrier, neuroglia, and elements involved in neurovascular coupling [9–13]. Finally, some hypotheses have emphasized the involvement of specific reaction types such as inflammation in the development of the disease [14]. All these hypotheses can explain the pathophysiology of the disease in part, but have not individually or together been able to explain fully the development of the disease.

It is a particular feature of the retina that the inner vascular supply is devoid of autonomic nerves. This implies that retinal blood flow is autoregulated, and it has been shown that the vascular changes in diabetic retinopathy may be related to impairment of this autoregulation [15]. The disturbances affect both pressure autoregulation, so that retinal resistance vessels contract insufficiently when the systemic blood pressure is increased [16], and metabolic autoregulation, implying a reduction in the normal dilation of retinal arterioles when the retinal metabolism is increased, such as during exposure to flickering light [17]. Therefore, one of the key issues in the exploration of diabetic retinopathy is to understand the connection between diabetic metabolic dysregulation and disturbances in the regulation of retinal blood flow.

Development

Early changes with no vision loss

The initial morphological changes in diabetic retinopathy are red dots in the macular area representing capillary microaneurysms and dot hemorrhages. These two lesion types often have a similar funduscopic appearance, presenting as small, round, reddish lesions [18]. A differentiation of microaneurysms from hemorrhages requires fluorescein angiography, where microaneurysms are hyperfluorescent and hemorrhages appear as dark spots [19]. Therefore, the idea of counting microaneurysms alone in fundus photographs is meaningless. However, in clinical practice the distinction between microaneurysms and dot hemorrhages is conceptual, and the two lesion types should be considered together in the grading of retinopathy, just referred to as red dots.

The initial lesions typically develop in the area temporal from the fovea (Figure 38.2), probably because the intraluminal pressure is particularly high in this area where the capillaries are supplied by dilated arterioles from both the upper and the lower temporal vascular arcades [20]. The presence of up to a few red dots implies the same risk of progression of the disease, whereas the risk of progression to a vision-threatening condition is proportionate with higher numbers of red dots [21]. Retinal hemorrhages may also assume shapes other than circular when the extravasated blood distributes around the anatomical structures in the retina. One of the most striking examples is the stripe-shaped

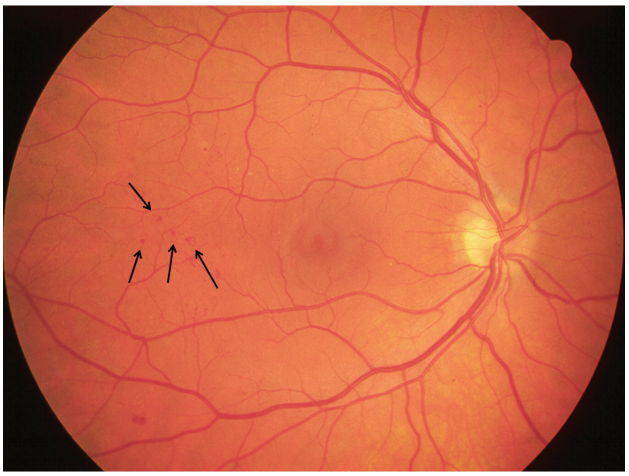

Figure 38.2 Early diabetic retinopathy with red dots (arrows) predominantly located temporally in the macular area.

hemorrhages that may develop in the retinal nerve fiber layer. Microaneurysms and hemorrhages show a highly dynamic pattern of development with continuous new formation and resolution of lesions occurring within days to weeks [22, 23]. Therefore, the progression of the disease with an increase in the total number of lesions over months to years is due to a change in this balance where the number of newly formed lesions is higher than the number of lesions that are resolved.

The progression of diabetic retinopathy (Figure 38.3) implies an increase in the number of red dots and the occurrence of blot hemorrhages, defined as lesions with a diameter larger than that of the vascular arcades at the crossing of the border of the optic disk [19]. Hemorrhages developing around the larger vascular arcades may indicate that impaired autoregulation has resulted in a higher than normal arterial blood pressure being transmitted to the smaller retinal vessels, resulting in damage to the capillary system adjacent to these arcades [24].

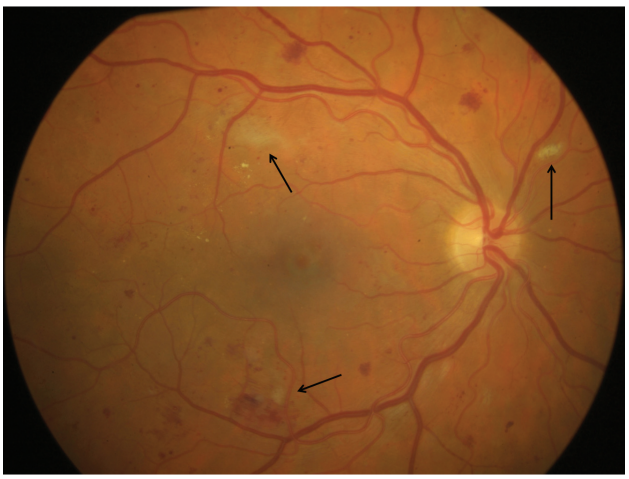

Figure 38.3 Moderate diabetic retinopathy with red dots, larger blot hemorrhages, and cotton-wool spots (arrows).

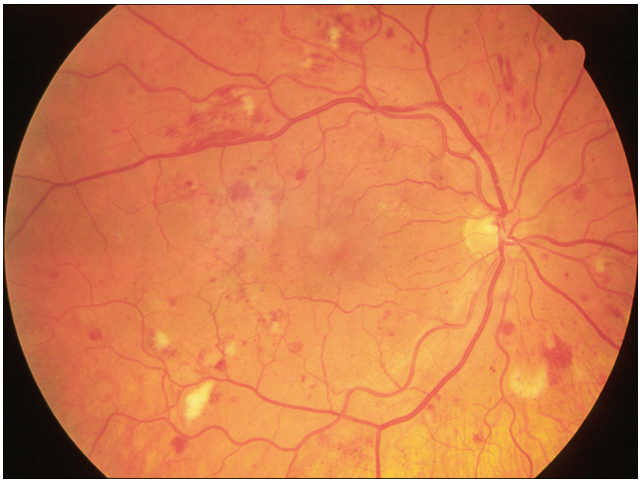

Figure 38.4 Severe diabetic retinopathy with many whitish cotton-wool spots developing during a period with poor metabolic control.

Diabetic retinopathy may also lead to the development of cotton-wool spots, which are localized whitish lesions about the size of one-third disk diameter located at the inner surface of the retina (Figure 38.4). The lesions represent swelling of the retinal nerve fibers because the axoplasmic transport has been arrested in a focal area with a consequent intracellular accumulation of the organelles transported to the site of the lesion [25]. Therefore, cotton-wool spots are most frequently located in the arcuate areas, where the retinal nerve fiber layer is thick, and never in the foveal area or the retinal periphery, which are devoid of retinal nerve fibers. The lesions reflect a response potential to disturbed axoplasmic transport in the retinal nerve fiber layer, but do not point to a specific cause of this disturbance. Therefore, it is erroneous to refer to the lesions per se as retinal infarctions, although this may be the background for the lesions in some cases. Cotton-wool spots have a dynamic cycle of development and disappearance lasting weeks to months and only rarely affect visual function [26]. The development of a single cotton-wool spot without any other retinopathy lesions does not imply a risk of progression of the disease, but the development of many cotton-wool spots in people with other retinopathy changes (Figure 38.4) may be an indication of unstable regulation of the blood glucose levels and of imminent progression to vision-threatening diabetic retinopathy [27].

Vision-threatening diabetic retinopathy

The early retinopathy changes may progress to one or both of the two vision-threatening complications, proliferative diabetic retinopathy and diabetic maculopathy, each preceded by transition forms.

Proliferative diabetic retinopathy

Mechanism of development

This complication is assumed to be initiated by occlusion of the capillaries in the retinal periphery. The resulting ischemia and

hypoxia stimulate the release of growth factors such as vascular endothelial growth factor (VEGF) that diffuse to the nearest retinal venule with an angiogenic potential and eventually initiate neovascularization [18]. This response reflects the normal angiogenesis during fetal development, where the retinal microcirculation is formed by vascular outgrowth from the retinal venules to reach the arterioles and complete the circulation. The vascular occlusion preceding neovascularization is not directly visible by inspection of the ocular fundus. However, retinal ischemia should be suspected when the retinal fundus has a more yellowish appearance than normal and other causes such as cataract with pronounced nuclear sclerosis that absorbs short-wavelength light have been ruled out. Retinal capillary occlusion can be demonstrated by fluorescein angiography, where the lesions appear as uniform dark areas, probably due to diffusion of the choroidal vascular pattern from fluid accumulated between the photoreceptor outer segments and the pigment epithelium [28]. Fluorescein angiography may also show localized areas of capillary occlusion at earlier stages, and it has been hypothesized that these changes could be involved in the early development of the disease [29].

The peripheral capillary occlusion and the consequent release of angiogenic factors progress to initiate growth of new vessels from the larger retinal venules. This neovascularization requires the presence of both an angiogenic stimulus and viable vessels with an angiogenic potential that is present in the larger venules proximal to areas of capillary occlusion. The proliferating new vessels are unable to grow inside the mature retina and therefore cannot replace the occluded vessels. Alternatively, the vessels grow along the posterior hyaloid membrane to expand preretinally. Therefore, the new vessels never reach an arteriole to complete the circulation, but are recursive back to the site of origin. Since there is no difference between the intravascular pressure of the legs at the origin of the neovascularization there is no blood flow through the vessel. The lack of contact between the new vessel and the retinal tissue precludes normal development of the vessels, which remain immature and fragile, eventually resulting in rupture and spontaneous hemorrhages into the vitreous body. The new vessels developing from venules at the optic nerve head are accompanied with a higher risk of progression to visual loss than neovascularizations located elsewhere [36], but the background for this difference is unknown. The clinical observation of proliferative diabetic retinopathy as a chronically progressive condition may give the impression that the disease process is irreversible, but the fact that retinal neovascularizations may disappear a few days after anti-VEGF therapy, and even under certain conditions spontaneously [31], suggests that the growth of these lesions depends on a continuous stimulation by growth factors.

Clinical presentation

The presence of preproliferative changes with capillary occlusion in the retinal periphery can be suspected when one or more of the following signs (Figure 38.5) are observed [19, 32]:

- The occurrence of many blot hemorrhages temporal in the macular area. These hemorrhages may develop in the foveal region with a consequent reduction in visual acuity, which is one of the few signs of severe diabetic retinopathy that can be noticed subjectively by the person with diabetes [33].
- Intraretinal microvascular abnormalities (IRMAs) that represent dilations of existing vessels from the retinal microcirculation. On fluorescein angiograms, these lesions are located at the border of areas of capillary occlusion and are therefore assumed to represent shunt formations to bypass the areas of capillary occlusion.
- Many cotton-wool spots, probably representing an aggravation of disturbances in blood flow and metabolism.
- Abundant reflexes from the posterior hyaloid membrane visible in younger persons where the optical media are clear. The reflections originate from the vertex of local swellings of the retina, probably reflecting localized areas of subclinical retinal edema.
- Caliber changes of the larger retinal venules that may develop to resemble beads on a string, so-called venous beading. Under normal conditions, the diameter of retinal vessels decreases with increasing distance from the optic disk, and therefore a localized increase in the diameter can be considered to be abnormal. The background for this manifestation of diabetic retinopathy is unknown, but may be related to metabolic acidosis or stagnant retinal blood flow.

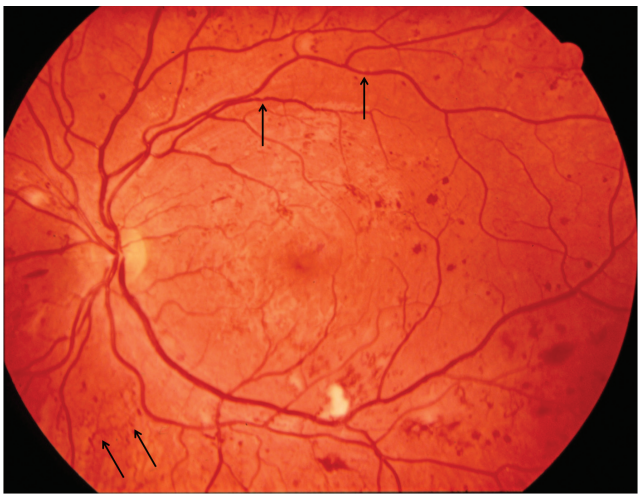

Figure 38.5 Preproliferative diabetic retinopathy with blot hemorrhages temporal in the macular area, cotton-wool spots, venous beading (upper arrows), IRMA vessels (lower arrows), and vivid reflexes from the posterior hyaloid membrane in the macular area.

The occurrence of neovascularizations (Figure 38.6) is a pivotal event since this prompts the initiation of treatment. In clinical practice, it is important to differentiate neovascularizations from shunt vessels, which can almost always be done on the basis of the following criteria [34] (Table 38.2):

- Retinal neovascularization is initiated by proliferation of retinal endothelial cells that penetrate the vascular wall to grow out of the vessel. However, endothelial cell proliferation may also develop inside retinal venules. These proliferations lead to occlusion of the venule of origin, which is slow enough to allow the development of shunt vessels to bypass the site of occlusion. These shunt

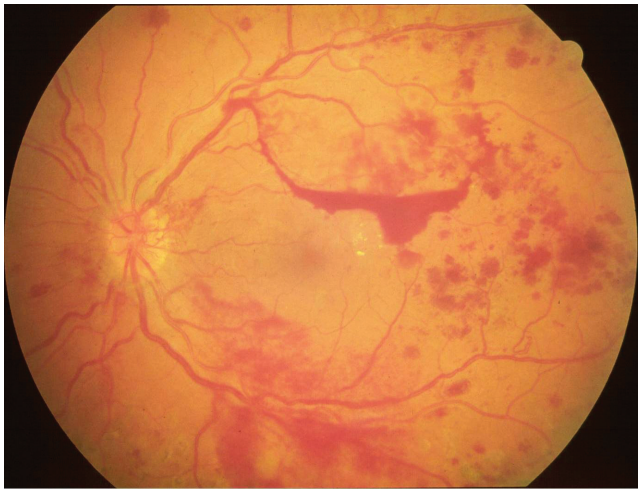

Figure 38.6 Proliferative diabetic retinopathy with new vessels blurring the optic disk. A neovascularization at the upper temporal arcade has given rise to a preretinal hemorrhage extending close to the fovea.

vessels may have the appearance of an omega loop or reduplicated bypass channels (Figure 38.7). When these changes are observed, the patient will usually already have developed preretinal neovascularizations and the condition should therefore be handled as any other case of proliferative diabetic retinopathy [35, 36].

- Retinal neovascularizations will in most cases become sites of origin of spontaneous hemorrhages, either as preretinal hemorrhages located behind the posterior hyaloid membrane resulting in a localized scotoma in the visual field, or will break through to the vitreous body. This progression of the hemorrhage results in a severe reduction in visual acuity, typically to hand movements, and a severely blurred view to the retinal fundus. If untreated, the vitreous hemorrhage may organize and together with traction from connective tissue in the new vessels the course may result in retinal detachment and total blindness.

Diabetic maculopathy

Mechanism of development

The progression of early diabetic retinopathy may result in the development of retinal edema and/or exudates representing precipitations of plasma proteins predominantly in the macular area. These changes are due to breakdown of the blood–retina barrier

Table 38.2 The differences between neovascularizations and shunt vessels.

Neovascularizations	Shunt vessels
Grow preretinally	Develop intraretinally
Develop from venules and are recursive back to the site of origin	Connect a venule with an arteriole
Many branchings	Few branchings, but often tortuous
May cross feeder vessel	Do not cross feeder vessel
May contain connective tissue	Do not contain connective tissue

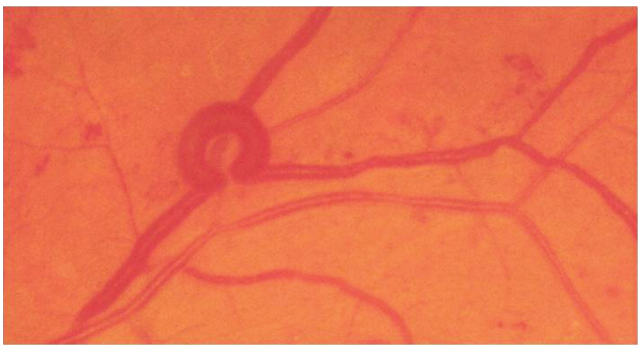

Figure 38.7 A segment of the upper vascular arcade. An omega loop represents a shunt formed to bypass an occlusion of a larger venule because of intravascular proliferation of endothelial cells. The venule extending peripheral from the loop displays changing caliber.

secondary to structural changes in the retinal vessels and impaired autoregulation so that a higher than normal blood pressure is transmitted to the capillary system [37, 38]. These factors compromise the tight junctions between the vascular endothelial cells and cause the exudation of plasma proteins that precipitate as hard exudates.

Clinical presentation

Diabetic maculopathy can be observed in the macular area and a short distance beyond the temporal vascular arcades and nasal from the optic disk, but not in the retinal periphery. Hard exudates may develop in circular precipitation lines around focal points of leakage or more randomly in the macular area when points of leakage are more distributed (Figure 38.8). Retinal edema has been categorized according to whether it is focal or diffuse [39], which may be an indication of the severity of the condition, but the practical significance of this distinction is disputed [40].

Retinal exudates and/or edema can progress and potentially threaten central vision as clinically significant macular edema when exudates and/or retinal edema either (Figure 38.9) (1)

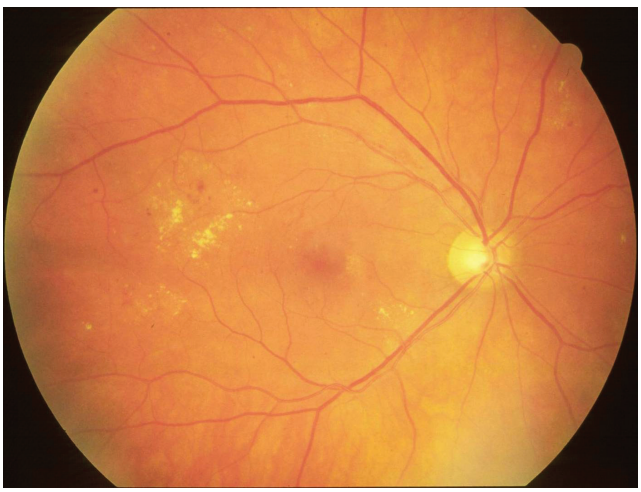

Figure 38.8 Diabetic maculopathy with exudates located temporally in the macular area.

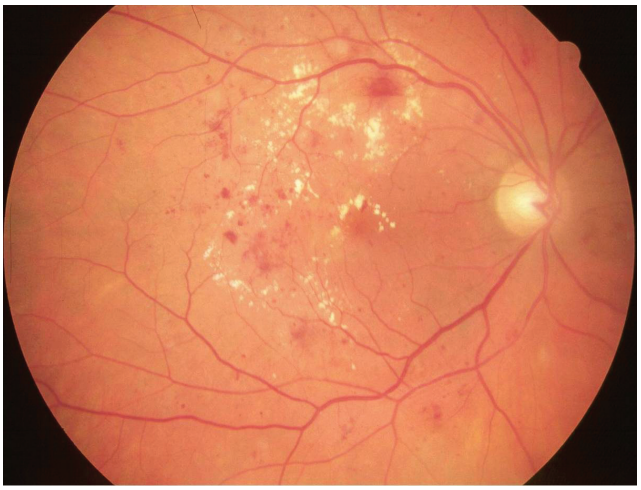

Figure 38.9 Diabetic maculopathy with clinically significant macular edema. Exudates extend over a larger part of the macular area and involving the foveal region.

extend over an area larger than one disk diameter of which a part is located within one disk diameter from the fovea, and/or (2) are located within half a disk diameter from the fovea [41]. Retinal edema together with exudates is termed exudative maculopathy and is the most common type of diabetic maculopathy. However, on rare occasions, macular edema may be due to an extension of capillary occlusion from the retinal periphery to the macular area [42]. The resulting macular ischemia is accompanied by edema that appears yellowish in the retinal fundus with many hemorrhages, but with no exudates. The two types of maculopathy can be differentiated by fluorescein angiography that can identify leakage and capillary occlusion.

Epidemiology

Diabetes mellitus is assumed to affect ~415 million people worldwide, of whom one-third have retinopathy and one-tenth have vision-threatening retinopathy [43]. However, these estimates cover ethnic, socioeconomic, and genetic variations. The pattern of development of diabetic retinopathy differs in the two diabetes types and is influenced by the success of the prevention, detection, and therapy of the disease. Thus, in countries with limited access to antidiabetes medication and lack of systematic population screening, retinopathy changes may develop after a few years' duration of diabetes and may be detected by the occurrence of vision-threatening changes. Therefore, the incidence and prevalence of diabetic retinopathy vary considerably, and estimates of the occurrence of the disease refer to countries with organized population-based screening and management of diabetic retinopathy.

In type 1 diabetes mellitus (T1DM), a few microaneurysms and/or dot hemorrhages may occur at the time of onset of the disease, but these lesions disappear so that the initial signs of diabetic retinopathy in progression appear after ~10 years' duration of diabetes [44]. The prevalence of diabetic retinopathy subsequently increases gradually until ~20 years' duration of diabetes, when almost all people with diabetes have some retinopathy [45]. The incidence of vision-threatening diabetic retinopathy gradually increases until ~25 years' duration of diabetes, after which it declines. This suggests the existence of constitutional risk factors that affect the risk of developing vision-threatening retinopathy within the first decades' duration of diabetes that overlie the risk of disease progression related to the cumulated exposure to metabolic dysregulation. In populations with comprehensive and organized screening and treatment programs, half of all individuals with T1DM develop vision-threatening retinopathy, of whom two-thirds develop proliferative diabetic retinopathy and one-third develop diabetic maculopathy [46].

In type 2 diabetes mellitus (T2DM), the onset of the disease is gradual, and although a large part of the population will remain undiagnosed in the early stages [44], the occurrence of retinopathy in this group is negligable [47]. At the time of diagnosis of T2DM, retinopathy can be observed in a considerable number of individuals, some of whom have already developed vision-threatening retinopathy [48]. After the time of diagnosis, the annual incidence of vision-threatening diabetic retinopathy is constant, and less than 10% of the individuals reach one of the treatment-requiring conditions, proliferative diabetic retinopathy and diabetic maculopathy. Since the number of persons with T2DM is larger than the number of those with T1DM, the absolute number of individuals developing vision-threatening retinopathy is approximately the same in the two groups.

Prevention

The occurrence and development of diabetic retinopathy are influenced by a number of modifiable or non-modifiable risk factors. Studies of non-modifiable risk factors such as ethnicity [49], actual age, and age at onset of diabetes [50] have provided important information about the pathophysiology of the disease. However, modifiable risk factors have received much more attention because of the potential for clinical intervention. Thus, it has been shown that the development of diabetic retinopathy correlates with glycemic control [51], and that intervention to improve this reduces the risk of progression of the disease in both T1DM [52] and T2DM [53]. Similarly, it has been documented that the development of diabetic retinopathy correlates with the systemic blood pressure [54], and that lowering blood pressure can reduce the progression of retinopathy changes in both T2DM [54] and T1DM [55]. Close monitoring of blood glucose and blood pressure can halt the progression of diabetic retinopathy, and are especially relevant during pregnancy where lifestyle and metabolism may be difficult to maintain at a stable level.

Recent evidence suggests that the formation of hard exudates may be related to the cholesterol level in the plasma [43], but clinical intervention studies are lacking to document that a reduction in plasma cholesterol can reduce the risk of diabetic maculopathy.

The development of diabetic retinopathy also depends on the type of diabetes and several studies have reported a higher frequency of retinopathy in men than in women, which may be due to men paying less attention to lifestyle [56].

Screening

Diabetic retinopathy is suitable for screening because the disease fulfills all of the following criteria [57]:

- *The development and early progression of the disease are not detected by the individual with retinopathy.* Since diabetic retinopathy initially develops and progresses outside the foveal area, the individual will not have subjective symptoms until at late stages when damage to central vision has started. Therefore, a screening examination with inspection of the ocular fundus is needed in order to detect early retinopathy lesions before they become a threat to central vision.
- *The disease is frequent.* The frequency of diabetes is increasing, but does not justify screening for diabetic retinopathy in the general population. However, diabetic retinopathy is frequent among the individuals in whom diabetes has been diagnosed and therefore justifies screening for diabetic retinopathy in this population [58, 59].
- *The disease can be detected.* Diabetic retinopathy can be detected by inspection of the ocular fundus, which is achievable in all persons unless impeded by cataract or other media opacities.
- *The disease can be treated.* A number of studies have confirmed the beneficial effect of retinal photocoagulation, intravitreal angiostatic pharmacotherapy, and vitrectomy for the treatment of diabetic retinopathy. This implies that therapeutic consquences can be taken from the detection of diabetic retinopathy.
- *Screening is cost-efficient.* A number of health economic analyses have documented that in addition to the beneficial effects for individuals screened for diabetic retinopathy, the procedure is also highly cost-efficient for society [60].

Screening for diabetic retinopathy consists of inspection of the ocular fundus, which may be supplemented with a measurement of visual acuity in order to assess the consequences of the disease for central vision [61]. It is recommended that the funduscopic appearance is documented by photography, which (1) gives an overview of lesions in all parts of the fundus background, (2) allows retinopathy lesions to be reviewed in order to obtain second opinions, and (3) allows a detailed evaluation of changes in the morphological appearance of the disease over time.

It has been a matter of debate whether screening examinations should be performed without dilation of the pupil (nonmydriatically) in order to allow a faster and more feasible examination procedure for the patient, and the availability of cameras for imaging of the retina through small pupils has facilitated this approach. The disadvantage of this photographic procedure is a reduced quality of images from the retinal periphery.

A single fundus photograph only provides indirect information about depth relations in the retina, which can be inferred from differences in focus. However, the examination can be supplemented with stereo fundus photography, where duplicate fundus photographs are recorded with the camera moved sligthly to each side and the light path tangential to the left and right pupil margins. The resulting images have different disparities and when studied binocularly the grader will obtain a stereoscopic view of the retina, which can be used to diagnose macular edema. However, the evaluation of depth relations in the retina by stereopsis is subjective, and nowadays the evaluation of macular edema should be performed by optical coherence tomography (OCT) scanning [62].

Fundus photography should cover retinal areas where relevant retinopathy changes can be detected, which can be achieved by seven photographic fields using a 30° field of view as in the United States standard [63] or by two 60° images as in the European standard [61]. Grading of retinopathy is performed by comparing the pattern of retinopathy with a set of standard images representing the different stages of the disease, and is designed so that at all levels of retinopathy the risk of progression from one level to the next is the same. This semiquantitative grading method considers the type, overall severity, and location of lesions in different quadrants and in relation to the fovea, but there is considerable morphological information that is not used, such as the number, shape, size, detailed location, and dynamics of the lesions. In order to include this information in the evaluation, initiatives have been taken to develop computer algorithms for quantitative analysis of diabetic retinopathy lesions. This work has been challenged by the lack of gold standards for lesion detection. Hence the interpretation of findings in the retina depends on image quality, and even experienced clinicians may disagree about the identification of retinal lesions [64].

The immense task of evaluating fundus photographs obtained during population screening for diabetic retinopathy has stimulated the training and certification of non-academic graders to manage this task. The grading of diabetic retinopathy should result in answers to the following two questions: (1) what is the time interval to the next screening examination? or (2) should the patient be referred for further diagnostic evaluation or treatment? The time interval to the next screening examination is generally determined by rule-based decision algorithms. On the basis of the diabetes type, diabetes duration, and retinopathy grade, a standard interval is recommended so that the disease will not progress undetected to a vision-threatening stage, even in persons with the fastest disease progression [65]. However, this conservative approach implies that the individuals in whom disease progression is slow will experience a number of superfluous examinations because the disease has not progressed by the time of the next screening examination. Therefore, new algorithms are being developed with the aim of individualizing the control interval and optimizing screening by reducing the number of superfluous examinations. These algorithms consider individual risk factors in order to prolong the control interval as much as possible while ensuring that the condition does not progress to vision-threatening retinopathy [66–68]. However, individualized control intervals may be difficult to remember for both the person

with diabetes and the doctors and other personnel involved in patient care, which is further complicated if optimized retinopathy screening implies that the examinations are not synchronized with visits for metabolic regulation and screening examinations for other late diabetic complications.

Overall, screening for diabetic retinopathy is a complex challenge that involves ophthalmological, technical, and organizational elements, and should therefore be adapted to the local healthcare system in each country. The potentials of such efforts have been proved in countries where screening for diabetic retinopathy has reduced the occurrence of blindness secondary to diabetic retinopathy to a negligible level [69].

Diagnosis

Diabetic retinopathy is defined and diagnosed by inspection of the ocular fundus to identify the typical morphological lesions of disease. Observation of the retina in red-free light may increase the contrast to improve the detection of lesions, but a detailed evaluation of the disease requires information about colors in order to distinguish red lesions from pigmentation. When diabetic retinopathy has progressed to a stage where treatment should be considered, supplementation with other imaging techniques may be required.

Fluorescein angiography (Figure 38.10) is a photographic recording of retinal morphology after intravenous injection of fluorescein, where the fluorescent dye is distributed in the systemic circulation and reaches the eye. In order to detect fluorescein in the retina, an excitation filter that transmits short-wavelength light is inserted into the light path that illuminates the retina, and a barrier filter that transmits longer wavelengths is inserted in front of the photographic film. Previously, the method was used routinely for the diagnosis of diabetic retinopathy but has to a large extent been replaced by less invasive techniques, and at present fluorescein angiography is restricted to special diagnostic cases. The method can detect (1) leakage of fluorescein from the retinal vessels as an indication of breakdown of the blood–retina barrier [70] and (2) capillary occlusion that appears as well-delimited and uniformly black areas [42]. The method plays a particular role in the differentiation of exudative macular edema from ischemic macular edema, which should be managed differently.

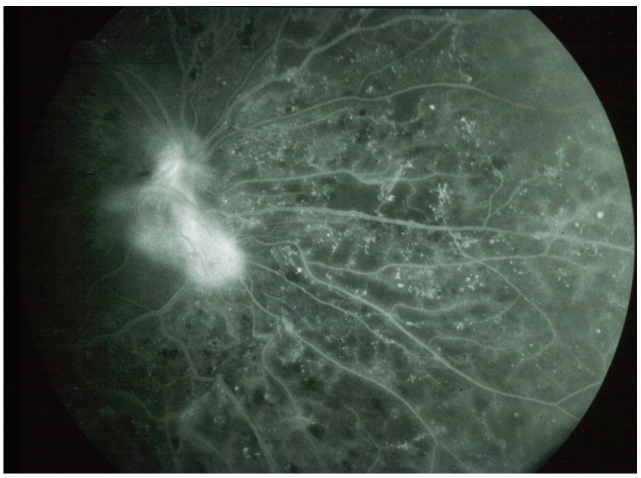

Figure 38.10 Fluorescein angiogram showing focal areas of capillary occlusion and leakage from bordering vessels. Microaneurysms are seen to fill with fluorescein. The hyperfluorescent area to the left represents a neovascularization.

OCT scanning records the latency of light pulses reflected from different retinal layers, which is translated to a measure of distance in the retina (Figure 38.11). The method can determine the location of individual layers in the retina with an accuracy of less than 10 µm and is therefore suitable for detecting pathological lesions in the retina not visible by clinical inspection [71] and for quantifying retinal edema in diabetic maculopathy [72]. This allows the monitoring of the effect of treatment of retinal edema, but the method is also suitable for differentiating diabetic macular edema from other causes of retinal swelling, such as traction from the posterior hyaloid.

A number of other techniques are used for the study of vascular changes in diabetic retinopathy, such as vessel analysis, oximetry, adaptive optics imaging, and flow measurement [73–76]. However, these techniques are research tools and do not at present have a role in daily clinical practice.

Treatment

Retinal photocoagulation

Retinal photocoagulation was the first available treatment with a documented effect on diabetic retinopathy [77]. The treatment is typically applied through a contact lens as localized laser burns with a width of 200–500 µm arranged in a grid pattern with a spacing corresponding to the width of one burn. The adverse effects of the treatment are related to the destructive effects on retinal tissue. At the beginning of a treatment session, the patient will have a strong feeling of glare, which often disappears after adaptation to the intense light. During the treatment, the applications may induce a distinct feeling of pain, especially when applied in the retinal periphery corresponding to the horizontal and the vertical meridians. After treatment, the patient will need a few minutes to adapt to ambient light conditions, and during the following days or weeks may experience blurred vision and flashes in the visual field corresponding to the laser applications. The treatment will induce permanent shrinkage of the visual field and reduce dark adaptation, but in most cases the patient will adapt to this new situation, especially when both eyes have been treated and the visual impression is comparable in the two eyes.

In proliferative diabetic retinopathy, the treatment is applied outside the macular area extending to the retinal periphery, and the beneficial effect is assumed to be related to the elimination of ischemic and hypoxic retinal tissue with a reduction in the release of the growth factors that stimulate neovascularization. The treatment typically requires 2000–3000 applications and is

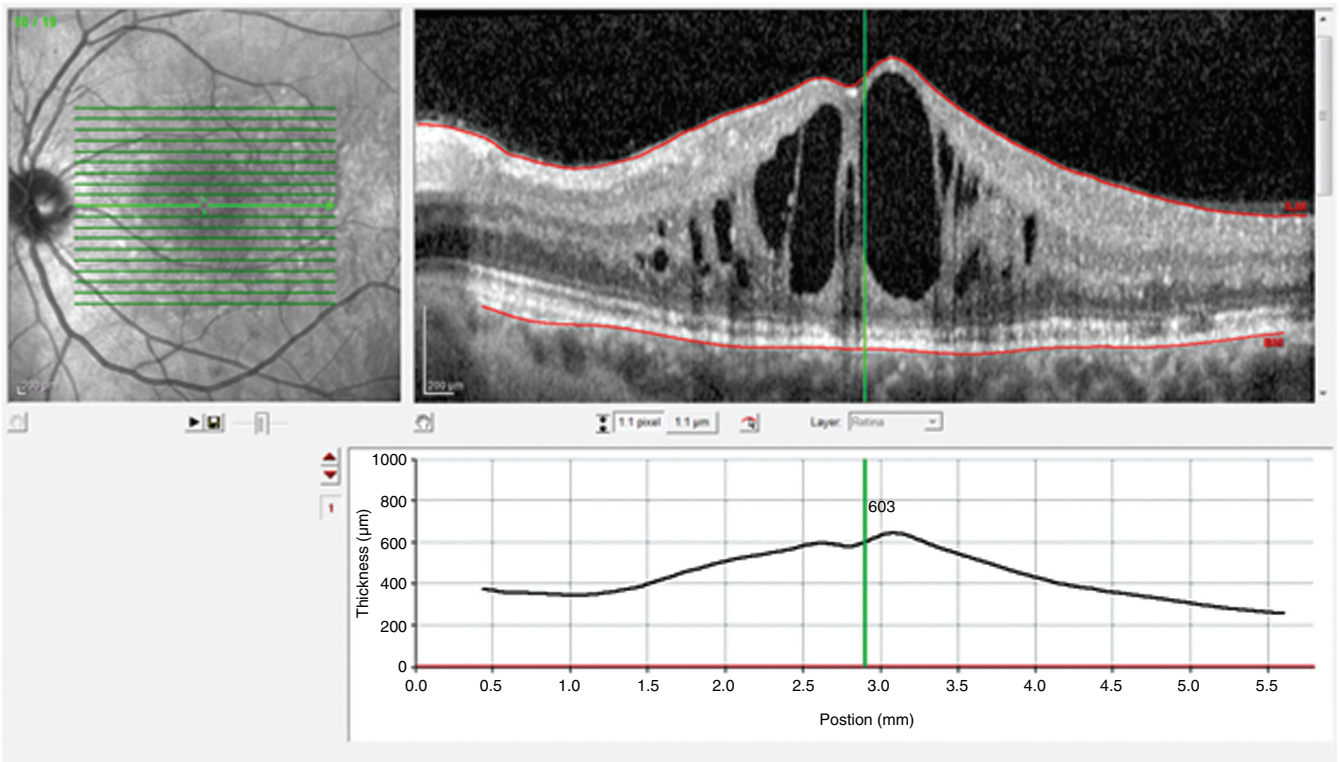

Figure 38.11 In the top left image, horizontal green lines represent the optical coherence tomography (OCT) scanning lines in the macular area from a person with diabetes mellitus. In the top right image, the OCT scan through the fovea shows cystic macular edema secondary to diabetic maculopathy. The graph represents the profile of the retinal surface along the OCT scan.

performed in several sessions until the intended clinical response has been obtained (Figure 38.12). The visual prognosis depends on age and visual acuity before treatment, whereas the number of laser applications necessary to halt the disease has no influence on the visual prognosis [78].

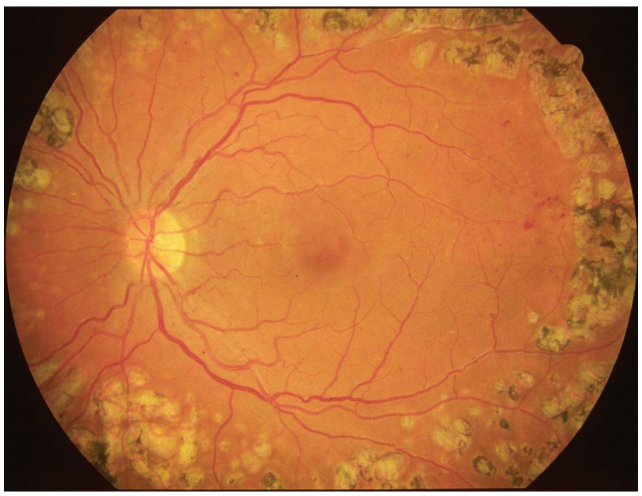

Figure 38.12 Fundus photograph 1 year after panretinal photocoagulation of the case shown in Figure 38.6. The hyperpigmented laser scars extend to the retinal periphery beyond the borders of the image.

Proliferative diabetic retinopathy may lead to vitreous hemorrhage, which can be the initial sign of retinopathy if progression to this stage has not been detected otherwise, but may also occur in individuals who have received photocoagulation and in whom retinal neovascularizations have not regressed. Vitreous hemorrhage leads to a sudden reduction in visual acuity and therefore the patient is generally referred to an ophthalmologist. If the patient has not received photocoagulation it is important to perform ultrasound B-scan examination to rule out retinal detachment. Generally, spontaneous resolution of the vitreous hemorrhage should be awaited for a few weeks to allow inspection and/or treatment of the retina [79]. If the hemorrhage does not resolve spontaneously, the treatment of choice is vitrectomy with surgical removal of the vitreous opacities [80]. The clearing of the vitreous body may at the same time establish a clear view to the retina to allow retinal photocoagulation. The visual prognosis depends on the damage to the retina induced by the diabetic retinopathy changes before treatment. Interestingly, vitrectomy has also been suggested for the treatment of diabetic maculopathy, since the replacement of the vitreous body with saline can improve diffusion and thereby facilitate the exchange of oxygen and other metabolites to the retina [69]. Retinal photocoagulation and vitrectomy will also often lead to regression of new vessels in the iris and the anterior chamber angle of the eye, but if this regression is insufficient the patient may need treatment for neovascular glaucoma.

In diabetic maculopathy, retinal photocoagulation is assumed to facilitate diffusion of oxygen and other nutrients from the choroid, and the elimination of metabolically active tissue induces a contraction of the pathologically dilated retinal vessels [81]. It is a general misconception that focal treatment of microaneurysms is effective. Owing to the fast turnover, the lesions disappear spontaneously whether treated or not [23]. However, focal treatment in other areas of leakage may reduce permeability of the retinal vessels and result in regression of hard exudates that have precipitated in circles around the leaking point [82]. The treatment is applied corresponding to areas with retinal edema, but sparing the papillomacular bundle and a zone within 500 µm from the fovea, which can often be achieved by a few hundred applications. Persons with reduced visual acuity may have extrafoveal points of fixation, and care should be taken not to photocoagulate these areas. Visual acuity may also be reduced in ischemic maculopathy with occlusion of perifoveal capillaries so that the foveal avascular zone is enlarged. In these cases, retinal photocoagulation may reduce central vision further and is therefore not recommended.

Intravitreal angiostatic treatment

Recently, several new approaches for intravitreal medication have been introduced for the treatment of diabetic retinopathy and other retinal vascular diseases. Thus, intravitreal injection with triamcinolone has been shown to reduce diabetic macular edema, which supports the hypothesis that inflammation is involved in the disease process. The effect of the treatment is transient, but may provide a time window for the initiation of other therapies with a more permanent effect. However, the treatment is also accompanied by the risk of adverse effects such as glaucoma and cataract, which should be included in the considerations about which treatment strategy to follow [843].

The introduction of intravitreal treatment with anti-VEGF medication has significantly improved the visual prognosis of diabetic retinopathy [84]. Thus, the treatment has beneficial effects on diabetic macular edema [85–87] and can reduce neovascularization in proliferative diabetic retinopathy [88]. The advantage of the treatment is that it is not accompanied by destruction of retinal tissue, but the treatment should often be repeated with an interval of months with accumulation of the risk of adverse effects such as infection, glaucoma, cataract, and retinal detachment. Therefore, the prospects of life-long repeated intravitreal injections are less attractive in younger people. The treatment consists of a loading phase with three injections separated by 1 month, followed by regular controls where the treatment can be repeated depending on the clinical response. The treatment is the first choice in persons with diabetic maculopathy where the retinal edema is mainly located in the foveal area centrally from the zone that is accessible for retinal photocoagulation (Figure 38.13), and also in those in whom macular photocoagulation has not had a sufficient effect.

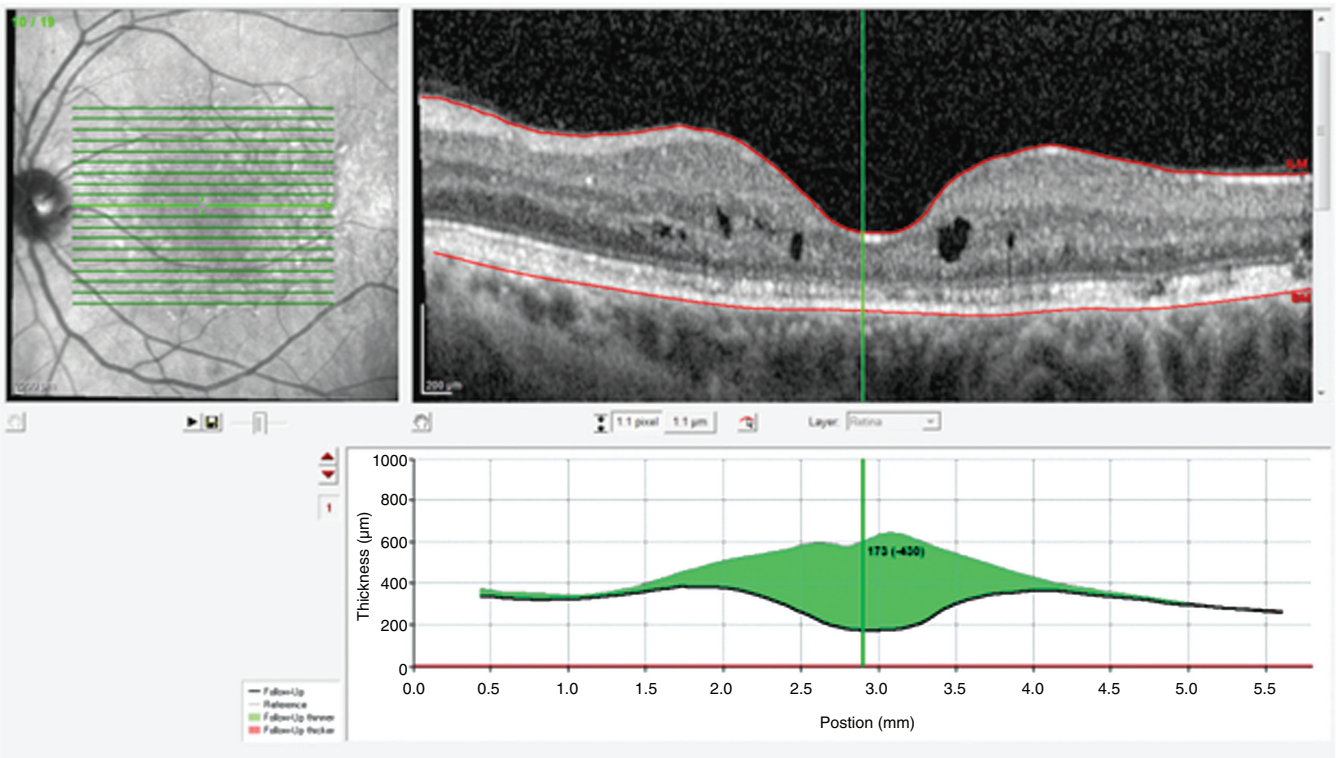

Figure 38.13 In the top left image, horizontal green lines represent the OCT scanning lines in the patient shown in Figure 38.11 and recorded 3 months after intravitreal injections of VEGF inhibitor. In the top right image, the OCT scan through the fovea shows that the retinal swelling has been reduced to a few cysts and the fovea has been restituted. The graph represents the retinal profile along the OCT scan before and after treatment. The green area represents the reduction in retinal thickness along the scan.

Additionally, the treatment may lead to regression of retinal neovascularizations and thereby reduce the risks to vision after photocoagulation or vitrectomy in proliferative diabetic retinopathy.

Exploration of diabetic retinopathy

During the past 50 years, immense research efforts have been invested in exploring diabetic retinopathy, and several developments have significantly shifted the understanding and management of the disease. In the 1960s, the beneficial effect of retinal photocoagulation was discovered by serendipity and once fluorescein angiography was accepted by the ophthalmological community, this diagnostic method added significantly to the diagnosis and understanding of the disease. In the 1980s, the introduction of vitrectomy was refined for the treatment of severe proliferative diabetic retinopathy, and systematic screening programs for diabetic retinopathy were initiated worldwide. In the 2000s, intravitreal angiostatic treatment was introduced, based on the discovery of VEGF as a key compound involved in increasing vascular permeability and stimulating neovascularization.

However, there is still a lack of understanding of how the diabetic metabolic dysregulation triggers the processes in the retina that initiate and accelerate diabetic retinopathy. Vascular changes resembling early diabetic retinopathy have been induced in small rodents, and more advanced diabetic retinopathy-like changes have been induced in diabetic dogs, pigs, and monkeys, but the full spectrum of lesions observed in human diabetic retinopathy has not been reproduced in these models, which is a major barrier for studying the pathophysiology of the disease. This lack of direction has opened up numerous working hypotheses and studies of diabetic retinopathy viewed from a number of different perspectives, depending considerably on the interests and opinions of individual researchers rather than firm knowledge. Being a systemic disease, diabetes affects all elements of the eye, and almost any working hypothesis suggesting a change in a measurement in the eyes of persons with diabetes can be confirmed. This implies that the research field of diabetic retinopathy is productive, but it is uncertain which research direction will contribute to the next breakthrough in the understanding and management of this condition. The art of research in diabetic retinopathy is to make the right choices for such experimental strategies.

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39 Diabetic Nephropathy

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Key points

- Classically, diabetic nephropathy is characterized by gradually increasing urine albumin excretion over many years, accompanied by slowing rising blood pressure and declining glomerular filtration rate (GFR).
- A small number of individuals with type 1 diabetes and about 30% of those with type 2 diabetes who develop chronic kidney disease have a progressive fall in GFR with no or minimal albuminuria. This may be a different form of kidney disease.
- Individuals with nephropathy are at greatly increased risk of other microvascular and macrovascular complications of diabetes.
- The risk of cardiovascular disease (CVD) increases as albuminuria increases and independently as GFR decreases.
- Approximately 30–50% of white European individuals with diabetes will develop albuminuria grade A2; the prevalence is higher in non-Caucasian people.
- One-third of people with diabetes will progress to albuminuria grade A3 and be at high risk of end-stage renal disease.
- Factors most closely associated with progression of nephropathy are poor glucose and blood pressure control and baseline albuminuria.
- Screening for diabetic kidney disease should be done annually, by measuring the urine albumin : creatinine ratio and estimated GFR (eGFR).
- Good blood glucose and blood pressure control are key to the prevention of nephropathy.
- If albuminuria grade A2 or greater is present, an inhibitor of the renin–angiotensin system (RAS) should be commenced and titrated up to the maximum tolerated dose.
- Maintaining blood pressure at 120–130/75 mmHg, with the addition of other antihypertensive agents as necessary, will reduce the rate of decline of GFR from 10–12 to 3–5 mL/min/1.73 m^2.
- Reducing dietary protein intake to 0.7–1.0 g/kg body weight per day may slow the deterioration in renal function.
- Aggressive management of other cardiovascular risk factors and prescription of aspirin reduce the incidence of cardiovascular events and of progression to nephropathy by ~60%.
- Renal failure due to diabetes is the commonest single cause of entry to renal replacement programs worldwide; the majority of patients have type 2 diabetes plus major comorbidities.
- People with end-stage renal disease and significant comorbidities should be offered dialysis. Fitter individuals benefit from kidney or kidney–pancreas transplantation, but need full cardiovascular assessment and if necessary treatment before transplantation.

Introduction

Worldwide, chronic kidney disease (CKD) remains an important, common complication of diabetes. End-stage renal disease (ESRD) is devastating to the individual and of enormous financial and social consequences to society. The proportion of individuals commencing renal replacement therapy in 2012 because of diabetes varied enormously, ranging from 12% in Ukraine to 66% in Singapore [1]. In the United States, incidence rates of ESRD in diabetes increased by 50% between 1996 and 2006, but have fallen slowly since then, and in 2012 it was ~150 per million per year [1]. The incidence of ESRD in type 1 diabetes mellitus (T1DM) remained stable or declined over the last decade, but increased in type 2 diabetes mellitus (T2DM) [2–4]. Most people with diabetes on renal replacement therapy have T2DM.

Definitions

Diabetic nephropathy refers to the chronic condition developing over many years, characterized by gradually increasing urinary albumin excretion (UAE), blood pressure and cardiovascular risk, falling glomerular filtration rate (GFR) and eventual ESRD. The clinical syndrome is associated with characteristic histopathological features [5]. A small proportion of individuals with T1DM [6, 7], and ~50% of those with T2DM [8] with progressively declining GFR have no or minimal albuminuria. We will refer

Textbook of Diabetes, Fifth Edition. Edited by R. Holt, C. Cockram, A. Flyvbjerg and B. Goldstein.

Table 39.1 Glomerular filtration rate (GFR) categories in chronic kidney disease.

GFR category	GFR (mL/min/1.73 m^2)	Description
G1	≥90	Normal or high
G2	60–89	Mildly decreased[a]
G3a	45–59	Mildly to moderately decreased
G3b	30–44	Moderately to severely decreased
G4	15–29	Severely decreased
G5	<15	Kidney failure

[a]Relative to young adult level.

to this clinical phenotype as non-classical diabetic nephropathy. "Diabetic kidney disease" refers to both classical and non-classical diabetic nephropathy. Chronic kidney disease (CKD) refers to kidney disease of any etiology, including non-diabetes-related causes.

Screening for and classification of chronic kidney disease

Guidelines suggest systematic screening, as part of the "annual review." Albuminuria and GFR should be measured, allowing identification of proteinuric and non-proteinuric disease. Screening should be undertaken when the person is free from acute illness and in stable glucose control, because many acute illnesses and acute hyperglycemia increase albuminuria temporarily.

As albuminuria may increase in the upright posture and with exercise, measurements are best made in an early-morning urine sample; however, a spot urine sample is acceptable if there is no alternative. Both urine albumin and creatinine are measured and the albumin : creatinine ratio (ACR) is calculated. Because of the high day-to-day variation in UAE, if the first sample is positive, further samples should be obtained, ideally within 1–3 months. At least two out of three measurements should be abnormal before a diagnosis of albuminuria is made.

Serum creatinine should be measured annually, using an accredited assay standardized to the recommended isotope dilution mass spectrometry reference method. Most laboratories calculate the estimated GFR (eGFR) using the four-variable Modification of Diet in Renal Disease (MDRD) equation, adjusting for age, sex, and ethnicity [9]. This equation provides more reliable information than serum creatinine and is sufficiently accurate for clinical use when eGFR is <60 mL/min/1.73 m^2 [10, 11]. However, the MDRD equation underestimates GFR at higher levels and is not a good indicator of hyperfiltration [12, 13]. The CKD-EPI equation uses the same variables as the MDRD equation, but estimates measured GFR more accurately, particularly at higher levels of GFR [14]. The CKD-EPI equation also categorizes risk of mortality and ESRD more accurately than the MDRD equation in a wide range of populations, including those with diabetes [15, 16]. Hence recent guidelines advocate using the CKD-EPI rather than MDRD equation to estimate eGFR [17].

The 2012 Kidney Disease: Improving Global Outcomes (KDIGO) Clinical Practice Guideline for the Evaluation and Management of CKD advocates that final screening status should indicate both the GFR and UAE status, as in Tables 39.1 and 39.2, along with the cause of the kidney disease [17, 18]. The information can then be used as a measure of renal prognosis (Figure 39.1).

There is no agreement that cystatin C-based estimates of GFR are superior to creatinine-based estimates [19, 20]. KDIGO guidelines recommend calculating cystatin-based eGFR in adults whose creatinine-based eGFR is 45–59 mL/min/1.73 m^2 without other markers of kidney disease [17]. However, we do not know that this approach improves the identification of individuals with progressive CKD compared with frequent measures of creatinine-based eGFR.

Natural history and histopathology

Classical diabetic nephropathy

Gradually increasing UAE over many years is the hallmark of classical diabetic nephropathy (Figure 39.2). At presentation of T1DM, albuminuria grade 2 or 3 may be present. As glycemia is controlled, albuminuria returns to normal. In those who will never develop nephropathy, UAE remains normal, except during periods of particularly poor glucose control, or during acute intercurrent illness, when a transient increase in UAE may occur.

Table 39.2 Albuminuria categories in chronic kidney disease.

		ACR (approximate equivalent)			
Category	AER (mg/24 h)	mg/mmol	mg/g	Description	Previous terminology
A1	<30	<3	<30	Normal to mildly increased	Normal
A2	30–300	3–30	30–300	Moderately increased[a]	Microalbuminuria
A3	>300	>30	>300	Severely increased[b]	Proteinuria

[a]Relative to young adult level.
[b]Including nephrotic syndrome.
ACR, urine albumin : creatinine ratio; AER, albumin excretion rate.

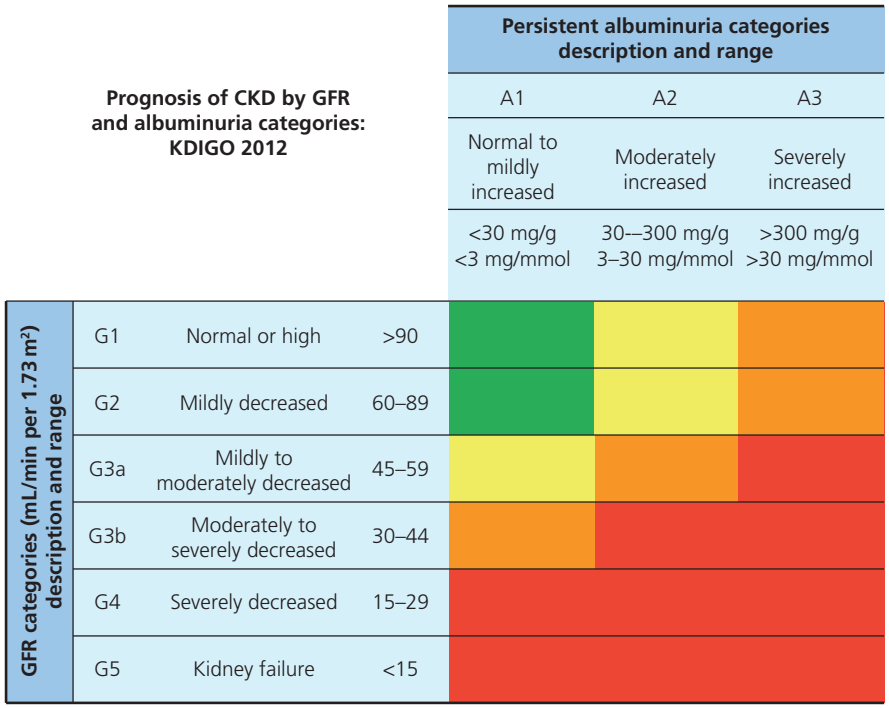

Figure 39.1 Prognosis of chronic kidney disease by estimated glomerular filtration rate and albuminuria. Source: Reprinted by permission from Macmillan Publishers Ltd: *Kidney International*, Levin A, Stevens PE [18], copyright 2014.

In those who will develop diabetic nephropathy, UAE increases gradually, with albuminuria grade A2 usually appearing within 5–15 years of diabetes. Untreated, the mean increase in UAE is 20% per year. In people with T1DM, ~1.5–2.5% per annum develop albuminuria grade A2 [21, 22], and 50% develop persistent grade A2 at some point [23, 24]. Approximately one-third with albuminuria grade A2 progress gradually over a further 5–15 years to albuminuria grade A3, one-third will remain at grade A2, and one-third will revert to grade A1 [25, 26]. In the short term, reversion from albuminuria grade A2 to grade 1 appears common, one study reporting regression in 58% of participants over 6 years [27]. Short-duration grade A2 albuminuria, and lower HbA_{1c}, systolic blood pressure, total cholesterol, and triglycerides were all independently associated with regression. The eventual outcome in those who regress, or who do not initially progress, remains unclear. However, they probably remain at increased risk of nephropathy compared with individuals who have never had albuminuria grade A2.

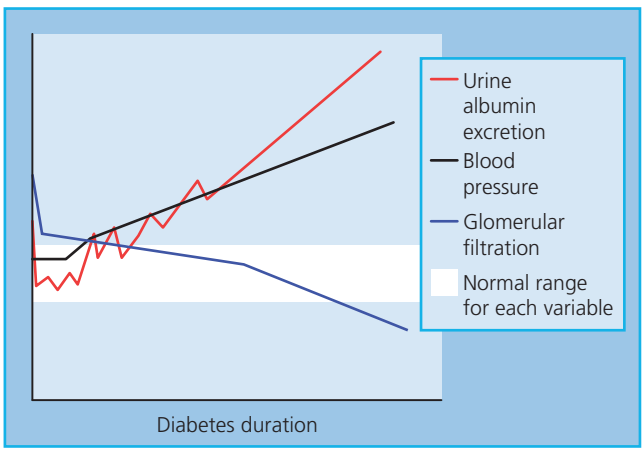

Figure 39.2 Natural history of classical diabetic nephropathy. The white bar represents the normal range for each variable.

Almost all people with T1DM and albuminuria grade A3 eventually progress to ESRD. The use of eGFR rather than serum creatinine has unmasked a decline in eGFR within the normal range in individuals with progressive albuminuria grade A2, but eGFR <60 mL/min/1.73 m^2 is rare at this stage. However, in albuminuria grade A3, the mean annual rate of decline of GFR is 10–12 mL/min/1.73 m^2 untreated.

One group has suggested that GFR falls before the onset of albuminuria in T1DM [7]. Using serial estimates of eGFR derived from serum creatinine and cystatin C, they reported a median annual decline in eGFR of 1.5% per year in individuals with albuminuria grade A1 and 2.2% in those with grade A2. They argued that albuminuria is therefore not a good guide to diabetic nephropathy [28]. Alternative explanations are suppression of albuminuria by renin–angiotensin system (RAS) inhibitors or that kidney disease with and without albuminuria are different pathological processes, as discussed below.

The natural history of diabetic nephropathy is generally similar in T2DM. Albuminuria grade A2 or A3 may be present at diagnosis, and may persist in individuals who have had undiagnosed diabetes for some years. GFR is usually >60 mL/min/1.73 m^2 at onset of albuminuria grade A2, only declining to CKD stage 3 or more when albuminuria grade A3 develops [29, 30].

The characteristic structural changes of classical diabetic nephropathy include basement membrane thickening,

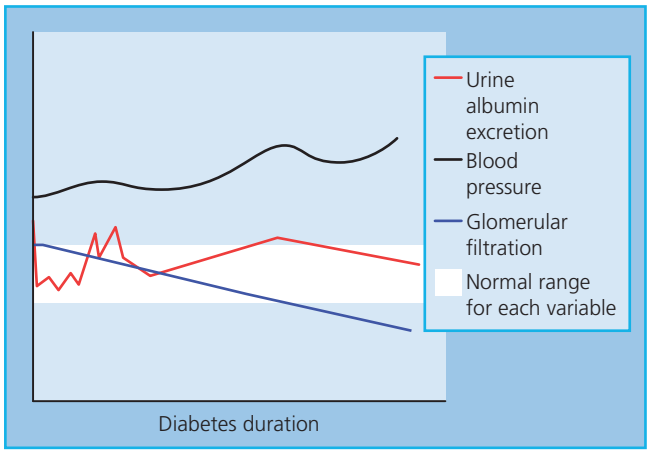

Figure 39.3 Natural history of non-classical diabetic nephropathy. The white bar represents the normal range for each variable.

progressive mesangial expansion, alteration and loss of podocytes, and tubulo-interstitial fibrosis, eventually leading to glomerulosclerosis [5].

Non-classical diabetic kidney disease

Some 7–22% of individuals with T1DM [6, 31] and 50% of those with T2DM [8, 32] who develop progressive CKD do not have preceding albuminuria (Figure 39.3). Identification of people with non-diabetic renal changes on the basis of clinical features, including the absence of diabetic retinopathy [33], is difficult. Individuals with T2DM and CKD stage 3 or more plus albuminuria grade A2 or 3 are very likely to have histological features of diabetic glomerulosclerosis, whereas those with albuminuria grade A1 are much more likely to have arteriosclerosis [34]. The underlying disease process in non-classical diabetic CKD probably reflects a combination of aging, hypertension, and atherosclerotic vascular disease in addition to diabetes. Obesity, with ectopic lipid accumulation in the kidney, may also be important [35].

The rate of progression of CKD in the absence of significant albuminuria is slower than in those with albuminuria in both T1DM [7] and T2DM [36, 37]. Low eGFR and albuminuria synergistically increase the risk of ESRD.

Changing epidemiology of kidney disease in diabetes

T1DM

Recent data suggest that in T1DM, albuminuria grade A2 and A3 and ESRD may be less common than previously, at least in some countries [38].

Older studies suggested a lifetime risk of developing albuminuria grade A2 of ~50%, appearing generally between 10 and 20 years' duration of T1DM. In the Diabetes Control and Complications Trial/Epidemiology of Diabetes Interventions and Complications (DCCT/EDIC) cohort, the cumulative incidence of persistent albuminuria grade A2 was 38% after 30 years in the conventional group and 25% in the intensive group [39]. The incidence appeared to plateau in both groups after 25–30 years. Grade A2 albuminuria developed most frequently in the second decade of diabetes in the conventional group, the incidence being blunted particularly during this time in the intensive group.

Older data suggest that the cumulative incidence of albuminuria grade A3 is ~40% after 40 years' duration of T1DM. In the DCCT, after 30 years' duration, 25% of the conventional group and 9% of the intensively managed group had albuminuria grade A3 [40]. Several Scandinavian studies also reported low rates of ~13% after 20–25 years' duration [41, 42]. However, in the Pittsburgh cohort, the incidence has remained relatively steady at 32% after 25 years [43].

Several European countries report a current incidence of ESRD in T1DM of 2.5–7.8% after 30 years of diabetes [44, 45]. The Pittsburgh Epidemiology of Diabetes Complications Study [46] and the WESDR cohort [47] suggested a declining incidence in those diagnosed after 1970. Survival with ESRD may also have improved.

Hence the incidence of all stages of diabetic nephropathy in T1DM may be declining, at least in some centers. However, in the United Kingdom, in the Golden Years cohort of individuals with duration of T1DM >50 years, 36% had albuminuria grade A2 or A3 [48]. In a similar cohort in the USA, the prevalence of albuminuria, defined using a higher cut-off than in the UK cohort, was 13.1% [49]. Thus the observed decline in incidence of nephropathy may be delay rather than true prevention.

T2DM

A widely varying prevalence of albuminuria grade A2, from 10 to 42%, has been reported. Longitudinal studies suggested that the rate of progression from albuminuria grade A1 to A2 is 3–4% per annum. One older study demonstrated equivalent cumulative incidence of albuminuria grade A3 in T1DM and T2DM after 25 years' duration of diabetes [50]. In the Pima Indians, the incidence of ESRD has declined since 1990 [51]. National US survey data reported a prevalence of chronic kidney disease (eGFR <60 mL/min/1.73 m^2 or UAE >30 mg/g) of 43.5% in the overall T2DM population and 61.0% in those aged ≥65 years [52]. In the UK, using a similar definition, the prevalence was 42.3% [53]. The increasing number of individuals with diabetes commencing renal replacement therapy in many countries is due mainly to persons with T2DM [1] and is accounted for in part by an increased acceptance of older, sicker individuals and improved cardiovascular survival.

Risk factors and markers for chronic kidney disease in diabetes

Many factors are associated with CKD in diabetes (Figure 39.4). Some are associated with both classical and non-classical kidney disease, and some with one but not the other phenotype [54]. Associations may be with both albuminuria and GFR or with one measurement only. Some factors influence initial development of

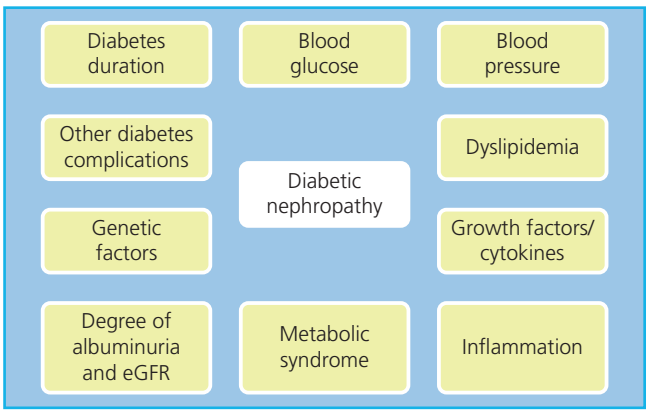

Figure 39.4 Clustering of risk factors and markers for classical diabetic nephropathy.

kidney disease and others progression of disease. Duration of diabetes is one of the strongest risks factors for diabetic nephropathy, particularly in T1DM.

Glucose control

Recent studies reinforce the importance of glucose control in the development and progression of diabetic nephropathy. An unselected Swedish cohort of individuals with T1DM was followed from diagnosis for 20–24 years [55]. No individuals with a long-term weighted mean HbA_{1c} < 60 mmol/mol (7.6%) developed albuminuria grade A2. In contrast, 23% of those with mean HbA_{1c} >80 mmol/mol (9.5%) did so. There is a strong, graded positive association between HbA_{1c} and incident eGFR <60 mL/min/1.73 m^2, independent of other risk factors and present even in the absence of albuminuria [56]. Greater variability in HbA_{1c} is associated independently with albuminuria and diabetic nephropathy [57, 58]. In the DCCT, stimulated C-peptide was associated inversely with albuminuria [59]. Whether the protection afforded by preservation of C-peptide secretion is through improved blood glucose control or by a direct effect is unclear.

Blood pressure

Blood pressure is critical in the development and progression of diabetic kidney disease. The excess prevalence of hypertension in T1DM is confined to those with nephropathy [60]. In young people with albuminuria grade A2, changes in blood pressure are subtle, perhaps manifesting only as reduced nocturnal diastolic blood pressure dipping [61]. Once albuminuria grade A3 is present, frank hypertension is present in 80% of patients, and is almost universal in ESRD. Variability in systolic and diastolic blood pressure independently predicts the development of albuminuria in T1DM [62].

In T2DM, the link between hypertension and renal disease is less striking, because hypertension is so common. Almost all with albuminuria grade A2 or worse have hypertension. In people with diabetic nephropathy, variability in systolic blood pressure is independently associated with the development of ESRD [63].

Other metabolic factors

Blood lipids, including triglycerides [48], contribute to the development and progression of nephropathy, although the lipid phenotype alters as nephropathy progresses [64, 65]. Current smoking predicts the development of albuminuria [66]. Insulin resistance increases the risk of albuminuria and a rapid decline in eGFR in T1DM [67] and of albuminuria in T2DM [68]. Uric acid predicts the development of albuminuria grade A3 [69, 70]. Individuals with T1DM or T2DM and nephropathy are more likely to have the metabolic syndrome [71–73].

Hyperfiltration

Hyperfiltration is common at onset of T1DM and is also present in some individuals at diagnosis of T2DM. In the majority, GFR returns to normal as glucose is controlled, but in some individuals, hyperfiltration persists. The hypothesis that individuals with persistent hyperfiltration are most at risk of subsequent diabetic nephropathy remains controversial [74–76].

Genetic factors

Genetic factors influence susceptibility to diabetic nephropathy [77]. If one sibling with T1DM has nephropathy, the risk to a second sibling is increased 4–8-fold compared with siblings where neither has nephropathy [78]. The clustering of conventional cardiovascular risk factors and CVD in people with diabetic nephropathy also occurs in their parents [79]. This suggests that the genetic susceptibility to nephropathy also influences the associated CVD. Multiple genes are involved, either protective or deleterious. Different loci may influence albuminuria and GFR separately [80]. Epigenetic modification may also be important [81].

Ethnicity

Albuminuria and CKD stages 4 and 5 are more common in UK Afro-Caribbean and South Asian individuals than white European people [82, 83]. The prevalence of early CKD (defined as albuminuria grade A2 or greater and eGFR<60 mL/min/1.73 m^2) is higher in Latino and African American individuals than white people [84]. Albuminuria and CKD are also more common in Pima Indians [85] and in Māoris and Pacific Islanders [86, 87] than white Europeans. Reasons for this varying prevalence may include differing genetic influences and altered response to, or poorer access to, treatments.

T2DM developing in young people

Individuals who develop T2DM in youth have a high prevalence of hypertension and albuminuria grade A2 [88]. ESRD and death are particularly common in young people from ethnic minorities [89–91]. However, in some of these populations, there is a high prevalence of non-diabetic kidney disease [92].

Albuminuria and GFR

Baseline albuminuria and eGFR independently influence the development and rate of progression of CKD [93]. Baseline albuminuria strongly predicts ESRD [94]. Higher levels of

albuminuria grade A1 [95] and lower eGFR [96] predict a faster decline in eGFR.

Other risk factors

Other risk factors for nephropathy include pre-eclampsia [97], inflammatory markers [98, 99], cytokines and growth factors [100], periodontitis [101], and serum bilirubin levels [102, 103]. Obstructive sleep apnea [104] and non-alcoholic fatty liver disease are both independently associated with diabetic nephropathy [105, 106]. Circulating levels of tumor necrosis factor-α receptor 1 are independently associated with the cumulative risk of ESRD in T1DM and T2DM [107–109].

Association of diabetic kidney disease with cardiovascular disease

The prognosis for people with diabetes and CKD is much poorer than for those without CKD. Both albuminuria (Figure 39.5) and eGFR <60 mL/min/1.73 m^2 (Figure 39.6) contribute independently and synergistically to the increased all-cause and cardiovascular risk [37, 110–112].

Type 1 diabetes

In T1DM, the relative risk of premature mortality is 2–3-fold higher in grade A2 albuminuria, 9-fold in grade A3, and 18-fold in ESRD compared with the non-diabetic population (Figure 39.7) [113]. Individuals with T1DM and grade A1 albuminuria do not have a higher risk of premature death [113, 114]. CVD is 1.2-fold more common in people with grade A2 albuminuria [115] and 10-fold higher in those with albuminuria grade A3 compared with those with grade A1 [116]. The cumulative incidence of CVD by the age of 40 years is 43% in people with T1DM and albuminuria grade A3, compared with 7% in individuals with albuminuria grade A1, with a 10-fold risk of coronary heart disease and stroke. In ESRD, the risk of CVD is even higher. Median survival on renal replacement therapy is 3.84 years [117].

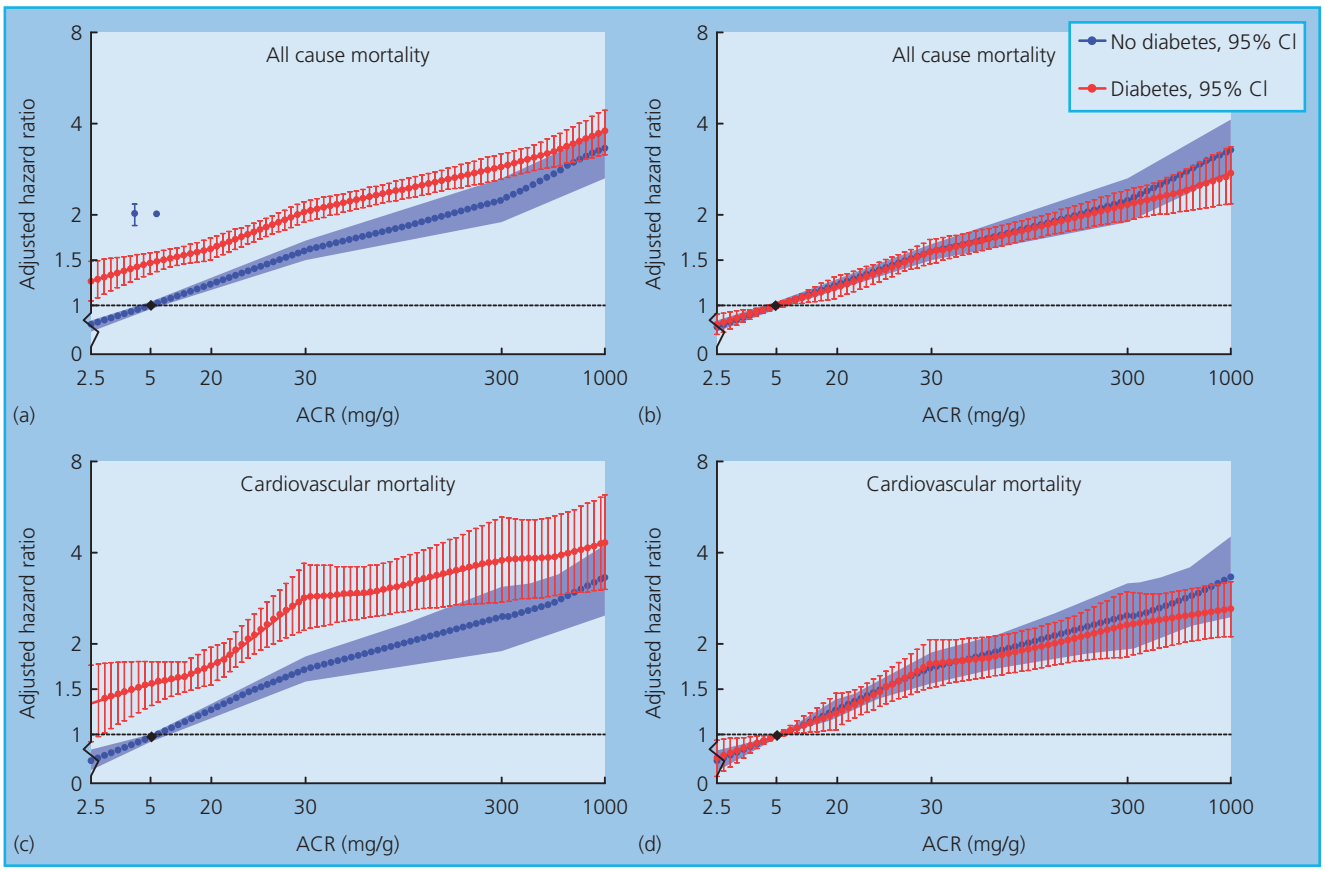

Figure 39.5 Hazard ratios for all-cause and cardiovascular mortality in the combined general and high-risk populations according to urine albumin : creatinine ratio (ACR) in participants with and without diabetes. (a, b) All-cause mortality; (c, d) cardiovascular mortality. Panels (a) and (c) use one reference point (diamond, ACR of 5 mg/g in the no diabetes group), for both individuals with and without hypertension to show the main effect of diabetes on risk. Panels (b) and (d) use separate references (diamonds) in the diabetes and no diabetes groups to assess interaction with diabetes specifically. Hazard ratios were adjusted for age, sex, race, smoking, history of cardiovascular disease, serum total cholesterol concentration, body mass index, and estimated glomerular filtration rate. Blue and red circles denote $p < 0.05$ compared with the reference (diamond). Significant interaction between diabetes and ACR is shown by × signs. Source: Reproduced from Fox et al. 2012 [201], Copyright 2012, with permission from Elsevier.

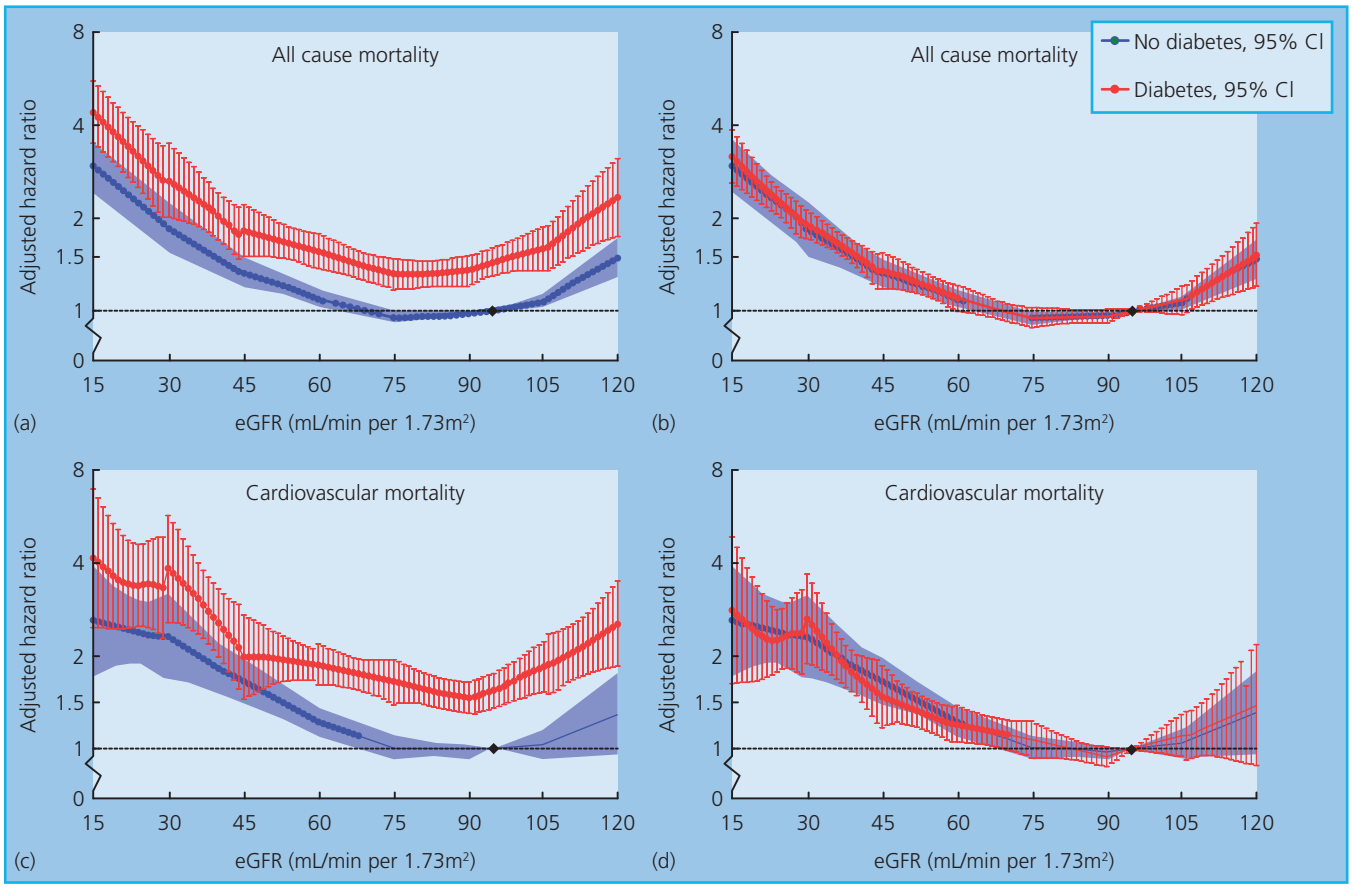

Figure 39.6 Hazard ratios for all-cause and cardiovascular mortality in the combined general and high-risk populations according to estimated glomerular filtration rate in individuals with and without diabetes. (a, b) All-cause mortality; (c, d) cardiovascular mortality. Panels (a) and (c) use one reference point (diamond, eGFR of 95 mL/min/1.73 m^2 in the no diabetes group) for both individuals with and without diabetes to show the main effect of diabetes on risk. Panels (b) and (d) use separate references (diamonds) in the diabetes and no diabetes groups to assess interaction with diabetes specifically. Hazard ratios were adjusted for age, sex, race, smoking, history of cardiovascular disease, serum total cholesterol concentration, body mass index, and albuminuria (log albumin-to-creatinine ratio, log protein-to-creatinine, or categorical dipstick proteinuria [negative, trace, 1+, ≥2+]). Blue and red circles denote $p < 0.05$ compared with the reference (diamond). Significant interaction between diabetes and eGFR is shown by × signs. eGFR, estimated glomerular filtration rate. Source: Reproduced from Fox et al. 2012 [201], Copyright 2012, with permission from Elsevier.

Type 2 diabetes

In T2DM, CVD risk is increased 2–4-fold with grade A2 albuminuria [118] and 9-fold in grade A3 [119]. Once serum creatinine is outwith the normal range, cardiovascular risk increases exponentially [120]. Median survival from initiation of renal replacement therapy is 2.16 years [117].

Microvascular complications

People with diabetic nephropathy invariably also have other microvascular complications. Significant retinopathy is almost always present in people with T1DM and albuminuria grade A2 or more. Progression of retinopathy and development of nephropathy each increases the risk for the other, supporting the notion of a common etiology [121]. In people with T2DM, the relationship is less clear-cut [122]. Those with classical nephropathy and progressively increasing albuminuria usually have significant retinopathy, and indeed albuminuria grade A2 predicts the development and progression of retinopathy in T2DM [123, 124]. In those with non-classical disease, retinopathy may be absent.

Peripheral neuropathy is also more common in diabetic nephropathy, associating with both albuminuria and declining GFR [125]. Autonomic neuropathy, reflected in loss of nocturnal blood pressure dipping, occurs frequently [126] and predicts renal function decline [127].

Investigation of kidney disease in diabetes

Excluding other treatable causes of kidney disease

It is uncommon to find a specific treatable cause of chronic kidney disease if the natural history is classical. However, if there is doubt, ultrasound of the renal tract, measurement of autoantibodies and immunoglobulins, and renal biopsy may help.

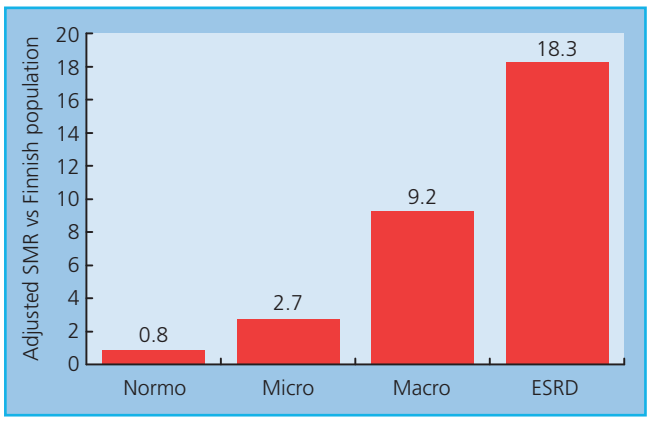

Figure 39.7 Risk of mortality in individuals with T1DM from the FinnDiane study associated with each level of albuminuria and end-stage renal disease (ESRD). Adjusted SMRs are provided standardized against the age- and sex-matched Finnish general population (arbitrary value of 1.0). Source: Based on Groop et al. 2009 [113].

Monitoring kidney disease

Once UAE is abnormal, the ACR should be measured every 3 months and eGFR 3–6 monthly, depending on the stage of CKD. There is a linear relationship with time and eGFR, which is useful in assessing changes in response to therapy and in predicting when an individual will reach ESRD.

Prevention and management of diabetic kidney disease

Prevention of kidney disease is crucial. Although much can be done to slow progression, it may not be possible to avoid ESRD. The risk of developing diabetic nephropathy is particularly reduced by good blood glucose and blood pressure control.

Glucose control

Glucose control in T1DM

Among the participants in the DCCT who initially had albuminuria grade A1, the relative risk reduction for development of albuminuria grade A2 was 39% and for grade A3 54% in those allocated to the intensively treated group compared with those in the conventionally managed group over the 6.5-year study [128]. Mean achieved HbA_{1c} was 52 mmol/mol (7.0%) and 76 mmol/mol (9.1%), respectively. There is no HbA_{1c} threshold below which risk is not reduced [129].

In the open follow-up of the DCCT cohort, HbA_{1c} in the previously intensively and conventionally managed groups became similar, ~64 mmol/mol (8.0%). Despite this, the incidence of albuminuria grades A2 and A3 [130], eGFR <60 mL/min/1.73 m^2, and ESRD [131] were significantly reduced in those who had previously received intensive management, as summarized in Table 39.3. These results are supported by an observational study of individuals with T1DM and CKD stages 1–3 with albuminuria grade A3 at baseline [132]. The cumulative risk of ESRD after 15 years was significantly lower in those whose HbA_{1c} improved compared with those whose HbA_{1c} remained stable or deteriorated. Hence improving glucose control significantly reduces the risk of development and progression of all stages of diabetic nephropathy in T1DM. The beneficial effects extend far beyond the actual period of good glucose control, a phenomenon termed "metabolic memory." In highly selected patients undergoing serial renal biopsies after successful pancreas transplantation, renal structural changes regressed after 10 but not 5 years [133]. Thus, prolonged periods of "normoglycemia" are necessary to reverse renal structural changes.

Table 39.3 Renal benefits of intensive insulin therapy demonstrated by the Diabetes Control and Complications Trial/Epidemiology of Diabetes Interventions and Complications Cohort.

Parameter	Duration of observation (years)	Conventional insulin therapy	Intensive insulin therapy
Albuminuria grade A2	8	15.8%	6.8%
Albuminuria grade A3	8	9.4%	1.4%
eGFR <60 mL/min/1.73 m^2	22	46 (*n*)	24 (*n*)
ESRD	22	16 (*n*)	8 (*n*)

n, Number.
eGFR estimated glomerular filtration rate; ESRD, end-stage renal disease.
Source: Data from [130] and [131].

Glucose control in T2DM

In the UKPDS, although the mean achieved HbA_{1c} in the intensively managed group was 53 mmol/mol (7.0%) compared with 63 mmol/mol (7.9%) in the less strictly managed group, there was a reduction in the relative risk of developing albuminuria grades A2 and A3 of 30% after 9–12 years [134]. No threshold of HbA_{1c} and risk was observed, suggesting that the lower the HbA_{1c}, the lower is the risk of nephropathy [135]. In the open follow-up of the UKPDS cohort, HbA_{1c} was similar in the previously intensively and conventionally managed groups after 1 year [136]. Despite this, microvascular risk remained lower, confirming the "metabolic memory" seen in the DCCT/EDIC study. In the ADVANCE study, the HbA_{1c} achieved in the intensively managed group was 48 mmol/mol (6.5%), compared with 56 mmol/mol (7.3%) in the standard care group [137]. In the intensive group there was a 9% relative risk reduction in new-onset albuminuria grade A2, a 30% reduction in the development of albuminuria grade A3, and a 65% reduction in ESRD over 5 years [138]. The ACCORD study also demonstrated significant reductions in new-onset albuminuria grades A2 and A3 and of ESRD with intensive glucose management [139]. Progression of albuminuria was reduced and regression increased. However, in those with CKD at baseline, the risk of all-cause and cardiovascular mortality was

significantly increased in the intensive glucose management group [140]. Hence the renal benefits of extremely tight glucose control are outweighed by the excess mortality. A less tight HbA_{1c} target in individuals with T2DM and duration >10 years seems sensible.

Dipeptidyl peptidase 4 inhibitors and sodium–glucose cotransporter 2 inhibitors may have added renal benefits beyond glucose lowering [141, 142].

Glucose control in ESRD

Most [143–145] but not all [146] observational studies have demonstrated increasing all-cause and cardiovascular mortality with increasing HbA_{1c} in people with diabetes on renal replacement therapy. Some also showed a U-shaped relationship, with mortality increasing at low HbA_{1c} levels [144, 145]. However, there have been no studies that demonstrated improved survival with improving glucose control.

Blood pressure control

Rigorous blood pressure control improves the prognosis in diabetic nephropathy dramatically. Conservative estimates suggest that good blood pressure management doubles the time taken from first appearance of albuminuria grade A3 to need for renal replacement therapy, from a mean of 9 to 18 years. Improved management in albuminuria grade A2 may prevent progression and promote regression to grade A1. Blood pressure and blood glucose lowering effects are independent of one another, but have synergistic effects [147, 148]. In contrast to glucose "metabolic memory," the benefits of blood pressure reduction are lost rapidly when control deteriorates [149]. The effects of angiotensin-converting enzyme (ACE) inhibitors and angiotensin II receptor blockers (ARBs) are broadly similar [150].

T1DM

RAS inhibitors do not prevent albuminuria grade A2 in normotensive people with T1DM [151–153]. There is also no evidence that control of hypertension in T1DM and grade 1 albuminuria prevents progression of albuminuria and renal decline. However, it seems highly likely.

Once albuminuria grade A2 or A3 is present, inhibition of the RAS is the backbone of therapy, because it reduces intraglomerular pressure. A meta-analysis summarized the effects of ACE inhibitors in people with T1DM and grade A2 albuminuria [154]. The odds ratio for progression to albuminuria A3 was reduced by ACE inhibition to 0.35, and for regression to albuminuria grade A1 it increased to 3.07, compared with placebo treatment. After 2 years of treatment, the mean reduction in albumin excretion was 50.5% with ACE inhibition, and was greatest in those with highest baseline levels. However, the response to treatment plateaued with time, suggesting that treatment delays, rather than prevents, progression.

Addition of an ACE inhibitor to non-ACE inhibitor antihypertensive therapy reduced the risk of a doubling of the serum creatinine by 48% and the composite end-point of death, need for dialysis or renal transplantation, by 50%, in people with T1DM and with albuminuria grade A3 and hypertension [155]. Both benefits were independent of blood pressure. In short-term studies, the effects of ARBs on blood pressure and UAE were similar to those of ACE inhibitors in T1DM and grade A3 albuminuria [156].

For a similar reduction in blood pressure, there is a greater reduction in protein excretion using ACE inhibitors compared with other classes of antihypertensive agents [157]. This may be beneficial, as the passage of protein across the glomerular filtration barrier may accelerate the progression of nephropathy [158]. Animal data show that this is due to preferential reduction in intraglomerular pressure with ACE inhibitors [159].

RAS inhibitors should be offered to all individuals with T1DM and albuminuria, regardless of blood pressure. The dose should be titrated up to the maximum recommended or tolerated, to obtain maximal antiproteinuric effect. If blood pressure remains >125/75 mmHg on maximum dose of RAS inhibitor, antihypertensive therapy should be intensified. Lower blood pressure reduces the rate of decline of GFR from 10–12 mL/min/year untreated to <5 mL/min/year [160]. Regression from albuminuria grade A3 to A2 can be achieved, with the fall in GFR reduced to <1 mL/min/year [161]. The choice of agent should be made on an individual basis, as there is no evidence in T1DM that any one add-on agent is better than any other. Often multiple agents are needed in CKD stage 3 and beyond.

T2DM

Control of hypertension reduces the risk of developing albuminuria grade A2 or A3 [162–165]. There may be a particular benefit of RAS inhibition in prevention of nephropathy [166, 167], but lowering blood pressure sufficiently is the key. Achieved blood pressure in these studies was generally ~140/80 mmHg, but most guidelines now suggest a blood pressure target of 130/80 mmHg in T2DM.

As with T1DM, there is good evidence in T2DM that inhibition of the RAS should be the backbone of therapy if albuminuria grade A2 or A3 is present. RAS blockade reduces progression of albuminuria grade A2 to A3 [163, 168] and increases regression to grade A1 [168]. The benefits are at least partly independent of blood pressure lowering. In more advanced diabetic nephropathy, RAS inhibition with ARB reduces progression, defined as doubling of serum creatinine, ESRD, or death [169, 170]. Hence people with T2DM and albuminuria grade A2 or A3 should be prescribed a RAS inhibitor, titrated to the maximum tolerated dose [171]. Hyperkalemia is common in individuals with T2DM and nephropathy taking an ARB and is associated with increased risk of renal failure [172]. Introduction of a RAS inhibitor often leads to an acute decline in GFR, which then stabilizes. Individuals with the greatest initial fall in GFR have the slowest subsequent decline in renal function [173].

Most people with T2DM and albuminuria will require additional antihypertensive therapy. The choice of additional agents

should be made on an individual basis, with diuretics and calcium channel blockers often being appropriate.

In the UKPDS, there was no blood pressure level below which risk of developing albuminuria grade A2 or beyond increased, i.e. no "J" shape [174]. The ADVANCE study explored the effects of reduction of blood pressure below the currently recommended targets of 130/80 mmHg in individuals with albuminuria grade A1 or A2 and 125/75 mmHg in those with grade A3 [175]. Over 4 years, the risk of renal events was reduced by 21%, mainly because of reduced risk of developing albuminuria grade A2 or A3. However, an achieved systolic blood pressure below 120–130 mmHg was associated with increased mortality and ESRD [176]. Therefore, extremely tight blood pressure control should be avoided.

Dual blockade of the RAS

Addition of an ARB to an ACE inhibitor [177, 178] or of the direct renin inhibitor aliskiren to an ARB [179] reduces blood pressure and albuminuria more than each agent individually. However, in the longer term, dual blockade increases the risk of hyperkalemia, hypotension, and acute, irreversible renal failure [180–183]. Hence dual blockade is not recommended.

Sodium intake

Short-term dietary sodium restriction (target sodium intake 50 mmol Na^+ per day), added to RAS blockade, reduces albuminuria [184]. The treatment effects of ARB are greater in patients with lower rather than higher dietary sodium intake [185]. Hence dietary counseling to reduce sodium intake is essential.

Non-classical diabetic kidney disease

There is no specific evidence for the use of RAS inhibition in individuals without albuminuria. However, control of blood pressure remains crucial to slow progression.

Low-protein diet

A meta-analysis concluded that such a diet significantly improves GFR but not albuminuria, across all subtypes of diabetes and stages of nephropathy [186]. Protein intake should not be restricted to less than 0.7 g protein/kg body weight/day because of concerns about malnutrition in ESRD.

Lipids

There is some evidence that lipid-lowering agents are beneficial to the kidney. In a post hoc analysis of the Collaborative Atorvastatin Diabetes Study, the rate of decline of eGFR was significantly less in those individuals taking atorvastatin 10 mg daily compared with placebo [187]. Fibrates also reduce albuminuria, although they reversibly increase serum creatinine [188].

Cardiovascular risk—other factors

There have been no good trials of smoking cessation and use of aspirin in diabetic kidney disease. However, smoking cessation should clearly be encouraged, and the use of aspirin considered.

Weight loss

In a trial comparing intensive lifestyle intervention with diabetes support and education in T2DM, individuals randomized to intensive lifestyle modification were less likely to develop CKD over 8 years [189]. The effect was partly attributable to reductions in body weight, HbA_{1c}, and systolic blood pressure. Low-carbohydrate, Mediterranean, and low-fat diets have similar beneficial effects on change in eGFR and albuminuria over 2 years [190]. In individuals with T2DM who have undergone bariatric surgery, albuminuria grades A2 and A3 regresses to grade A1 [191].

Further management of chronic kidney disease stage 3 or poorer

Monitoring anemia and bone chemistry

In progressive CKD from stage 3 onwards, bone chemistry, full blood count, and iron stores should be assessed 3–6 monthly.

Monitoring glucose control

Red blood cell and protein turnover are abnormal in CKD, making the interpretation of HbA_{1c}, glycated albumin, and fructosamine results difficult. Thus, more reliance should be placed on self-monitoring of blood glucose and continuous glucose monitoring.

Glucose-lowering agents (Table 39.4)

Metformin and its metabolites are excreted mainly by the kidney. In renal failure, they accumulate and inhibit lactate oxidation. Metformin should therefore be used cautiously in those with eGFR <40 mL/min/1.73 m^2, and stopped completely when eGFR <30 mL/min/1.73 m^2.

The sulfonylureas glibenclamide, gliclazide, and tolbutamide are excreted predominantly renally and accumulate in CKD. Their dose, and indeed the dose of any sulfonylurea, may need to be reduced as CKD progresses. Only ~10% of the meglitinides repaglinide and nateglinide is renally excreted, making them suitable alternative agents. The thiazolidinediones rosiglitazone and pioglitazone are predominantly metabolized in the liver. However, their use in ESRD may be limited by fluid retention.

Insulin is also excreted by the kidney so that reduced dosage, and perhaps a switch to shorter acting preparations, may be required.

The dose of some but not all DPP-4 inhibitors and GLP-1 receptor agonists may need to be reduced as renal function deteriorates. The SGLT-2 inhibitors become less effective as GFR falls.

Table 39.4 Glucose-lowering agents in chronic kidney disease.

Drug	Comment
Metformin	Risk of accumulation and possibly lactic acidosis Caution when eGFR <40 mL/min/1.73 m^2 Stop when eGFR <30 mL/min/1.73 m^2
Sulfonylureas	Glibenclamide, gliclazide, and tolbutamide predominantly renally excreted; may need to reduce dose
Meglitinides	~10% excreted via kidney; usually safe
Thiazolidinediones	Predominantly hepatic metabolism; use may be limited by fluid retention
Dipeptidyl peptidase IV inhibitors	Probably safe. Dose may need to be reduced in some agents
Glucagon-like peptide-1 receptor agonists	Few data when eGFR <45 mL/min/1.73 m^2
Sodium–glucose co-transporter 2 inhibitors	Ineffective at eGFR <45 mL/min/1.73 m^2
Insulin	Excreted by kidney; may need to reduce dose and/or switch to shorter-acting preparations

eGFR, estimated glomerular filtration rate.

Anemia

Anemia is common in people with diabetes and CKD stage 3 or poorer [192]. Full investigation of iron deficiency anemia may be needed to exclude a non-renal cause. Those with anemia have a higher mortality, higher rates of hospital admission with heart failure, and poorer quality of life. Iron stores should be repleted, with oral or parenteral iron as necessary, and erythropoietin replacement commenced if indicated.

When to refer to nephrology

Patients who begin dialysis as an emergency do less well than those in whom treatment is planned [193]. Referral to nephrology should be made when serum creatinine is 150–200 μmol/L or eGFR <45 mL/min/1.73 m^2. This allows structured physical and psychological preparation for renal replacement therapy. Earlier referral may be necessary in particular circumstances (Box 39.1). The need for renal replacement therapy should be discussed with all patients and those who wish it should have access. People without significant comorbidities will usually be offered transplantation. Full cardiovascular assessment and treatment are essential before transplantation.

Organization of care

Structured care, delivered by trained specialists working to clear protocols with specific, multiple treatment goals for all the variables described above, reduces the incidence of albuminuria grade A2 [194] and provides greater renal and cardiovascular benefits than routine care for individuals with T2DM and CKD [195, 196]. Progression to ESRD or death, need for laser therapy, and cardiovascular endpoints are all reduced by such multifactorial intervention.

Box 39.1 Indications for referral to nephrology.

Diagnosis uncertain
Hypertension difficult to control
Fluid overload
Anemia unresponsive to oral iron
Abnormal bone chemistry
eGFR 30–45 mL/min/1.73 m^2
Nephrotic syndrome
eGFR fall >5 mL/min/1.73 m^2 per year

Pregnancy in women with diabetes and chronic kidney disease

Women with diabetic nephropathy have poor pregnancy outcomes [197]. They remain at increased risk of hypertension, pre-eclampsia, abnormal fetal growth, and preterm delivery [198]. In a recent series, the prevalence of diabetic nephropathy and albuminuria grade A2 in early pregnancy was similar in women with T1DM or T2DM, and pregnancy outcomes were comparable regardless of the type of diabetes [199]. Women with any evidence of CKD therefore should be counseled pre-pregnancy. RAS inhibitors should be stopped and therapies safe in pregnancy, such as methyldopa, labetolol, and nifedipine, substituted. In women with T1DM, maintenance of BP <135/85 mmHg and proteinuria <300 mg/24 h with methyldopa improves outcomes [200].

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40 Diabetic Peripheral and Autonomic Neuropathy

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Key points

- Approximately one in three individuals with diabetes is affected by diabetic sensorimotor polyneuropathy (DSPN) which represents a major health problem, as it may present with excruciating neuropathic pain and is responsible for substantial morbidity, increased mortality, and impaired quality of life.
- Neuropathic pain exerts a substantial impact on the quality of life, particularly by causing considerable interference with sleep, daily activities, and enjoyment of life.
- Treatment is based on four cornerstones: (1) intensive diabetes therapy and multifactorial risk intervention, (2) treatment based on pathogenetic mechanisms, (3) symptomatic treatment, and (4) avoidance of risk factors and complications.
- Recent experimental studies suggest a multifactorial pathogenesis of diabetic neuropathy. From the clinical point of view, it is important to note that, based on these pathogenetic mechanisms, therapeutic approaches could be derived, some of which are currently being evaluated in clinical trials.
- Management of chronic painful DSPN remains a challenge for the physician who should consider the following practical rules: the appropriate and effective drug has to be tried and identified in each patient by carefully titrating the dose based on efficacy and side effects. Lack of efficacy should be judged only after 2–4 weeks of treatment using an adequate dose. Analgesic combination therapy may be useful, and potential drug interactions have to be considered given the frequent polypharmacy in people with diabetes.
- Epidemiological data indicate that not only increased alcohol consumption but also the traditional cardiovascular risk factors such as prediabetes, visceral obesity, hypertension, hyperlipidemia, and smoking play a role in the development and progression of diabetic neuropathy and hence need to be prevented or treated.
- The manifestations of diabetic autonomic neuropathy cause multiple symptoms and involve:
  - Cardiovascular system: resting tachycardia, reduced heart rate variability and circadian rhythm of heart rate and blood pressure, painless myocardial ischemia/infarction, orthostatic hypotension, exercise intolerance, perioperative instability, sudden death.
  - Respiratory system: reduced ventilatory drive to hypercapnia/hypoxemia, sleep apnea.
  - Gastrointestinal tract: esophageal motor dysfunction, diabetic gastroparesis, gallbladder atony, diabetic enteropathy, colonic hypomotility, anorectal dysfunction.
  - Urogenital system: diabetic cystopathy, erectile dysfunction, female sexual dysfunction.

Diabetic peripheral neuropathy

Classification, epidemiology, and clinical impact

Diabetic neuropathy has been defined as a demonstrable disorder, either clinically evident or subclinical, that occurs in the setting of diabetes mellitus without other causes for peripheral neuropathy. It includes manifestations in the somatic and/or autonomic parts of the peripheral nervous system [1], which are classified along clinical criteria. However, owing to the variety of the clinical syndromes with possible overlaps, there is no universally accepted classification. The most widely used classification of diabetic neuropathy, proposed by Thomas [2], has subsequently been modified [3]. This proposal differentiates between rapidly reversible, persistent symmetric polyneuropathies, and focal or multifocal neuropathies (Table 40.1). Diabetic distal symmetrical sensory or sensorimotor polyneuropathy (DSPN) represents the most relevant clinical manifestation, affecting ~30% of hospital-based populations with diabetes and 20% of community-based individuals with diabetes [4]. There is emerging evidence to suggest that prediabetes is associated with an increased risk of DSPN. In the general population (Augsburg region, southern Germany), the prevalence of polyneuropathy was 28.0% in people with diabetes, 13.0% in those with impaired glucose tolerance

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Table 40.1 Classification of diabetic neuropathies.

Type	Neuropathy
Rapidly reversible	Hyperglycemic neuropathy
Persistent symmetric polyneuropathies	Distal somatic sensory/motor polyneuropathies involving predominantly large fibers
	Autonomic neuropathies
	Small-fiber neuropathies
Focal/multifocal neuropathies	Cranial neuropathies
	Thoracoabdominal radiculopathies
	Focal limb neuropathies
	Proximal neuropathies
	Compression and entrapment neuropathies

Source: Adapted from Sima et al. 1997 [3].

(IGT), 11.3% in those with impaired fasting glucose (IFG), and 7.4% in those with normal glucose tolerance (NGT) [5]. The incidence of DSPN is ~2% per year [4].

The most important etiological factors that have been associated with DSPN are poor glycemic control, visceral obesity, diabetes duration, height, hypertension, age, smoking, hypoinsulinemia, and dyslipidemia [4]. DSPN is related to both lower extremity impairments such as diminished position sense and functional limitations such as walking ability [6]. Measures of polyneuropathy such as nerve conduction velocity and vibration perception threshold predict mortality in people with diabetes [7, 8]. Elevated vibration perception threshold also predicts the development of neuropathic foot ulceration, one of the most common causes for hospital admission and lower limb amputations among people with diabetes [9]. Three more recent studies underline the major impact of DSPN on cardiovascular morbidity and mortality. In the DIAD study [10], both sensory deficits and neuropathic pain were independent predictors of cardiac death or non-fatal myocardial infarction. In a community-based study in the United Kingdom, reduced touch or pressure sensation predicted cardiovascular morbidity [11]. History of neuropathy was the most important predictor for increased mortality in people with type 2 diabetes (T2DM) allocated to very intensive diabetes therapy aimed at HbA_{1c} <6.0% in the ACCORD trial [12].

However, the impact of DSPN is still being underestimated by both physicians and people with diabetes. In a German population-based survey, 77% of the cases with DSPN were unaware of having the disorder, defined as answering "no" to the question, "Has a physician ever told you that you are suffering from nerve damage, neuropathy, polyneuropathy, or diabetic foot?" Approximately one-quarter of the participants with known diabetes had never undergone a foot examination. Even among individuals with known diabetes who reported having had their feet examined by a physician, 72% of those with DSPN were unaware of having DSPN. Hence there is still a high prevalence of unawareness of having clinical DSPN among persons with diabetes and an insufficient frequency of professional foot examinations, suggesting inadequate attention to diabetic foot prevention practice [13].

Pain is a subjective symptom of major clinical importance as it is often this complaint that motivates people to seek healthcare. Pain associated with diabetic neuropathy exerts a substantial impact on the quality of life, particularly by causing considerable interference in sleep and enjoyment of life [14]. However, in one UK survey, only 65% of people with diabetes received treatment for their neuropathic pain, although 96% had reported the pain to their physician [15]. Pain treatment consisted of antidepressants in 43.5% of the cases, anticonvulsants in 17.4%, opiates in 39%, and alternative treatments in 30%. Although 77% of the patients reported persistent pain over 5 years, 23% were pain free over at least 1 year [15]. Hence neuropathic pain persists in the majority of individuals with diabetes over periods of several years.

Chronic painful neuropathy is present in up to 26% of people with diabetes [4, 16, 17]. In the general population (Augsburg region, southern Germany), the prevalence of painful neuropathy was 13.3% in the people with diabetes, 8.7% in those with IGT, 4.2% in those with IFG, and 1.2% in those with NGT [16]. Among survivors of myocardial infarction from the Augsburg Myocardial Infarction Registry, the prevalence of neuropathic pain was 21.0% in the individuals with diabetes, 14.8% in those with IGT, 5.7% in those with IFG, and 3.7% in those with NGT [17]. Thus, people with macrovascular disease appear to be prone to neuropathic pain. The most important risk factors of polyneuropathy and neuropathic pain in these surveys were age, obesity, and low physical activity, and the predominant comorbidity was peripheral arterial disease, highlighting the paramount role of cardiovascular risk factors and diseases in prevalent DSPN.

Clinical manifestations

Diabetic sensorimotor polyneuropathy

DSPN is a symmetrical, length-dependent sensorimotor polyneuropathy attributable to metabolic and microvessel alterations as a result of chronic hyperglycemia exposure (diabetes) and cardiovascular risk covariates [18]. It is commonly associated with autonomic involvement. Its onset is insidious and, in the absence of intervention, the course is chronic and progressive. It seems that the longer axons to the lower limbs are more vulnerable towards the nerve lesions induced by diabetes (length-related distribution). This notion is supported by the correlation found between the presence of DSPN and height. DSPN typically develops as a dying-back neuropathy, affecting the most distal extremities (toes) first. The neuropathic process then extends proximally up the limbs and later it may also affect the anterior abdominal wall and then spread laterally around the trunk. Occasionally the upper limbs are involved, with the fingertips being affected first (glove-and-stocking distribution) (Figure 40.1). Variants including painful small-fiber or pseudosyringomyelic syndromes and an atactic syndrome (diabetic pseudotabes) have been described. Small-fiber unmyelinated (C) and thinly myelinated (Aδ) fibers and also large-fiber myelinated (Aα, Aβ) neurons are

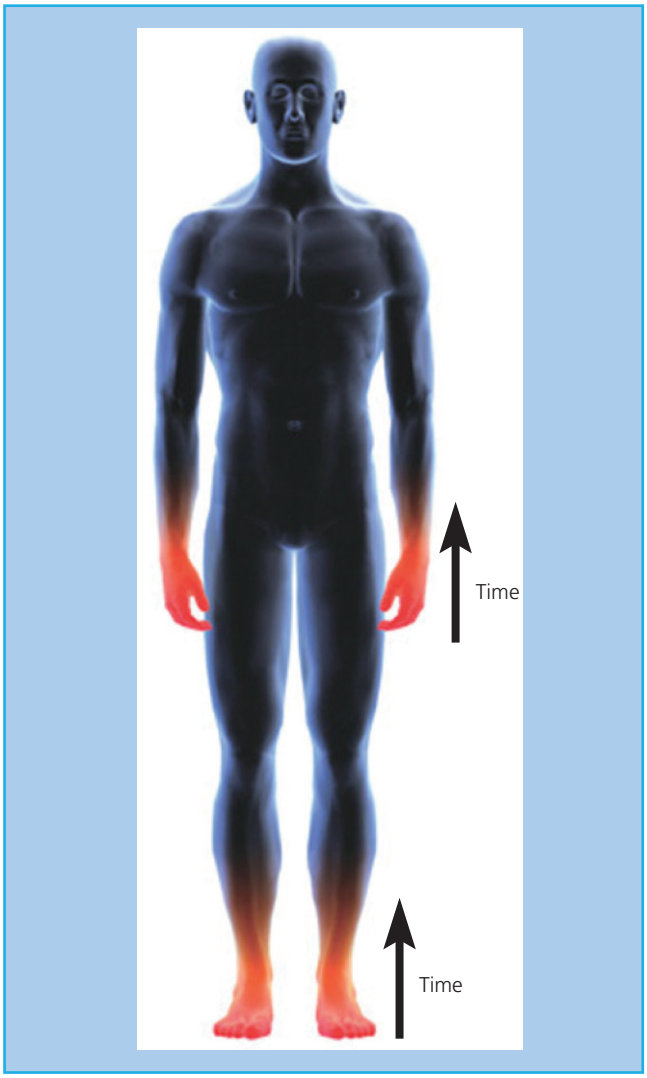

Figure 40.1 The typical glove-and-stocking distribution of diabetic distal symmetric sensory or sensorimotor polyneuropathy (DSPN).

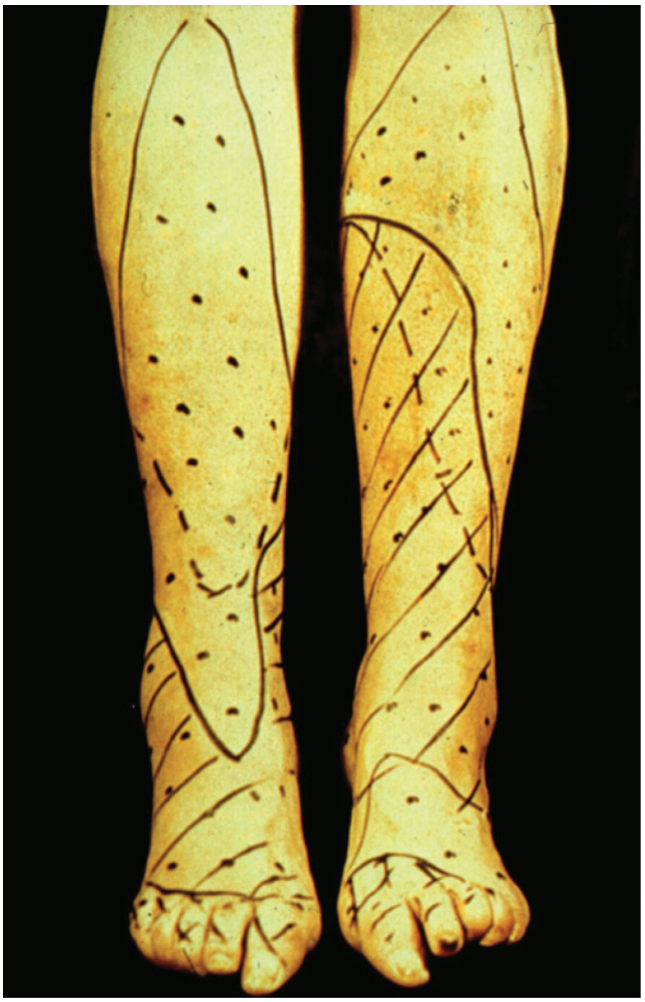

Figure 40.2 A typical example of the distribution of sensory deficits (dots, reduced thermal sensation; lines, reduced pain sensation; crossed lines, reduced touch sensation) in a person with distal symmetric sensory or sensorimotor polyneuropathy (DSPN).

typically involved. However, it is as yet uncertain whether the various fiber-type damage develops following a regular sequence, with small fibers being affected first, followed by larger fibers, or whether the small-fiber or large-fiber involvement reflects either side of a continuous spectrum of fiber damage. However, there is evidence suggesting that small-fiber neuropathy may occur early, often presenting with pain and hyperalgesia before sensory deficits or nerve conduction slowing can be detected [2]. The reduction or loss of small-fiber-mediated sensation results in loss of pain sensation (heat pain, pin-prick) and temperature perception to cold (Aδ) and warm (C) stimuli. Large-fiber involvement leads to nerve conduction slowing and reduction or loss of touch, pressure, two-point discrimination, and vibration sensation, which may lead to sensory ataxia (atactic gait) in severe cases. A typical example of the distribution of sensory deficits is shown in Figure 40.2. Sensory fiber involvement causes "positive" sensory symptoms such as paresthesia, dysesthesia, numbness, and pain, in addition to "negative" symptoms such as reduced sensation.

Persistent or episodic pain that typically may worsen at night and improve during walking is localized predominantly in the feet. The pain is often described as a deep-seated aching but there may be superimposed lancinating stabs or it may have a burning thermal quality. In a clinical survey of 105 people with painful polyneuropathy, the following locations of pain were most frequent: 96% feet, 69% balls of feet, 67% toes, 54% dorsum of foot, 39% hands, 37% plantum of foot, 37% calves, and 32% heels. The pain was most often described as "burning/hot," "electric," "sharp," "achy," and "tingling," and was worse at night-time and when tired or stressed [14]. The average pain intensity was moderate, ~5.75/10 on a 0–10 scale, with the "least" and "most" pain being 3.6 and 6.9/10, respectively. Allodynia (pain due to a stimulus that does not normally cause pain, e.g. stroking) may occur. The symptoms may be accompanied by sensory loss, while those

with severe pain may have few clinical signs. Pain may persist over several years [15, 19], causing considerable disability and impaired quality of life in some individuals [14], whereas it remits partially or completely in others, despite further deterioration in small-fiber function [20]. Pain remission tends to be associated with sudden metabolic change, short duration of pain or diabetes, preceding weight loss, and less severe sensory loss [20].

Compared with the sensory deficits, motor involvement is usually less prominent and restricted to the distal lower limbs, resulting in muscle atrophy and weakness at the toes and foot. Ankle reflexes are frequently reduced or absent. At the foot level, the loss of the protective sensation (painless feet), motor dysfunction, and reduced sweat production resulting in dry and chapped skin due to autonomic involvement increase the risk of callus and foot ulcers. Hence the person with neuropathy is at high risk for developing severe and potentially life-threatening foot complications such as ulceration, osteoarthropathy (Charcot foot), and osteomyelitis, and also medial arterial calcification and neuropathic edema. Because DSPN is the major contributory factor for diabetic foot ulcers and the lower limb amputation rates in people with diabetes are 15 times higher than those without diabetes, an early detection of DSPN by screening is of paramount importance [9]. This is even more imperative because many people with DSPN are asymptomatic or have only mild symptoms. In view of these causal pathways, the majority of amputations should potentially be preventable if appropriate screening and preventive measures are adopted.

Acute painful neuropathy

Acute painful neuropathy has been described as a separate clinical entity [21]. It is encountered infrequently in both people with type 1 diabetes mellitus (T1DM) and T2DM, presenting with continuous burning pain particularly in the soles ("like walking on burning sand") with nocturnal exacerbation. A characteristic feature is cutaneous contact discomfort with clothes and sheets, which can be objectified as hypersensitivity to tactile (allodynia) and painful stimuli (hyperalgesia). Motor function is preserved, and sensory loss may be only slight, being greater for thermal than vibration sensation. The onset is associated with and preceded by precipitous and severe weight loss. Depression and erectile dysfunction are common associated features. The weight loss responds to adequate glycemic control, and the severe manifestations subside within 10 months in all cases. No recurrences were observed after follow-up periods of up to 6 years [21]. The syndrome of acute painful neuropathy seems to be equivalent to "diabetic cachexia" as described by Ellenberg [22].

The term *insulin neuritis* was used by Caravati [23] to describe a case with precipitation of acute painful neuropathy several weeks following the institution of insulin treatment. In the most recent series, the term treatment-induced neuropathy in diabetes (TIND) has been used to describe this relatively rare iatrogenic small-fiber neuropathy with neuropathic pain and autonomic involvement caused by an abrupt improvement in glycemic control in the setting of chronic hyperglycemia. With a decrease in HbA_{1c} of 2–3% over 3 months, there was a 20% absolute risk of developing TIND, and with a decrease in HbA_{1c} of >4% over 3 months this risk exceeded 80% [24]. In another series, painful symptoms gradually improved in all patients, allowing discontinuation of analgesic therapy within 3–8 months. Hence careful correction of glucose levels should be considered in individuals with long-standing uncontrolled diabetes [25]. Sural nerve biopsy shows signs of chronic neuropathy with prominent regenerative activity [26] and also epineurial arteriovenous shunting and a fine network of vessels, resembling the new vessels of the retina, which may lead to a steal effect rendering the endoneurium ischemic [27]. This may be analogous with the transient deterioration of a pre-existing retinopathy following rapid improvement in glycemic control.

Focal and multifocal neuropathies

Most of the focal and multifocal neuropathies tend to occur in people with long-term diabetes who are middle aged or older. The outlook for most of them is for recovery, either partial or complete, and for eventual resolution of the associated pain [28]. With this in mind, physicians should always maintain an optimistic outlook when dealing with patients with these afflictions.

Cranial neuropathy

Palsies of the third cranial nerve (diabetic ophthalmoplegia) are painful in about 50% of cases. The onset is usually abrupt. The pain is felt behind and above the eye, and at times precedes the ptosis and diplopia (with pupillary dysfunction in 14–18% of cases) by several days. Oculomotor findings reach their nadir within a day or at most a few days, persist for several weeks, and then begin gradually to improve. Full resolution is the rule and generally takes place within 3–5 months. The fourth, sixth, and seventh cranial nerves are next in frequency [28].

Mononeuropathy of the limbs

Focal lesions affecting the limb nerves, most commonly the ulnar, median, radial, and peroneal, may be painful, particularly if of acute onset, as may entrapment neuropathies such as the carpal tunnel syndrome that is associated with painful paresthesia [28].

Diabetic truncal neuropathy

Mononeuropathy of the trunk (thoracoabdominal neuropathy or radiculopathy) presents with an abrupt onset, with pain or dysesthesias being the heralding feature, sometimes accompanied by cutaneous sensory impairment or hyperesthesia. Pain has been described as deep, aching, or boring, but the descriptors jabbing, burning, sensitive skin, and tearing have also been used. The neuropathy is almost always unilateral or predominantly so. As a result, the pain felt in the chest or the abdomen may be confused with pain of pulmonary, cardiac, or gastrointestinal origin. Sometimes it may have a radicular or girdling quality, half encircling the trunk in a root-like distribution. Pain may be felt in one or several dermatomal distributions and, almost universally, it is worst

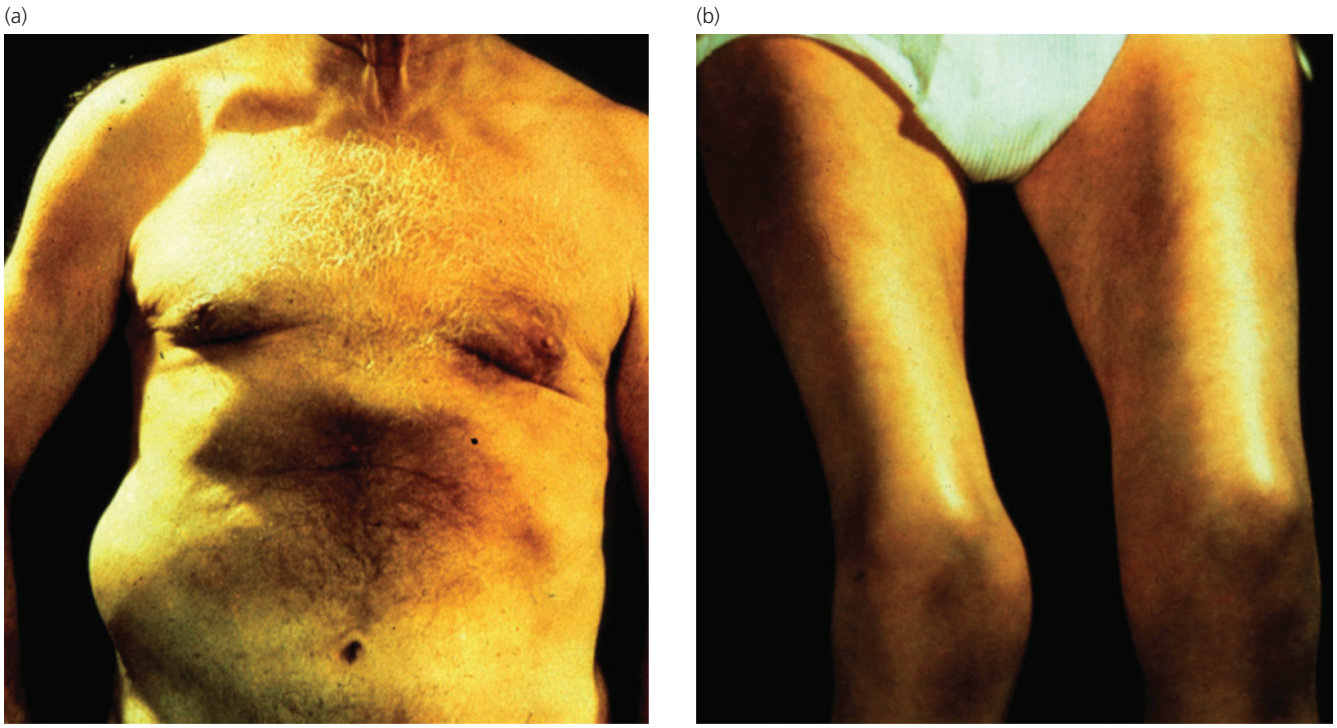

Figure 40.3 (a) Diabetic truncal neuropathy (thoracoabdominal neuropathy or radiculopathy) leading to herniation of the oblique abdominal muscle. (b) Diabetic amyotrophy (proximal neuropathy): pronounced bilateral atrophy and paresis of the quadriceps muscle.

at night. Rarely, abdominal muscle herniation may occur predominantly in middle-aged men, involving 3–5 adjacent nerve roots between T6 and T12 (Figure 40.3a).The time from first symptom to the peak of the pain syndrome is often just a few days, although occasionally spread of the pain to adjacent dermatomes may continue for weeks or even months. Weight loss of 7–18 kg occurs in >50% of the cases. The course of truncal neuropathy is favorable, and pain subsides within months with a maximum of 1.5–2 years [28].

Diabetic amyotrophy

Asymmetric or symmetric proximal muscle weakness and muscle wasting (iliopsoas, obturator, and adductor muscles) are easily recognized clinically in the syndrome of lower limb proximal motor neuropathy (synonyms: Bruns–Garland syndrome, diabetic amyotrophy, proximal diabetic neuropathy, diabetic lumbosacral plexopathy, ischemic mononeuropathy multiplex, femoral–sciatic neuropathy, femoral neuropathy). Pronounced bilateral atrophy and paresis of the quadriceps muscle are shown in Figure 40.3b. Pain is nearly universal in this syndrome. Characteristically, it is deep, aching, constant, and severe, invariably worse at night, and may have a burning, raw quality. It is usually not frankly dysesthetic and cutaneous. Frequently, pain is first experienced in the lower back or buttock on the affected side, or may be felt as extending from hip to knee. Although severe and tenacious, the pain of proximal motor neuropathy has a good prognosis. Concurrent distal sensory polyneuropathy is frequently present. Weight loss is also a frequently associated feature and may be as much as 15–18 kg. The weight is generally regained during the recovery phase [29, 30].

Central nervous system dysfunction

Relatively little attention has been directed towards impairment of the central nervous system (CNS) in people with diabetes with DSPN. Previous autopsy studies in people with diabetes have demonstrated diffuse degenerative lesions in the CNS including demyelination and loss of axon cylinders in the posterior columns [31, 32], degeneration of cortical neurons [33], and abnormalities in the midbrain and cerebellum [33, 34], which have been described as "diabetic myelopathy" [32] and "diabetic encephalopathy" [34].

Studies that evaluated CNS function in people with diabetes using evoked potentials in response to stimulation of peripheral nerves, event-related potentials, and neuropsychological tests have yielded variable results as to the existence of spinal or supraspinal (central) conduction deficits or cognitive dysfunction. However, we have shown that the degree of dysfunction along the somatosensory afferent pathways in persons with T1DM depends on the stage of peripheral neuropathy, is not related to the duration of diabetes or glycemic control, and can be characterized by an alteration of the cortical sensory complex and peripheral rather than spinal or supraspinal conduction deficits [35]. Magnetic resonance imaging showed an increased frequency of subcortical and brainstem lesions in people with T1DM with DSPN [36]. Moreover, individuals with DSPN showed a smaller cross-sectional chord area at C4/5 and T3/4 [37]. Using positron emission

tomography (PET) and [^{18}F]-2-deoxy-2-fluoro-D-glucose (FDG), we have demonstrated reduced cerebral glucose metabolism in people with T1DM with DSPN compared with people with newly diagnosed diabetes and healthy people without diabetes [38]. Spectroscopic measurement of brain metabolites such as *N*-acetyl aspartate (NAA) in the thalamus revealed a lower NAA : creatine ratio, suggesting thalamic neuronal dysfunction in DSPN [39]. Hence there is accumulating evidence suggesting that neuropathic involvement at central and spinal levels is a feature of DSPN, but it is not clear whether these are primary or secondary events.

Pathogenetic mechanisms

Recent experimental studies suggest a multifactorial pathogenesis of diabetic neuropathy [40, 41]. Most data have been generated in the diabetic rat model, on the basis of which two approaches have been chosen to contribute to the clarification of the pathogenesis of diabetic neuropathy. First, attempts have been made to characterize the pathophysiological, pathobiochemical, and structural abnormalities that result in experimental diabetic neuropathy. Second, specific therapeutic interventions have been employed to prevent the development of these alterations, to halt their progression, or to induce their regression despite concomitant hyperglycemia. At present, the following six pathogenetic mechanisms are under discussion, but, in contrast to earlier years, they are no longer regarded as separate hypotheses but mainly as a complex interplay with multiple interactions between metabolic and vascular factors:

1 Increased flux through the polyol pathway that leads to accumulation of sorbitol and fructose, *myo*-inositol depletion, and reduction in Na^+K^+-ATPase activity.

2 Disturbances in n-6 essential fatty acid and prostaglandin metabolism that result in alterations of nerve membrane structure and microvascular and hemorrheological abnormalities.

3 Endoneural microvascular deficits with subsequent ischemia and hypoxia, generation of reactive oxygen species (oxidative stress), activation of the redox-sensitive transcription factor NF-κB, and increased activity of protein kinase C (PKC).

4 Deficits in neurotrophism leading to reduced expression and depletion of neurotrophic factors such as nerve growth factor (NGF), neurotrophin-3 (NT-3), and insulin-like growth factor (IGF) and alterations in axonal transport.

5 Accumulation of non-enzymatic advanced glycation end-products (AGEs) on nerve and/or vessel proteins.

6 Immunological processes with autoantibodies to vagal nerve, sympathetic ganglia, and adrenal medulla in addition to inflammatory changes.

From the clinical point of view, it is important to note that, based on these pathogenetic mechanisms, therapeutic approaches could be derived, some of which have been evaluated in randomized clinical trials (see Treatment section).

Diagnostic assessment

Owing to the increasing recognition of diabetic neuropathy as a major contributor to morbidity and the recent expansion of clinical trials in this field on the one hand, but the lack of agreement on the definition and diagnostic assessment of neuropathy on the other, several consensus conferences were convened to overcome current problems. The Consensus Development Conference on Standardized Measures in Diabetic Neuropathy [42] recommended the following five measures to be employed in the diagnosis of diabetic neuropathy:

1 clinical measures;
2 morphological and biochemical analyses;
3 electrodiagnostic assessment;
4 quantitative sensory testing;
5 autonomic nervous system testing.

Clinical measures

Clinical measures include the following:

1 general medical history and neurological history;
2 neurological examination which consists of:
  a sensory (pain, light touch, vibration, position);
  b motor (graded as normal = 0, weak = 1–4 [25–100%]);
  c reflex (present or absent);
  d autonomic examination (bedside tests including heart rate variation during deep breathing and postural blood pressure response).

The basic neurological assessment comprises the general medical and neurological history, inspection of the feet, and neurological examination of sensation using simple semiquantitative bedside instruments such as the 10 g Semmes–Weinstein monofilament, the Neuropen (Figure 40.4a) [43] (touch), NeuroQuick (Figure 40.4b) [44], or Tiptherm [45] (temperature), calibrated Rydel—Seiffer tuning fork (Figure 40.4a) (vibration), pin-prick (pain), and tendon reflexes (knee and ankle). In addition, assessment of joint-position and motor power may be indicated. The normal range for the tuning fork on the dorsal distal joint of the great toe is ≥5/8 scale units in persons 21–40 years of age, ≥4.5/8 in those aged 41–60 years, ≥4/8 in those aged 61–71 years, and ≥3.5/8 scale units in those aged 72–82 years [46]. An indicator test for the detection of sudomotor dysfunction is the Neuropad, which assesses plantar sweat production by means of a color change from blue to pink. The patch contains the salt anhydrous cobalt(II) chloride. In the presence of water, this salt absorbs water molecules, normally changing its color from blue to pink. If the patch remains completely or partially blue within 10 min, the result is considered abnormal (Figure 40.4b) [47].

Clinical assessment should be standardized using validated scores for both the severity of symptoms and the degree of neuropathic deficits such as the Michigan Neuropathy Screening Instrument (MNSI) [48], Neuropathy Symptom Score (NSS) for neuropathic symptoms and Neuropathy Disability (NDS) for neuropathic deficits (impairments) [49].

The Toronto Consensus [18] has defined the following minimal criteria for the diagnosis of DSPN: (1) possible DSPN: the presence of symptoms or signs of DSPN; (2) probable DSPN: the presence of a combination of symptoms and signs of neuropathy including any two or more of the following: neuropathic

Figure 40.4 Bedside tests for the assessment of (a) large-fiber function and (b) small-fiber function.

symptoms, decreased distal sensation, or unequivocally decreased or absent ankle reflexes; (3) confirmed DSPN: the presence of an abnormality of nerve conduction and a symptom or symptoms or a sign or signs of neuropathy. If nerve conduction is normal, a validated measure of small-fiber neuropathy may be used; (4) subclinical DSPN: the presence of no signs or symptoms of neuropathy are confirmed with abnormal nerve conduction velocity or a validated measure of small-fiber neuropathy. It was recommended that definition 1, 2, or 3 be used for clinical practice and definition 3 or 4 for research studies [18].

Small-fiber neuropathy should be graded as follows: (1) possible: the presence of length-dependent symptoms and/or clinical signs of small-fiber damage; (2) probable: the presence of length-dependent symptoms, clinical signs of small-fiber damage, and normal sural nerve conduction; and (3) definite: the presence of length-dependent symptoms, clinical signs of small-fiber damage, normal sural nerve conduction, and altered intra-epidermal nerve fiber density at the ankle and/or abnormal thermal thresholds at the foot [18].

The intensity (severity) of neuropathic pain and its course should be assessed using an 11-point numerical rating scale (Likert scale) or a visual analog scale. Various screening tools (with or without limited bedside testing) have been developed to identify neuropathic pain such as the PainDetect, LANSS, NPQ, DN-4, and ID-Pain. These questionnaires use verbal descriptors and pain qualities as a basis for distinguishing neuropathic pain from other types of chronic pain such as nociceptive pain [50].

The following findings should alert the physician to consider causes for DSPN other than diabetes and referral for a detailed neurological work-up [51]:

- pronounced asymmetry of the neurological deficits;
- predominant motor deficits, mononeuropathy, cranial nerve involvement;
- rapid development or progression of the neuropathic impairments;
- progression of the neuropathy despite optimal glycemic control;
- development of symptoms and deficits only in the upper limbs;
- family history of non-diabetic neuropathy;
- diagnosis of DSPN cannot be ascertained by clinical examination.

The most important differential diagnoses include neuropathies caused by alcohol abuse, uremia, hypothyroidism, vitamin B_{12} deficiency, peripheral arterial disease, cancer, inflammatory and infectious diseases, and neurotoxic drugs [51].

Positive symptoms may reflect different pathophysiology than deficits, i.e. pain or paresthesia may be related to the degree of compensatory regeneration rather than to the degree of nerve fiber damage. Hence it has been suggested that symptom or pain scores should not be used to evaluate overall presence or progression of diabetic neuropathy but only to assess pain severity [42].

Electrodiagnostic measures

Electrophysiological techniques have the advantage of being the most objective, sensitive, specific, and reproducible methods that are available in many neurophysiological laboratories worldwide (Figure 40.5a).

Electrodiagnostic measures have also limitations inasmuch as they:

1 measure only function in the largest, fastest conducting myelinated fibers;
2 have relatively low specificity in detecting diabetic neuropathy;
3 show relatively high intra-individual variability for certain parameters (amplitudes);
4 are vulnerable to external factors such as electrode locations or limb temperature;
5 provide only indirect information about symptoms and deficits [42].

Quantitative sensory testing

Quantitative sensory testing (QST) is a psychophysical method used to quantify somatosensory function in response to controlled stimuli [52]. In clinical practice, the NeuPSIG Consensus [52] recommended the use of QST for screening for small- and large-fiber neuropathies, monitoring of somatosensory deficits, and monitoring of evoked pains, allodynia, and hyperalgesia. For the conduct of QST, it was recommended to use predefined standardized stimuli and instructions, validated algorithms of testing, and reference values corrected for anatomical site, age, and gender. Interpretation of results should always take into account the clinical context, and individuals with language and cognitive difficulties, anxiety, or litigation should not be considered eligible for QST [52]. Detection thresholds of touch-pressure, vibration, coolness, warmth, heat pain, cold pain, and mechanical pain can be used to characterize cutaneous sensation (Figure 40.5b).

The procedures that are being used for QST include the following:

1 the method of limits (continuous increase or decrease in intensity to appearance or disappearance threshold);
2 threshold tracking (combination of appearance or disappearance threshold);
3 titration method (graded steps to appearance and disappearance threshold);
4 the two-alternative forced-choice method (pairs of stimulus and null-stimulus phases) [52].

Morphological assessment

Sural nerve biopsy

Sural nerve biopsy does not represent a routine method in the diagnosis of diabetic neuropathy. It may be used to establish the diagnosis when the etiology of the neuropathy is in doubt. The limitations to this technique are that the information from the biopsy is of no direct benefit to the patient and that the procedure is associated with a certain morbidity and may result in complications [42].

Skin biopsy

Skin biopsy has become a widely used tool to investigate intra-epidermal nerve fiber density, dermal myelinated nerve fibers,

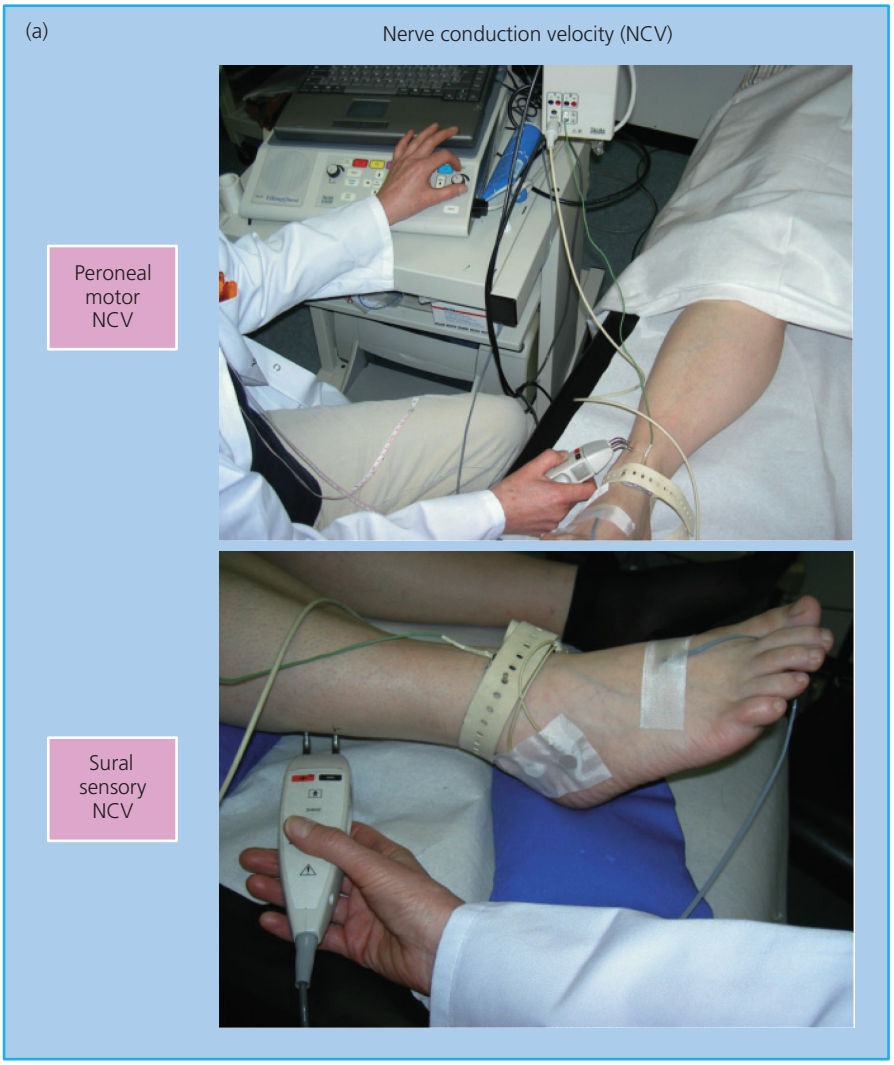

Figure 40.5 (a) Measurement of motor and sensory nerve conduction velocity. (b) Quantitative sensory testing.

and autonomic nerve fibers in peripheral neuropathies and other conditions (Figure 40.6). Different techniques for tissue processing and nerve fiber evaluation have been used. A Task Force of the European Federation of Neurological Societies (EFNS) updated the guideline on the use of skin biopsy in the diagnosis of peripheral neuropathies [53]. For diagnostic purposes in peripheral neuropathies, the guideline recommends performing a 3-mm punch skin biopsy at the distal leg and quantifying the linear density of intra-epidermal nerve fiber in at least three 50-µm thick sections per biopsy, fixed in 2% PLP or Zamboni's solution, by bright-field immunohistochemistry or immunofluorescence with anti-protein gene product 9.5 antibodies (PGP 9.5) (level A recommendation). Quantification of intra-epidermal nerve fiber density closely correlated with warm- and heat-pain threshold, and appeared more sensitive than sensory nerve conduction study and sural nerve biopsy in diagnosing small-fiber sensory neuropathy. The diagnostic efficiency and predictive values of this technique were very high (level A recommendation). Longitudinal studies of intra-epidermal nerve fiber density and regeneration rate are warranted to correlate neuropathological changes with progression of neuropathy and to assess the potential usefulness of skin biopsy as an outcome measure in peripheral neuropathy trials (level B recommendation). In conclusion, punch skin biopsy is a safe and reliable technique (level A recommendation) [53]. Age-dependent limits for normal intra-epidermal nerve fiber density are available [54].

Corneal confocal microscopy

The cornea of the human eye harbors a multitude of nerve fibers originating from the ophthalmic division of the trigeminal nerve and organized in three main groups: the sub-basal plexus, the sub-epithelial plexus, and the stromal nerves. *In vivo* laser-scanning corneal confocal microscopy (CCM), a non-invasive modality for the study of human cornea, has emerged as a promising technique for the detection of small-nerve fiber alterations [55]. CCM is being used to assess the corneal sub-basal nerve plexus lying between the basal epithelium and Bowman's membrane. CCM has good reproducibility and may contribute to the

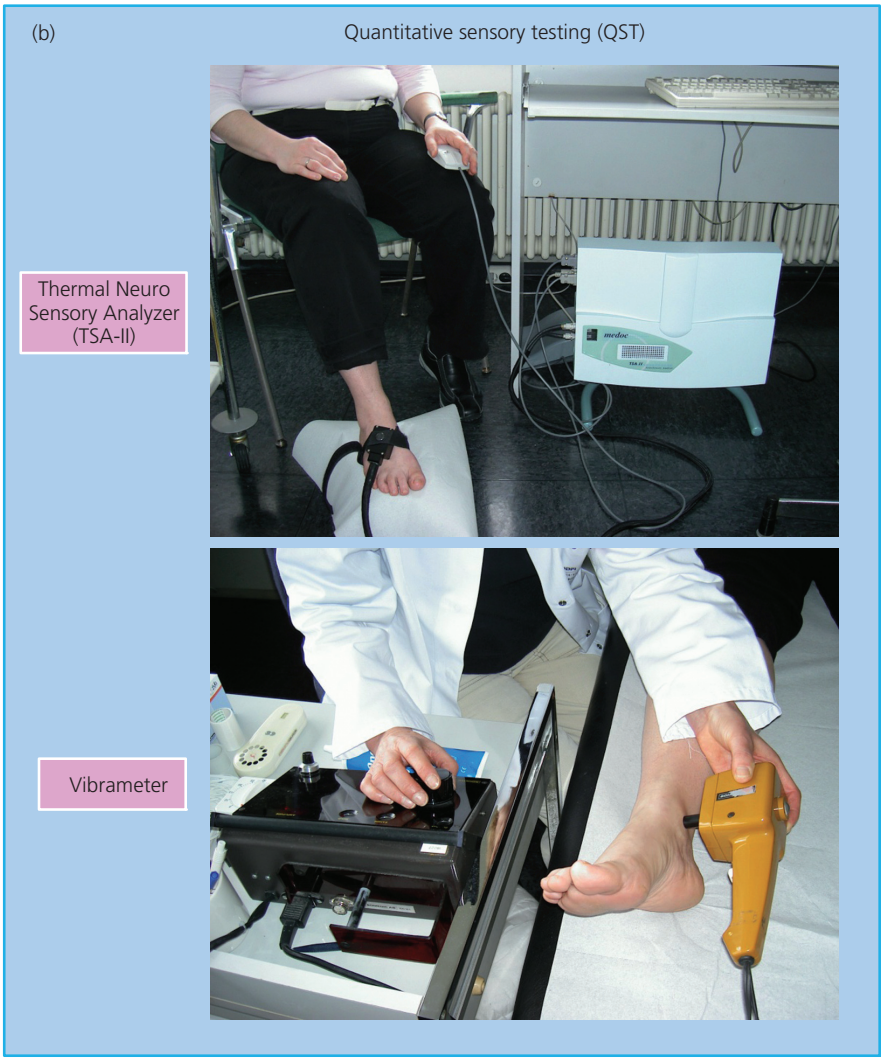

Figure 40.5 (*Continued*).

early diagnosis of diabetic polyneuropathy. It may also be useful to document favorable changes in nerve fiber structure early after therapeutic intervention [56]. Corneal nerve pathology is more pronounced in people with diabetic polyneuropathy and is associated with its clinical severity. The sensitivity and specificity of CCM for the diagnosis of polyneuropathy are moderate to high. Corneal nerve fiber loss by about 20% has been demonstrated in individuals with recent-onset T2DM despite good glycemic

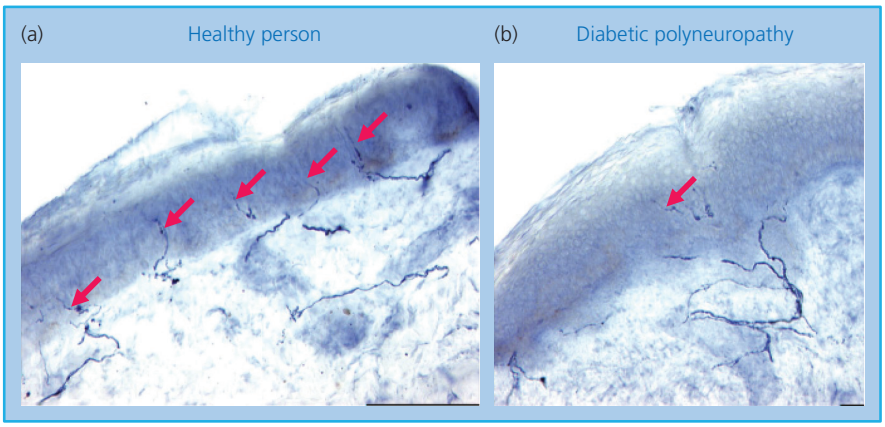

Figure 40.6 Loss of intra-epidermal nerve fibers in skin biopsy from the lateral lower leg in a person with diabetes with polyneuropathy (a) compared with a healthy person without diabetes (b) (red arrows indicate intra-epidermal nerve fiber). Bright-field immunohistochemistry with anti-protein gene product 9.5 antibodies (PGP 9.5).

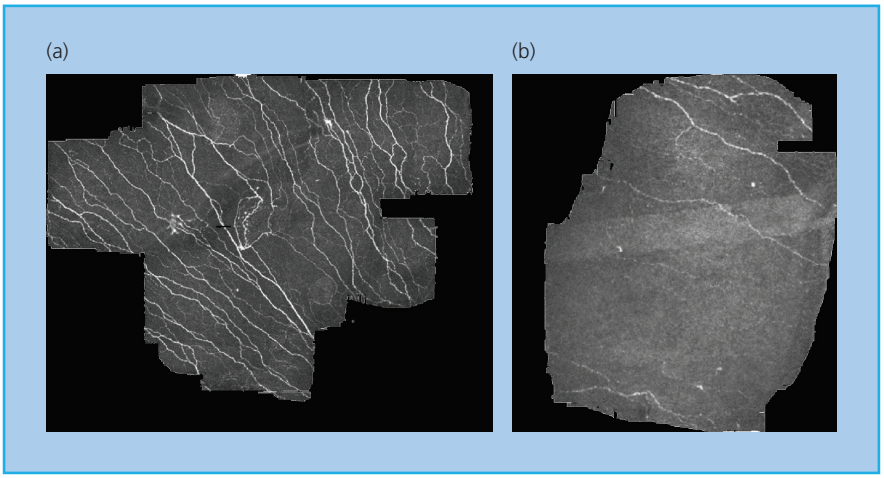

Figure 40.7 Corneal confocal microscopy showing the sub-basal nerve plexus. (a) Normal structure of corneal nerve fibers in a healthy individual; (b) loss of corneal nerve fibers in a person recently diagnosed with T2DM.

control [57]. Figure 40.7 shows CCM images of the sub-basal nerve plexus with normal appearance in a healthy individual (a) and corneal nerve fiber loss in a person recently diagnosed with T2DM (b). CCM now merits further use in large longitudinal studies to provide more information on the natural history of diabetic neuropathy and effects of treatment on corneal nerve regeneration [56].

Treatment

Role of intensive diabetes therapy in treatment and prevention of diabetic neuropathy

Several long-term prospective studies that assessed the effects intensive diabetes therapy on the prevention and progression of chronic diabetic complications have been published. The large randomized trials such as the Diabetes Control and Complications Trial (DCCT) and UK Prospective Diabetes Study (UKPDS) were not designed to evaluate the effects of intensive diabetes therapy on DSPN, but rather to study the influence of such treatment on the development and progression of the chronic diabetic complications [52, 53] Hence only a minority of the individuals enrolled in these studies had symptomatic polyneuropathy at entry.

Studies in persons with T1DM showed that intensive diabetes therapy retards but does not completely prevent the development of DSPN [58, 59]. In contrast, in those with T2DM, there is no evidence that intensive diabetes therapy or a target-driven intensified intervention aimed at multiple risk factors favorably influences the development or progression of DSPN in persons with T2DM [60, 61].

Treatment based on pathogenetic concepts

Recent experimental studies suggest a multifactorial pathogenesis of diabetic neuropathy. From the clinical point of view, it is important to note that, based on the various pathogenetic mechanisms, therapeutic approaches could be derived, some of which have been evaluated in randomized clinical trials, including aldose reductase inhibitors (alrestatin, sorbinil, ponalrestat, tolrestat, epalrestat, zopolrestat, zenarestat, fidarestat, ranirestat), the antioxidant α-lipoic acid (thioctic acid), essential fatty acid (γ-linolenic acid), ACE inhibitors (trandolapril), prostacyclin (PGI_2) analogs (iloprost, beraprost), prostaglandin derivatives (PGE_1.αCD), nerve growth factor (NGF), PKC β inhibitor (ruboxistaurin), C-peptide, vascular endothelial growth factor (VEGF), and benfotiamine (vitamin B_1 derivative) [62, 63]. These drugs have been designed to influence the underlying neuropathic process favorably rather than for symptomatic pain treatment. Since in the foreseeable future normoglycemia will not be achievable in the majority of persons with diabetes, the advantage of the aforementioned treatment approaches is that they may exert their effects despite prevailing hyperglycemia. Experimental studies of low-dose combined drug treatment suggest enhanced drug efficacy mediated by facilitatory interactions between drugs. Although considerable improvements in the quality of controlled trials has recently been made, no major breakthrough in slowing the progression of diabetic neuropathy in the long run has been achieved with drugs used on the basis of current pathogenetic concepts. Some of the newer drugs have shown promising results in phase II trials that require confirmation from large phase III trials. It is conceivable that drugs interfering with the pathogenesis of diabetic neuropathy may be most effective in terms of prevention, rather than intervention.

For clinical use only the antioxidant α-lipoic acid [64–68], the deproteinized hemo derivative of calf blood actovegin [69], and the lipid-soluble vitamin B_1 derivative benfotiamine [70] are licensed and used for treatment of symptomatic DSPN in several countries, and epalrestat is marketed in Japan and India. According to several meta-analyses, intravenous infusions of α-lipoic acid (600 mg/day) ameliorated neuropathic symptoms and deficits after 3 weeks [64–66]. Moreover, treatment for 5 weeks using 600 mg of α-lipoic acid orally once daily reduced the main symptoms of diabetic polyneuropathy including pain, paresthesia, numbness, and numbness to a clinically meaningful degree [65, 66]. In a multicenter, randomized, double-masked, parallel-group clinical trial (NATHAN 1), 460 people with diabetes with mild to moderate largely asymptomatic DSPN were randomly assigned to oral treatment with α-lipoic acid 600 mg once daily

($n = 233$) or placebo ($n = 227$) for 4 years. After 4 years, neuropathic deficits and symptoms, but not nerve conduction velocity, were improved, and the drug was well tolerated throughout the trial [67]. Clinical and post-marketing surveillance studies revealed a highly favorable safety profile [68].

Symptomatic treatment of painful neuropathy

Painful symptoms in diabetic polyneuropathy may constitute a considerable management problem. The efficacy of a single therapeutic agent is not the rule, and simple analgesics are usually inadequate to control the pain. There is agreement that patients should be offered the available therapies in a stepwise fashion [71–73]. Effective pain treatment considers a favorable balance between pain relief and side effects without implying a maximum effect. The following general considerations in the pharmacotherapy of neuropathic pain require attention:

- The appropriate and effective drug has to be tried and identified in each person by carefully titrating the dose based on efficacy and side effects.
- Lack of efficacy should be judged only after 2–4 weeks of treatment using an adequate dose.
- Because the evidence from clinical trials suggests only a maximum response of ~50% for any monotherapy, analgesic combinations may be useful.
- Potential drug interactions have to be considered given the frequent use of polypharmacy in individuals with diabetes.

A rational treatment algorithm including the various causal and symptomatic options is summarized in Table 40.2. Certain antidepressants (tricyclic drugs, duloxetine) and anticonvulsants (pregabalin, gabapentin) are considered as first-line treatments, and opioids are recommended as second-line options [72–74]. The advantages and disadvantages of the various drugs and drug classes used for treatment of painful diabetic neuropathy under consideration of the various comorbidities and complications associated with diabetes are summarized in Table 40.3. Prior to any decision regarding the appropriate treatment, the diagnosis of the underlying neuropathic manifestation allowing the estimation of its natural history should be established. In contrast to the agents that have been derived from the pathogenetic mechanisms

Table 40.2 Treatment options for painful diabetic neuropathy.

Approach	Compound/measure	Dose per day	Remarks	NNT (95% CI)
Optimal diabetes control	Lifestyle modification, OAD, insulin	Individual adaptation	Aim: HbA_{1c} ≤6.5–7%	–
Pathogenesis-oriented treatment	α-Lipoic acid (thioctic acid)[a]	600 mg i.v. infusion	RCT duration: 3 weeks	6.3[b]
		600–1800 mg orally	FSP; RCT duration: 4 yr	2.8–4.2[b]
	Actovegin[a]	2 g i.v., 1.8 g orally	FSP; RCT duration: 6 mo	8.3[b]
	Benfotiamine[a]	600 mg orally	FSP; RCT duration: 6 wk	?
Symptomatic treatment	*Tricyclic antidepressants*			3.6 (3.0–4.4)[c]
	Amitriptyline	(10–)25–150 mg	NNMH: 15	
	Desipramine	(10–)25–150 mg	NNMH: 24	
	Imipramine	(10–)25–150 mg	CRR	
	Clomipramine	(10–)25–150 mg	NNMH: 8.7	
	Nortriptyline	(10–)25–150 mg		
	SNRIs			6.4 (5.2–8.4)[c]
	Duloxetine	60–120 mg	Effective dose: 60 mg	
	α2–δ ligands			
	Gabapentin	900–3600 mg	Long titration	7.2 (5.9–9.1)[c]
	Pregabalin	300–600 mg	Dose-dependent effect	7.7 (6.5–9.4)[c]
	Weak opioids			
	Tramadol	50–400 mg	NNMH: 7.8	4.7 (3.6–6.7)[c]
	Local treatment			
	Capsaicin (0.025%) cream	q.i.d. topically	Max. duration: 6–8 weeks	5.7
	Capsaicin 8%	One time 179 mg topically	3-month repeat intervals as needed	10.6 (7.4–18.8)[c]
	Strong opioids			4.3 (3.4–5.8)[c]
Pain resistant to standard pharmacotherapy	Oxycodone, tapentadol		Add-on treatment	
	Electrical spinal cord stimulation		Invasive, specialist required	

[a] Available only in some countries.
[b] ≥50% symptom relief after 3 and 5 weeks.
[c] Source: Data from Finnerup et al. 2015 [72]. Copyright 2015 Elsevier.
CRR, concentration–response relationship; FSP, favorable safety profile; NNT, number needed to treat; NNMH, number needed for major harm; OAD, oral antidiabetes drug; RCT, randomized clinical trial; SNRIs, selective serotonin norepinephrine reuptake inhibitors; i.v., intravenous.

Table 40.3 Differential treatment of painful neuropathy considering frequent comorbidities and side effects.

Symptom	Duloxetine	Pregabalin	Tricyclics	Opioids	α-Lipoic acid
Depression	+[a]	n[a]	+	n	n
Obesity	n	–	–	n	n
Generalized anxiety disorder	+	+	na	na	na
Sleep disturbances	+	+	+	+	na
Coronary heart disease	n	n	–	n	n
Autonomic neuropathy	na	na	–	–	+
Fasting glucose	(–)	n	–	n	n[a]
Hepatic failure	–	n	[b]	[b]	n
Renal failure	–	Adapt dose	[b]	[b]	n
Drug interactions	–	n	–	n	n

[a]Minor decrease possible.
[b]Dependent on individual agent.
Effect: +, favorable; –, unfavorable; n, neutral; na, not available.

of diabetic neuropathy, those used for symptomatic therapy were designed to modulate the pain, without favorably influencing the underlying neuropathy.

The relative benefit of an active treatment over a control in clinical trials is usually expressed as the relative risk, the relative risk reduction, or the odds ratio (OR). However, to estimate the extent of a therapeutic effect (i.e. pain relief) that can be translated into clinical practice, it is useful to apply a simple measure that serves the physician to select the appropriate treatment for the individual patient. Such a practical measure is the "number needed to treat" (NNT), i.e. the number of people that need to be treated with a particular therapy to observe a clinically relevant effect or adverse event in one patient. This measure is expressed as the reciprocal of the absolute risk reduction, i.e. the difference between the proportion of events in the control group (P_c) and the proportion of events in the intervention group (P_i): $\text{NNT} = 1/(P_c - P_i)$. The 95% confidence interval (CI) of NNT can be obtained from the reciprocal value of the 95% CI for the absolute risk reduction. The NNT and NNH (number needed to harm) for the individual agents used in the treatment of painful diabetic neuropathy are given in Table 40.2.

Oral treatments

Tricyclic antidepressants

Psychotropic agents, among which tricyclic antidepressants have been evaluated most extensively, have constituted an important component in the treatment of chronic pain syndromes for more than 30 years. Putative mechanisms of pain relief by antidepressants include the inhibition of norepinephrine and/or serotonin reuptake at synapses of central descending pain control systems and the antagonism of *N*-methyl D-aspartate receptor that mediate hyperalgesia and allodynia. Imipramine, amitriptyline, and clomipramine induce a balanced reuptake inhibition of both norepinephrine and serotonin, while desipramine is a relatively selective norepinephrine inhibitor. The NNT for a ≥50% relief of neuropathic pain by tricyclic antidepressants is 3.6 (95% CI: 3.0–4.4) [72]. The most frequent adverse events of tricyclic antidepressants include tiredness and dry mouth. The starting dose should be 25 mg (10 mg in frail patients) and taken as a single nighttime dose 1 h before sleep. It should be increased by 25 mg at weekly intervals until pain relief is achieved or adverse events occur. The maximum dose is usually 150 mg/day. Tricyclic antidepressants are contraindicated in people with orthostatic hypotension, unstable angina, recent (<6 months) myocardial infarction, heart failure, history of ventricular arrhythmias, significant conduction system disease, and long QT syndrome.

Selective serotonin reuptake inhibitors (SSRIs)

Because of the relative high rates of adverse effects and several contraindications of tricyclic antidepressants, it has been reasoned whether people who do not tolerate them could alternatively be treated with SSRIs. These specifically inhibit presynaptic reuptake of serotonin but not norepinephrine, and unlike the tricyclic antidepressants they lack the postsynaptic receptor blocking effects and quinidine-like membrane stabilization. However, only weak or no effects on neuropathic pain were observed after treatment with fluoxetine, paroxetine, citalopram, and escitalopram [75]. Because of these limited efficacy data, SSRIs have not been licensed for the treatment of neuropathic pain.

Serotonin noradrenaline reuptake inhibitors (SNRIs)

Because SSRIs have been found to be less effective than tricyclic antidepressants, recent interest has focused on antidepressants with dual selective inhibition of serotonin and noradrenaline, such as duloxetine and venlafaxine. The efficacy and safety of duloxetine were evaluated in three controlled studies using doses of 60 and 120 mg/day over 12 weeks [76]. In all three studies, the average 24-h pain intensity was significantly reduced with both doses compared with placebo treatment, the difference between active and placebo achieving statistical significance after 1 week. The response rates, defined as ≥50% pain reduction, were 48.2%

(120 mg/day), 47.2% (60 mg/day), and 27.9% (placebo), giving an NNT of 4.9 (95% CI: 3.6–7.6) for 120 mg/day and 5.3 (95% CI: 3.8–8.3) for 60 mg/day. Pain severity but not variables related to diabetes or neuropathy predicts the effects of duloxetine in diabetic peripheral neuropathic pain. People with higher pain intensity tend to respond better than those with lower pain levels [77]. The most frequent side effects of duloxetine (60/120 mg/day) include nausea (16.7/27.4%), somnolence (20.2/28.3%), dizziness (9.6/23%), constipation 14.9/10.6%), dry mouth (7.1/15%), and reduced appetite (2.6/12.4%). These adverse events are usually mild to moderate and transient. To minimize them, the starting dose should be 30 mg/day for 4–5 days. In contrast to tricyclic antidepressants and some anticonvulsants, duloxetine does not cause weight gain, but a small increase in fasting blood glucose may occur.

In a 6-week trial comprising 244 participants, the analgesic response rates were 56, 39, and 34% in those given 150–225 mg venlafaxine, 75 mg venlafaxine, and placebo, respectively. Because people with depression were excluded, the effect of venlafaxine (150–225 mg) was attributed to an analgesic, rather than antidepressant, effect. The most common adverse events were tiredness and nausea [78]. Duloxetine but not venlafaxine has been licensed for the treatment of painful diabetic neuropathy.

Anticonvulsants

Calcium channel modulators (α2–δ ligands)

Gabapentin is an anticonvulsant structurally related to γ-aminobutyric acid (GABA), a neurotransmitter that plays a role in pain transmission and modulation. The exact mechanisms of action of this drug in neuropathic pain have not been fully elucidated. Among others, they involve an interaction with the system L-amino acid transporter and high-affinity binding to the α2–δ subunit of voltage-activated calcium channels. In an 8-week multicenter dose-escalation trial including 165 participants with diabetes and painful neuropathy, 60% of those on gabapentin (3600 mg/day achieved in 67%) had at least moderate pain relief compared with 33% on placebo. Dizziness and somnolence were the most frequent adverse events in ∼23% of both groups [79]. Pregabalin is a more specific α2–δ ligand with a sixfold higher binding affinity than gabapentin. The efficacy and safety of pregabalin were reported in a pooled analysis of six studies over 5–11 weeks in 1346 people with diabetes with painful neuropathy. The response rates, defined as ≥50% pain reduction, were 46% (600 mg/day), 39% (300 mg/day), 27% (150 mg/day), and 22% (placebo), giving NNTs of 4.2, 5.9, and 20.0 [33]. The most frequent side effects for 150–600 mg/day were dizziness (22.0%), somnolence (12.1%), peripheral edema (10.0%), headache (7.2%), and weight gain (5.4%) [80]. The evidence supporting a favorable effect in painful diabetic neuropathy is more solid and dose titration is considerably easier for pregabalin than gabapentin.

Sodium channel blockers

Although carbamazepine has been widely used for treating neuropathic pain, it cannot be recommended in painful diabetic neuropathy owing to very limited data. Its successor drug, oxcarbazepine [81], and also other sodium channel blockers such as valproate, mexiletine, topiramate [82], and lamotrigine [83], showed only marginal efficacy and have not been licensed for the treatment of painful diabetic neuropathy.

A single intravenous infusion of lidocaine (5 mg/kg body weight over 30 min during continuous ECG monitoring) resulted in a significant pain relief after 1 and 8 days in a controlled study of 15 people with diabetes and chronic painful neuropathy. [84].

Lacosamide

Lacosamide is an anticonvulsant that selectively enhances the slow inactivation of voltage-dependent sodium channels but, in contrast to the aforementioned sodium channel blockers, does not influence the fast sodium channel inactivation. Its second putative mechanism is an interaction with a neuronal cytosolic protein, the collapsin response mediator protein 2 (CRMP-2), which plays an important role in nerve sprouting and excitotoxicity [85]. Lacosamide has been evaluated in several studies in painful diabetic neuropathy. However, owing to insufficient efficacy, the drug was not approved by the FDA and EMEA for painful diabetic neuropathy.

Opioids

Tramadol acts directly via opioid receptors and indirectly via monoaminergic receptor systems. Because the development of tolerance and dependence during long-term tramadol treatment is uncommon and its abuse liability appears to be low, it is an alternative to strong opioids in neuropathic pain. In painful diabetic neuropathy, tramadol (up to 400 mg/day orally, mean dose 210 mg/day orally) was studied in a 6-week multicenter trial including 131 participants [86]. Pain relief was 44% on tramadol versus 12% on placebo. The most frequent adverse events were nausea and constipation. The NNH of 7.8 for dropouts due to adverse events was relatively low, indicating significant toxicity. Since tramadol has SNRI properties, it should not be combined with serotonergic drugs (*cave*: serotonin syndrome).

The most severe pain requires administration of strong opioids such as oxycodone or tapentadol. Although there are few data available on combination treatment, combinations of different substance classes have to be used in people with pain resistant to monotherapy. Several add-on trials have demonstrated significant pain relief and improvement in quality of life following treatment with controlled-release oxycodone, a pure mu-agonist in people with painful DSPN whose pain was not adequately controlled by standard treatment with antidepressants and anticonvulsants [87, 88]. As expected, adverse events were frequent and typical of opioid-related side effects. The results of these studies suggest that opioids should be included among the therapeutic options for painful DSPN, provided that careful selection of those unresponsive to standard treatments, regular monitoring, appropriate dose titration, and management of possible opioid-specific problems

(analgesic misuse or addiction, tolerance, opioid-induced hyperalgesia) are ensured. Recent recommendations have emphasized the need for clinical skills in risk assessment and management as a prerequisite to safe and effective opioid prescribing [71]. Treatment of painful DSPN with opioid agonists should generally be reserved for those who have failed to respond to or cannot tolerate the first-line medications.

Tapentadol is a novel centrally active analgesic with a dual mode of action: mu-opioid receptor agonist and norepinephrine-reuptake inhibitor. Recent phase III, randomized-withdrawal, placebo-controlled trials evaluated the safety and efficacy of tapentadol extended release (ER) in painful diabetic DSPN. Participants with at least a ≥1-point reduction in pain intensity at the end of a 3-week open-label titration phase were randomized to receive placebo or the optimal fixed dose over 12 weeks. Compared with placebo, tapentadol ER 100–250 mg twice daily was associated with a statistically significant difference in the maintenance of the initial improvement and was well tolerated [89, 90].

Topical agents

Capsaicin

Capsaicin (*trans*-8-methyl-*N*-vanillyl-6-nonenamide) is a selective transient receptor potential vanilloid 1 (TRPV1) agonist and the most pungent ingredient in the red pepper. It depletes tissues of substance P and reduces neurogenic plasma extravasation, the flare response, and chemically induced pain. Substance P is present in afferent neurones innervating skin, mainly in polymodal nociceptors, and is considered the primary neurotransmitter of painful stimuli from the periphery to the CNS. Several studies have demonstrated significant pain reduction and improvement in quality of life in people with diabetes with painful neuropathy after 8 weeks of treatment with capsaicin cream 0.075% [91]. The high concentration 8% adhesive capsaicin patch (Qutenza) is effective in several neuropathic pain conditions [92], and has recently been approved for treatment of painful diabetic neuropathy. The patch is applied for 30 min to the most painful areas, and this procedure may be repeated as needed every 3 months. In people with painful DSPN, a single 30-min application of the capsaicin 8% patch significantly improved pain relief and sleep quality compared to placebo over 12 weeks. In a 52-week, randomized trial, up to seven consecutive 30-min treatments with the capsaicin 8% patch as add-on to standard care was associated with sustained pain relief without adverse effects on sensory function.

Lidocaine

The topical lidocaine patch 5% (Lidoderm), a targeted peripheral analgesic, was associated with relief of pain and tactile allodynia with a minimal risk of systemic adverse effects or drug–drug interactions in people with post-herpetic neuralgia [93]. Controlled clinical trials in people with DSPN are under way.

Botulinum toxin A

Recent experimental evidence suggests that botulinum toxin type A (BTX-A) may not only inhibit the release of acetylcholine at the neuromuscular junctions, but also modulate afferent sensory fiber firing, thereby relieving neuropathic pain. In a recent randomized, double-blind, placebo-controlled trial, two administrations of botulinum toxin A 12 weeks apart, each of which comprised several injections, had a sustained analgesic effect against peripheral neuropathic pain of mixed origin [94]. Large scale studies are required to confirm this finding specifically in people with painful DSPN.

Combination pharmacotherapy

The response rates to analgesic monotherapy in painful diabetic DSPN are only ~50%. Therefore, combination pharmacotherapy is required in individuals who have only partial response or in whom the drug cannot be further titrated owing to intolerable side effects. Synergistic interactions of drug combinations might provide superior analgesia and fewer side effects than monotherapy by targeting of multiple mechanisms. In some trials, combined treatment showed superiority over monotherapy, but in others improved benefit or tolerability was not seen [95]. A crossover study examined the maximum tolerable dose of a combination treatment of gabapentin and morphine compared with monotherapy with each drug. The maximum tolerable dose was significantly lower and efficacy was better with combination therapy than with monotherapy, suggesting an additive interaction between the two drugs [96]. Other trials also showed that the combinations of antidepressants with α2–δ ligands [97, 98] and opioids with antidepressants [99] at the maximum tolerated dose were more effective than either monotherapy. In contrast, in people responding only partially to standard doses of duloxetine or pregabalin, combining both medications was not superior to increasing each drug in monotherapy to its maximum recommended dose. However, duloxetine at a dose of 60 mg/day was more effective than pregabalin at a dose of 300 mg/day [100].

Although several novel analgesic drugs have recently been introduced into clinical practice, the pharmacological treatment of chronic painful diabetic neuropathy remains a challenge for the physician. Individual tolerability remains a major aspect in any treatment decision. Little information is available from controlled trials on long-term analgesic efficacy and head-to-head comparisons of individual analgesics, and only a few studies have used drug combinations. Combination drug use or the addition of a new drug to a therapeutic regimen may lead to increased efficacy. In the future, drug combinations may also include those aimed at symptomatic pain relief and quality of life on the one hand, and improvement or slowing of the progression of the underlying neuropathic process on the other.

Non-pharmacological treatment

Because there is no entirely satisfactory pharmacotherapy of painful diabetic neuropathy, non-pharmacological treatment

options should always be considered. As for the pharmacological treatment, considerable efforts must also be made to develop effective non-pharmacological approaches. A systematic review assessed the evidence from rigorous clinical trials and meta-analyses of complementary and alternative therapies for treating neuropathic and neuralgic pain [101]. Data on the following complementary and alternative medicine treatments were identified: acupuncture, electrostimulation, herbal medicine, magnets, dietary supplements, imagery, and spiritual healing. The conclusion was that the evidence is not fully convincing for most complementary and alternative medicine modalities in relieving neuropathic or neuralgic pain. The evidence can be classified as encouraging and warrants further study for cannabis extract, magnets, carnitine, and electrostimulation.

Psychological support

A psychological component to pain should not be underestimated. Hence an explanation to the patient that even severe pain may remit, particularly in people with poorly controlled diabetes and acute painful neuropathy or in those with painful symptoms precipitated by intensive insulin treatment. Hence an emphatic approach addressing the concerns and anxieties of those with neuropathic pain is essential for their successful management [102].

Physical measures

The temperature of the painful neuropathic foot may be increased owing to arteriovenous shunting. Immersion in cold water may reduce shunt flow and relieve pain. Allodynia may be relieved by wearing silk pyjamas or the use of a bed cradle. Patients who describe painful symptoms on walking, likened to walking on pebbles, may benefit from the use of comfortable footwear [102].

Acupuncture

In a 10-week uncontrolled study in people with diabetes on standard pain therapy, 77% showed significant pain relief after up to six courses of traditional Chinese acupuncture without any side effects. During a follow-up period of 18–52 weeks, 67% were able to stop or significantly reduce their medications and only 24% required further acupuncture treatment [103]. Controlled studies using placebo needles should be performed to confirm these findings.

Transcutaneous electrical nerve stimulation (TENS)

TENS influences neuronal afferent transmission and conduction velocity, increases the nociceptive flexion reflex threshold, and changes the somatosensory evoked potentials. In a recent meta-analysis, reductions in the mean pain score were significantly greater with TENS than with sham treatment [104]. Hence TENS may be used as an adjunctive modality combined with pharmacotherapy to augment pain relief.

External muscle stimulation (high-tone therapy)

One randomized controlled study showed a better effect of mid-frequency external muscle stimulation than TENS on neuropathic symptoms after 1 week [105], but longer term controlled studies are not available.

Frequency-modulated electromagnetic nerve stimulation (FREMS)

FREMS applied during 10 sessions over 3 weeks resulted in significant pain reduction compared with placebo stimulation [106, 107].

Electrical spinal cord stimulation

It is generally agreed that electrical stimulation is effective in neurogenic forms of pain. Experiments indicate that electrical stimulation is followed by a decrease in the excitatory amino acid derivatives glutamate and aspartate in the dorsal horn. This effect is mediated by a GABAergic mechanism. In people with refractory painful diabetic neuropathy, spinal cord stimulation therapy over 6 months significantly reduced pain and improved quality of life [108]. This invasive treatment option should be reserved for those who do not respond to analgesic pharmacotherapy.

Surgical decompression

Surgical decompression at the site of anatomic narrowing has been promoted as an alternative treatment for people with symptomatic DSPN. A systematic review of the literature revealed only Class IV studies concerning the utility of this therapeutic approach. Given the current evidence available, this treatment alternative should be considered unproven (Level U). Prospective randomized controlled trials with standard definitions and outcome measures are necessary to determine the value of this therapeutic intervention [109, 110].

Diabetic autonomic neuropathy

Clinical impact

Diabetic autonomic neuropathy may affect any organ innervated by the autonomic nervous system. Although diabetic autonomic neuropathy has been appreciated as a clinical entity since the classical report by Rundles [111], in the past it has received less attention than peripheral sensorimotor neuropathy. This was because the onset of clinical features is insidious and severe clinical symptoms usually occur relatively late in the course of diabetes. Furthermore, non-invasive quantitative and reliable methods for assessment of diabetic autonomic neuropathy have been available only for the last two decades. Asymptomatic involvement of the autonomic nervous system can be widespread, but remains undetected without careful examination. Alternatively, severe symptoms confined to a single organ may result in extensive diagnostic evaluation and intense therapeutic efforts. The late stages of diabetic autonomic neuropathy are associated with considerable

Table 40.4 Clinical manifestations of diabetic autonomic neuropathy.

System	Manifestation
Cardiovascular system	Resting tachycardia, orthostatic hypotension
	Sudden death, malignant arrhythmia (?)
Respiratory system	Reduced ventilatory drive to hypercapnia/hypoxemia
	Sleep apnea, respiratory arrest (?)
Pupillary system	Pupillary reflex dysfunction, reduced dark adaptation
Gastrointestinal tract	Esophageal motor dysfunction
	Diabetic gastroparesis (gastropathy)
	Gallbladder dysfunction
	Diabetic enteropathy (diarrhea)
	Colonic hypomotility (constipation)
	Anorectal dysfunction (fecal incontinence)
Urogenital system	Diabetic cystopathy (neurogenic vesical dysfunction)
	Erectile dysfunction, female sexual dysfunction
Thermoregulation	Sudomotor dysfunction: distal hypohydrosis/anhidrosis, gustatory sweating
	Vasomotor dysfunction: vasodilatation, arteriovenous shunting, peripheral edema
Neuroendocrine system	Hypoglycemia-associated autonomic failure (HAAF):
	Defective counter-regulation, hypoglycemia unawareness
	Reduced hormonal responses to orthostatic changes/exercise

morbidity and increased mortality, hence early detection aimed at prevention of advanced symptomatic stages of this complication is essential. Since the clinical symptoms of autonomic neuropathy may be ambiguous and asymptomatic stages elude clinical examination, reliable, specific, and sensitive diagnostic methods are postulated. The clinical manifestations of diabetic autonomic neuropathy are summarized in Table 40.4.

There are no suitable test procedures available to screen for autonomic neuropathy. However, the following symptoms can serve as an indication, albeit with low specificity and sensitivity: resting tachycardia, gastrointestinal symptoms (dyspepsia, constipation, diarrhea, fecal incontinence), disorders of bladder function, sexual dysfunction, hypoglycemia unawareness, disordered sweat secretion, and blood glucose fluctuations that cannot be explained otherwise [51]. The Survey of Autonomic Symptoms (SAS), a simple questionnaire that consists of 11 items for women and 12 for men, has recently been validated. Each item is rated by an impact score ranging from 1 (least severe) to 5 (most severe). The SAS shows a high sensitivity and specificity (area under the receiver operating characteristic curve 0.828) that compares favorably with the detailed Autonomic Symptom Profile [112].

Cardiovascular autonomic neuropathy

Cardiovascular autonomic neuropathy (CAN) is a serious complication of diabetes that is associated with a poor prognosis and may result in severe postural hypotension, exercise intolerance, enhanced intraoperative instability, and increased incidence of silent myocardial infarction or ischemia, and may even predict the development of stroke. According to a meta-analysis, the overall mortality rates over periods up to 10 years were 30.4% in people with diabetes and CAN detected by reduced heart rate variability (HRV) compared with 13.4% in those without evidence of CAN. The relative risk of mortality from 15 studies ($n = 2900$) was increased in people with CAN by 2.14 (95% CI: 1.83–2.51) [113]. In the population-based KORA Augsburg Cohort Study, low HRV and prolonged QTc interval were independent predictors of all-cause and cardiovascular mortality in people with diabetes and in the general population [114, 115].

After cardiovascular reflex tests based on changes in HRV and blood pressure regulation had been introduced into clinical routine, it became evident that CAN may frequently be detected at early stages in asymptomatic people with diabetes. CAN can be divided into (1) subclinical, which is diagnosed only by tests, and (2) clinical, which presents with symptoms or signs [116]. The main clinical features of CAN are given in Table 40.5 [51]. In the population-based KORA S4 survey, the prevalence of CAN diagnosed by reduced HRV was 18% in people with known diabetes, 12% in those with newly detected diabetes, 11% in those with combined IFG/IGT, 8% in those with isolated IFG, 6% in those with isolated IGT, and 4.5% in those with NGT [115]. The presence of CAN is associated not only with the duration of diabetes and degree of glycemic control but also with smoking and the various components of the metabolic syndrome, including cardiovascular risk factors such as obesity, hyperlipidemia, hypertension, and albuminuria [117, 118].

It has long been recognized that resting tachycardia and fixed heart rate are characteristic findings in individuals with diabetes with advanced CAN. However, heart rate may decline with increasing severity of CAN and therefore does not provide a reliable diagnostic criterion. The hallmark and earliest indicator of, and the most frequent finding in, subclinical and symptomatic cardiac autonomic dysfunction is a reduced HRV, i.e. the magnitude of heart rate fluctuations around the mean heart rate, which can be detected using various non-invasive autonomic reflex tests described below. Postural hypotension is recognized as the clinical hallmark of CAN in persons with diabetes. It is characterized by weakness, faintness, dizziness, visual impairment, and even syncope following the change from the lying to the standing posture. In some cases this complication may become disabling, but the blood pressure fall may also be asymptomatic. It is generally agreed among diabetologists that postural hypotension is defined by a decrease in systolic blood pressure upon standing of 30 mmHg or more. It is important to note that orthostatic symptoms can be misjudged as hypoglycemia and be aggravated by a number of drugs, including vasodilators, diuretics, phenothiazines, and in particular tricyclic antidepressants and insulin [116, 119].

Silent ischemia

Several clinical studies have examined the possible relationship between CAN and silent myocardial ischemia. In a survey from the National Registry of Myocardial Infarction 2 (NRMI-2) among 434,877 individuals with myocardial infarction, 33% did not have

Table 40.5 Diabetic autonomic neuropathy of the cardiovascular, respiratory, neuroendocrine, sudomotor, vasomotor, and pupillomotor systems: clinical features, diagnostic work-up, and specific treatment.

Organ manifestations/clinical features	Diagnostic procedures	Treatment
Cardiovascular system		
Resting sinus tachycardia Reduced heart rate variability (HRV), fixed heart rate Orthostatic hypotension Exercise intolerance (inadequate increase in heart rate and blood pressure during physical activity) Perioperative instability with frequent drops in blood pressure and heart rate Reduced or absent perception of myocardial ischemia during physical activity Reduced left ventricular diastolic filling/ejection fraction Silent myocardial infarction Prolonged QT interval Sudden cardiac death	*Basic diagnostic work-up* HRV during deep breathing HRV after standing up Orthostatic test *Extended diagnostic work-up* Autonomic function tests: Resting HRV (time and frequency domain) E/I ratio during deep breathing; max./min. 30:15 ratio Valsalva ratio (Valsalva maneuver) Orthostatic test 24-h HRV, syncope work-up	*Cardiovascular autonomic neuropathy* In general, no specific treatment necessary (important: diagnosis and therapy of coronary heart disease and heart failure) For sinus tachycardia: cardioselective β-receptor blockers *Orthostatic hypotension* General measures: liberal salt intake, physical training, compression stockings, avoidance of hypotensive drugs Midodrine (α_1-adrenergic agonist) Fludrocortisone (9α-fluorohydrocortisone)
Respiratory system		
Central respiratory dysregulation with reduced respiratory drive in response to hypercapnia or hypoxia Sleep apnea syndrome Respiratory arrest	Sleep laboratory, as applicable	CPAP therapy, as applicable
Neuroendocrine system (endocrine dysfunction)		
Hypoglycemia-associated autonomic dysfunction Blunted or absent hormonal counter-regulation Hypoglycemia unawareness Increased glucose threshold for hypoglycemic symptoms at blood glucose lowering Decreased catecholamine secretion when standing or upon physical exertion	Optimal blood glucose control (in particular self-control), including during the night	Avoidance of symptomatic and asymptomatic (often nocturnal) hypoglycemia Hypoglycemia awareness training (blood glucose awareness training)
Sudomotor and vasomotor systems		
Dyshidrosis, anhidrosis ("dry feet") Gustatory sweating	Sweat tests: QSART: quantitative sudomotor axon reflex test TST: thermoregulatory sweat test SSI: Silastic sweat imprint ACHSST: acetylcholine sweatspot test Neuropad: indicator plaster	Topical agents containing fat or urea Avoidance of exposure to intense heat Prophylaxis in case of identified cause of sweating (dietary component) Anticholinergic drugs, clonidine (low dose) Topical glycopyrrolate cream In focal hyperhidrosis, botulinum toxin can be tried
Pupillomotor system		
Myosis Defective pupillary reflexes Reduced dark adaptation	Clinical examination Infrared pupillography (constriction rate, dilation rate, latency of pupillary light reflex)	Advise patient of impaired adaptation to dark and danger of night blindness Danger of glaucoma (check intraocular pressure)

Source: Modified from Ziegler et al. 2014 [51]. E/I: expiration/inspiration; CPAP: continuous positive airway pressure. Reproduced with permission. © Georg Thieme Verlag KG.

chest pain on presentation. The rates in people with diabetes were 32.6% among those presenting without chest pain versus 25.4% in the group with chest pain [120]. In the DIAD study, the prevalence of silent ischemia was 22% among persons with T2DM. CAN rather than traditional and emerging cardiovascular risk factors was a strong predictor of silent ischemia [121], and CAN also predicted incident cardiovascular morbidity [10]. A meta-analysis covering 12 studies (n = 1468) revealed an increased risk of silent myocardial ischemia during exercise by 1.96 (95% CI: 1.53–2.51) in people with diabetes with CAN compared with those without CAN [122]. In asymptomatic individuals with diabetes, the risk of major cardiac events was highest in those with both CAN and silent myocardial ischemia, but the latter was a weaker predictor of these events than CAN [122]. In persons with diabetes with exertional chest pain, a prolonged anginal perceptual threshold, i.e. the time from onset of 0.1 mV ST

depression to the onset of angina pectoris during exercise ECG, has been demonstrated compared with those without diabetes. This delay was associated with the presence of CAN [123]. Hence people with CAN and CAD are in jeopardy, because the longer threshold permits them to continue exercising despite increasing ischemia.

Diagnostic assessment

Cardiovascular autonomic reflex tests

During the past quarter of a century, several non-invasive cardiovascular reflex tests for computer-assisted assessment of abnormalities in HRV and blood pressure regulation have been described [124]. It is generally accepted that the diagnosis of CAN should be based on the results of a battery of autonomic tests rather than a single test [125]. HRV can be assessed either by calculation of indices based on statistical analysis of R–R intervals (time domain analysis) or by spectral analysis (frequency domain analysis) of an array of R–R intervals. Commercially available computer programs are usually employed to assess autonomic nerve function, but conventional ECG equipment can also be used. We previously validated a combination of autonomic function tests based on standard, spectral, and vector analysis of HRV [126, 127]. This test battery included measurement of the following indices: (1) Coefficient of variation (CV) of R–R intervals at rest, (2) spectral power in the very low-frequency band and (3) the low-frequency band, (4) HRV during deep breathing, including mean circular resultant of vector analysis or expiration/inspiration (E/I) ratio, (5) maximum–minimum 30:15 ratio, (6) Valsalva ratio, and (7) postural change in systolic blood pressure. The age-related normal ranges of these seven indices that have been selected following specific criteria (different physiological basis, independence of heart rate, and relatively high sensitivity and reproducibility) have been reported [128]. We suggested that definite CAN be defined as the presence of three or more abnormalities among these seven variables (specificity: 100%). Borderline or incipient CAN is assumed when two or more abnormal findings are present (specificity: 98%).

According to the Toronto Consensus [125], diagnosis of CAN should be based on the use of heart rate response to deep breathing, standing, and Valsalva maneuver, and blood pressure response to standing. For the diagnosis and monitoring of CAN, more than one heart rate test and the orthostatic hypotension test are required. The following criteria for the diagnosis and staging of CAN were proposed: (1) the presence of one abnormal cardiovagal test result identifies the condition of possible or early CAN, to be confirmed over time; (2) two or more abnormal cardiovagal test results are required for a definite or confirmed diagnosis of CAN; and (3) the presence of orthostatic hypotension in addition to abnormal HRV identifies severe or advanced CAN. The diagnostic work-up for CAN is presented in Table 40.5 [51]. Because of the potential risk of inducing retinal or vitreous hemorrhage, the Valsalva maneuver should not be performed in those with advanced diabetic retinopathy.

24-hour heart rate variability

Evidence has accumulated indicating a circadian variation in the frequency of acute cardiovascular events, with an increased incidence in the early morning hours. Neural activities represent typical examples of circadian rhythms, i.e. the day–night cycle, and it is well known that circulatory changes follow a similar circadian cycle. This highlights the importance of continuous 24-h monitoring of heart rate and blood pressure changes in studying the neural control of circulation in people with and without diabetes [129].

Cardiac radionuclide imaging

Radionuclide techniques for cardiac mapping have recently been used to quantify directly cardiac sympathetic innervation in various diseases including CAN. The non-metabolized norepinephrine analog *m*-iodobenzylguanidine (MIBG) participates in norepinephrine uptake in postganglionic sympathetic neurons. Several studies have demonstrated decreased myocardial MIBG uptake in persons with CAN as assessed by autonomic reflex tests [119, 130]. These defects in MIBG uptake usually remain unchanged over several years [131]. An example of reduced MIBG uptake in the left ventricular posterior wall in a person with long-term T1DM and renal failure before undergoing combined pancreas/kidney transplantation (P/KX) is shown in Figure 40.8a (white arrow). Eight years following successful P/KX, stable MIBG uptake was observed with the defect in MIBG uptake still visible in the left ventricular posterior wall (Figure 40.8b, white arrows). There is evidence to suggest that scintigraphic assessment using MIBG and single photon emission computed tomography (SPECT) using the norepinephrine analog [^{11}C]hydroxyephedrine is more sensitive in detecting CAN than indirect autonomic reflex testing, since MIBG uptake was reduced in people with normal autonomic tests [119, 130]. However, cardiac radionuclide imaging constitutes a research tool that is not available in the routine clinical setting.

Management

Causal treatment

In general, elimination of hyperglycemia, which is considered the permissive pathogenetic factor, is the primary approach of a causal treatment of any stage and manifestation of diabetic neuropathy. However, similarly to DSPN, studies in individuals with T1DM have shown that the progression of CAN may be delayed during long-term near-normoglycemia, whereas the majority of studies in those with T2DM could not convincingly demonstrate a favorable effect [132]. Interestingly, a multifactorial cardiovascular risk intervention aimed at improvements in glycemic control, weight loss, lipids, and hypertension in the Steno 2 study resulted in a slowing of progression of CAN but not DSPN [133].

Treatment based on pathogenetic concepts

A variety of experimental studies have provided new insights into the putative mechanisms implicated in the pathogenesis

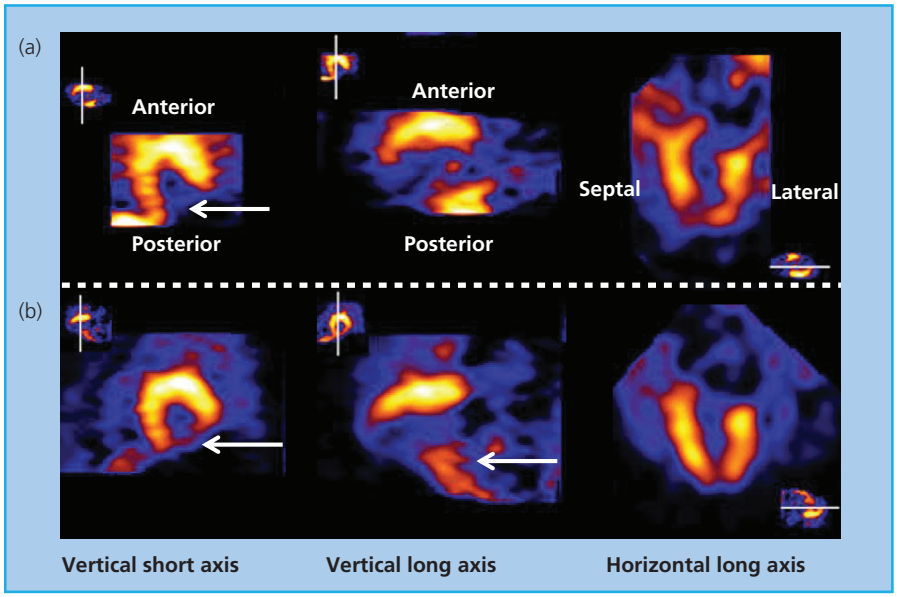

Figure 40.8 (a) Reduced MIBG uptake in the left ventricular posterior wall in a person with long-term T1DM and renal failure before undergoing combined pancreas/kidney transplantation (P/KX) (white arrow). (b) Eight years following successful P/KX, stable MIBG uptake with persisting defect in MIBG uptake in the left ventricular posterior wall (white arrows).

of diabetic neuropathy [40, 41]. Several experimental treatment approaches have been developed on the basis of pathogenetic concepts. From the clinical viewpoint, only limited data regarding these agents are available in persons with diabetes with CAN. Favorable effects on parasympathetic activity in people with diabetes have been shown in randomized controlled trials using the antioxidant α-lipoic acid (800 mg/day orally) after 4 months (DEKAN Study) [134], vitamin E (600 mg/day) after 4 months [135], and also ACE inhibitors, AT1 blockers and β-blockers [119, 136]. Further long-term studies are needed to confirm these findings.

Modulation of autonomic tone

Changes in autonomic nervous system activity play an important role in the genesis of cardiac arrhythmias. In general, parasympathetic withdrawal or sympathetic activation facilitate the formation of ventricular arrhythmias [137]. Drugs that adversely affect the autonomic tone by reducing HRV include class Ic antiarrhythmic agents (e.g. flecainide), β-blockers with intrinsic sympathomimetic activity (e.g. pindolol), clonidine, diltiazem, and tricyclic antidepressants (e.g. amitriptyline, imipramine, desipramine). An increase in HRV has been described for ACE inhibitors, cardioselective β-blockers without intrinsic sympathomimetic activity (e.g. metoprolol), digoxin, and verapamil. No consistent effect on HRV has been shown for longer acting dihydropyridine calcium channel blockers (e.g. nifedipine), amiodarone, and SSRIs (e.g. paroxetine, fluvoxamine) [119, 136]. Autonomic imbalance and high post-infarction morbidity and mortality are frequently observed in people with diabetes. As β-blockers without intrinsic sympathomimetic activity reduce both recurrent myocardial infarction and mortality post-infarction to a greater extent in people with diabetes than in those without diabetes, it has been suggested that this high-risk group could particularly benefit from these agents [137].

Symptomatic treatment

At present, the therapeutic strategies that are available in the routine clinical setting are limited to symptomatic treatment of CAN. Resting tachycardia usually does not require drug treatment, but in severe cases low-dose cardioselective β-blockers may be tried. In a considerable number of individuals with diabetes, postural hypotension remains asymptomatic and does not require any treatment. On the other hand, in severe cases it is the most disabling symptom of diabetic autonomic neuropathy. Drug treatment of symptomatic postural hypotension in people with diabetes and CAN may be difficult, because the goal of increasing blood pressure on standing has to be thoroughly balanced with the avoidance of a marked increase in supine blood pressure. This problem is particularly marked in those who develop arterial hypertension due to diabetic nephropathy, since the latter is commonly associated with CAN.

The first therapeutic approach should be an attempt to increase the venous return to the heart with mechanical measures such as an elasticized garment reaching from the metatarsals to the costal margin, careful and mild physical exercise such as swimming, head-up bed position during sleeping, and sitting on the edge of the bed before standing up. Simple physical maneuvers including leg crossing and squatting produce circulatory effects associated with an increase in blood pressure and improvement of orthostatic symptoms in persons with autonomic failure. In the absence of contraindications, salt intake may be increased by 2–6 g/day. Administration of psychotropic and diuretic drugs which may result in similar symptoms should be avoided, and electrolyte imbalance or volume depletion are to be excluded. When insulin

has been identified as a source aggravating postural hypotension, changing the timing of injections should be considered [115].

The efficacy of pharmacological treatment has been adequately substantiated for only a few drugs, is limited for others, particularly in people with advanced disease, and significant adverse reactions are frequent. Therefore, before any symptomatic treatment is initiated, its potential risk should be thoroughly weighed against its possible benefit. As first-line treatment the α_1-adrenergic agonist midodrine can be administered [138]. Another effective drug for treatment of orthostatic hypotension is the mineralocorticoid hormone fludrocortisone (9α-fluorohydrocortisone). This compound leads to an increase in systolic and diastolic blood pressure on standing and to improvement of orthostatic symptoms [139] (Table 40.5).

Gustatory sweating

Clinical features

Gustatory sweating refers to facial sweating, often accompanied by a flush, that follows the ingestion of food or drink. The prevalence of diabetic gustatory sweating is unknown, but it occurs particularly in individuals with either diabetic nephropathy or neuropathy [140]. Diabetic gustatory sweating is believed to be triggered by the taste buds by chewing inert substances, thinking of food, and smelling it; placing foods or alcohol in the stomach by a gastric tube does not evoke it. The tongue is the most sensitive area, and even cocainization fails to inhibit gustatory sweating completely. The etiology of diabetic gustatory sweating is uncertain. It has been assumed that it is a physiological response reflecting a compensatory mechanism to anhidrosis induced by diabetic autonomic neuropathy.

Management

Since sweating is controlled by sympathetic cholinergic pathways, oral anticholinergic drugs such as propantheline have been suggested for the treatment of diabetic gustatory sweating. However, these agents have a high side-effect profile and therefore are frequently unacceptable. A controlled trial using a 0.5% glycopyrrolate cream applied to affected areas on alternate days showed efficacy in reducing both the severity and frequency of diabetic gustatory sweating [140]. As it is not possible to apply this topical antimuscarinic agent beyond the hairline, it is limited to persons who do not experience sweating on the scalp. More recently, after intracutaneous injections of botulinum toxin type A into the affected facial skin areas, sweating ceased within 4 days, with the maximal follow-up time lasting 24 weeks [141] (Table 40.5).

Gastrointestinal dysfunction

Autonomic neuropathy may involve the esophagus, stomach, gallbladder, pancreas, small intestine, and large intestine (See Chapter 50). Abnormalities include both motor function with generally hypotonic and poorly contractile smooth muscle and regulation of gastrointestinal hormone secretion. The clinical features, diagnostic work-up, and specific treatment of diabetic autonomic neuropathy involving the gastrointestinal tract are listed in Table 40.6.

Esophageal dysfunction

Esophageal motility disturbances are frequently demonstrable using scintigraphic techniques, but symptoms including dysphagia, retrosternal discomfort, and heartburn are uncommon. People who complain about these symptoms should undergo endoscopy to exclude an obstructive lesion [51]. Manometric studies show diminished pharyngeal and esophageal contractions and reduced lower sphincter tone. Prokinetic drugs can be tried empirically. Since people with reduced esophageal motility may be at risk of delayed transit and hold-up of tablets, potentially leading to localized mucosal ulceration and delayed drug absorption, they always should drink after taking their medication.

Gallbladder dysfunction

The gallbladder may become atonic in association with autonomic neuropathy, which increases the gallbladder volume by retention of bile [51]. It is unknown whether these changes result in symptoms. Possibly biliary stasis explains the increased risk of gallstones, as shown by recent epidemiological data.

Diabetic gastroparesis

The speed of stomach emptying is important in the regulation of glucose homeostasis. Severe gastroparesis is an uncommon diabetic complication but is very difficult to manage. The rate of gastric emptying depends on the physicochemical composition of food (carbohydrates leave the stomach most rapidly, proteins less so, and fats remain longest, while liquids empty much more quickly than solids), its consistency (large chunks of meat remain in the stomach longer than small pieces), motor activity of the stomach, and the interaction of stomach and duodenum, including involvement of gastrointestinal hormones. The stomach receives nerve impulses from sympathetic and parasympathetic fibers and its movements are coordinated so that chyme (the food/gastric secretion mixture) is transported from the fundus, through the antrum to the pylorus, and then to the duodenum. Thus, fundal contraction is followed by antral contraction and then by sequential contraction of the pylorus and duodenum, with relaxation of the pyloric sphincter [142].

Diagnostic assessment

The terms diabetic gastroparesis and delay in gastric emptying are often used interchangeably, but caution should be exercised as delayed gastric emptying may also be due to hyperglycemia per se. The typical symptoms of gastroparesis are nausea, vomiting, anorexia, postprandial fullness, and early satiety, each affecting 10–20% of individuals with diabetes. However, abnormalities of gastric motor function correlate with symptoms only imperfectly, often have no clinical manifestations, and severe symptoms may remit spontaneously. Unstable blood glucose levels with

Table 40.6 Diabetic autonomic neuropathy of the gastrointestinal tract: clinical features, diagnostic work-up, and specific treatment.

Organ manifestations/clinical features	Diagnostic procedures	Treatment
All gastrointestinal manifestations	*Basic GI diagnostic work-up:*	
	History	
	Exclusion of structural and infectious diseases	
Dysphagia and reflux disease	*Extended diagnostic work-up:*	*Dysphagia:*
	Stage 1:	General measures
	Esophagogastroduodenoscopy	Prokinetic agents in individual cases
	Other imaging, as applicable	*Reflux:*
	Stage 2:	Proton pump inhibitors
	Esophagus manometry	
	24-h pH monitoring	
Diabetic gastroparesis (gastropathy)	Stage 1:	Gastroparesis
	Esophagogastroduodenoscopy	Dietary change: frequent, small, low-fiber meals with less fat
	Abdominal sonography	Adjust injection to meal interval
	Other imaging, as applicable	Prokinetic agents: metoclopramide, domperidone
	Laboratory tests	Erythromycin (off-label)
	Stage 2:	For severe refractory symptoms:
	Gastric emptying scintigraphy	Gastric electrical stimulation ("gastric pacemaker")
	[^{13}C]Octanoic acid breath test	Jejunal feeding tube
		Parenteral nutrition
Diabetic cholecystopathy	Laboratory tests	
	Abdominal sonography	
Diabetic diarrhea (enteropathy) and exocrine pancreatic insufficiency	Stage 1:	Diarrhea
	Endoscopy	Bulking agents
	Abdominal sonography	Loperamide
	Laboratory tests, including examination of stool for pathogenic organisms	Cholestyramine
		Clonidine
	Other imaging, as applicable	Octreotide
	Stage 2:	Bacterial overgrowth of the small intestine: broad-spectrum antibiotics (e.g. ciprofloxacine, metronidazole, and doxycycline one after the other, each for 10 days) with medical yeast (e.g. perenterol)
	Lactose, fructose, sorbitol hydrogen breath test	
	Glucose hydrogen breath test	
	Fecal elastase-1, as applicable	
	Lactulose hydrogen breath test, as applicable	Severe exocrine pancreatic insufficiency
	D-Xylose absorption test, as applicable	Pancreatic enzymes
Diabetic constipation (colonic hypomotility)	Stage 1:	Constipation:
	Digital rectal examination	Sufficient fluids, fiber, and physical activity
	Ileocolonoscopy	Gelling agents (pectins, psyllium preparations)
	Laboratory tests	Fiber-rich foods (e.g. wheat bran, linseed)
	Abdominal sonography, as applicable	Laxatives (e.g. sodium picosulfate, bisacodyl, macrogol, lactulose/lactitol))
	Other imaging, as applicable	
	Stage 2:	Depending on tolerance and efficacy
	(MRI) defecography	Biofeedback for rectal emptying disorder
	Anorectal manometry	Prucalopride (licensed only in women)
	Hinton test	
	Neurological examination	
Diabetic fecal incontinence	Stage 1:	Fecal incontinence:
	Digital rectal examination	Antidiarrheal medications
	Rectal endosonography	Pelvic floor gymnastics
	(MRI) defecography	Biofeedback
	Stage 2:	Sacral nerve stimulation in refractory cases
	Anorectal manometry	
	Neurological examination, as applicable	

Source: Modified from Ziegler et al. 2014 [51]. Reproduced with permission. © Georg Thieme Verlag KG.

postprandial hypoglycemia may give rise to considerable problems in achieving satisfactory glycemic control. The actual incidence and prevalence of diabetic gastroparesis have not been adequately studied [142]. Since gastrointestinal symptoms are nonspecific and frequent both in people with and without diabetes, but may be absent in diabetic gastroparesis, possibly owing to a visceral afferent neuropathy, specific and sensitive diagnostic tests are required to confirm or exclude the diagnosis. Since the scintigraphic technique, which is generally accepted as the "gold standard" in the evaluation of disordered gastric emptying in people with diabetes is associated with exposure to radiation and requires expensive equipment, an alternative non-invasive and non-adversive approach is needed to allow for routine clinical application. A suitable candidate for this purpose appears to be the [^{13}C]octanoic acid breath test for emptying of solids, which has the advantage of avoiding radiation by using a stable isotope [143]. The [^{13}C]acetate breath test may be used to measure liquid emptying. Other techniques include ultrasonography, duplex sonography, electrogastrography, manometry, radiopaque markers, double sampling gastric aspiration technique, and magnetic resonance imaging. Endoscopy should be performed if other gastrointestinal diseases are suspected of causing the symptoms.

Management

General measures in the management of diabetic gastroparesis include first, multiple small feedings with nutritional modification by increasing the intake of liquid carbohydrate and decreasing the intake of fat and high-fiber-containing food, and second, optimization of insulin treatment by individual adaptation of the insulin dose, omission of the injection–meal interval (*cave*: insulin lispro) or postprandial insulin application if necessary.

The pharmacological treatment of symptomatic diabetic gastroparesis includes three prokinetic agents. At present, metoclopramide and domperidone are used as the first-line drugs, but the development of tachyphylaxia after long-term treatment is a problem. In December 2013, the European Medicines Agency (EMA) issued a warning that owing to the risk of neurological and other adverse reactions, metoclopramide should no longer be used in chronic conditions such as gastroparesis. In May 2014, the EMA issued a warning that owing to an increased risk of potentially serious cardiac adverse effects, domperidone should be used at the lowest effective dose for the shortest possible duration. The maximum treatment duration should not usually exceed 1 week. Domperidone has since then been licensed only for treating nausea and vomiting, and no longer for the relief of symptoms of fullness or epigastric bloating and discomfort. Erythromycin acts as a motilin agonist, but its use is limited by considerable side effects such as skin reactions, abdominal cramps, and diarrhea. Hence erythromycin (if necessary given 3 mg/kg i.v.) can be administered to people who did not respond to the aforementioned drugs. Whether motilin agonists (erythromycin analogs) may be added to these compounds in the future is currently being tested in multicenter trials. It has not been adequately assessed whether asymptomatic patients may also benefit from drug treatment by more stable glycemic control. In people who experience vomiting that is refractory to drug treatment, the implantation of a gastric pacemaker for high-frequency/low-energy gastric electrical stimulation may be considered [144]. In a few cases of intractable vomiting, satisfactory relief could be achieved by a 70% gastrectomy [145].

Diabetic diarrhea

Clinical features

Diabetic diarrhea is characterized by intermittent, brown, watery, and voluminous stools, and is occasionally accompanied by tenesmus. Diarrhea is reported by up to 20% of people with diabetes and may reflect rapid or slow transit, frequently complicated by bacterial overgrowth [146]. It may occur at any time of the day but is often thought to be nocturnal. However, some authors found it to be unusually nocturnal. Steatorrhea is also common and may occur in as many as 75% of people with diabetes with diarrhea. Typically, diabetic diarrhea occurs in middle-aged individuals with a long-standing and poorly controlled T1DM. It is more common in men than in women, with a ratio of 3:2. It is often episodic, separated by periods of normal bowel movements or constipation, and the episodes may last a few days to weeks. Unequivocal evidence for peripheral neuropathy is present in the majority of people and the visceral autonomic manifestations are common. Diabetic diarrhea seldom occurs in the absence of diabetic neuropathy. Multiple pathogenic mechanisms have been implicated, e.g. autonomic neuropathy, bacterial overgrowth, and pancreatic exocrine insufficiency. However, diabetic diarrhea does not have a uniform and unequivocal pathogenesis [147].

Medications are often a cause of chronic diarrhea, and the medication list should always be carefully scrutinized for those with diarrhea as a side effect. In individuals with diabetes, metformin is a common cause of diarrhea. Such individuals are also more likely to have associated diseases (e.g. celiac sprue and microscopic colitis) that present with diarrhea as the sole complaint. Ingested sugar-free foods that may contain sorbitol or other agents can cause diarrhea in persons with diabetes [148].

Management

Since the pathogenesis of diabetic diarrhea is not always clear, the treatment is symptomatic and often empirical. However, it has been suggested that treatment should be directed at the identified cause of diarrhea rather than sequential empirical trials. There have been no controlled studies that examined the effect of improved glycemic control on the frequency and severity of diabetic diarrhea. The use of broad-spectrum antibiotics to counteract the bacterial overgrowth, if present, should be the first therapeutic approach. Courses of 1–2 weeks in each month have shown a transient or persistent improvement in uncontrolled studies. The use of clonidine, an α_2-adrenergic agonist, has been shown to reduce the frequency and volume of episodes of diarrhea. The mechanism of action has been attributed to regulation of water

and salt metabolism mediated by stimulation of α_2-adrenergic receptors on enterocytes. For people in whom the pathogenesis of diarrhea is unclear, antidiarrheal agents such as loperamide may decrease the number of stools, particularly if the diarrhea is associated with rapid intestinal transit, but usually do not reduce the stool volume. However, retardation of motility may actually promote stasis and thereby potentially aggravate bacterial overgrowth. In general, diabetic diarrhea is frequently difficult to manage and, owing to its intermittent nature, it is difficult to determine the efficacy of a therapeutic attempt [147–149].

Colonic dysfunction

Clinical features

Constipation is one of the major gastrointestinal symptoms, affecting ~20% of persons with T2DM. After a 1000-calorie meal, people with diabetes and constipation have no increase in colonic spike activity, suggesting that the gastrocolonic response to a meal is abnormal. Dysfunction of colonic motility in people with diabetes may be primarily due to an abnormality in the autonomic neural control. The cholinergic nervous system appears to be disturbed. The underlying pathophysiological processes include loss of enteric neurons in the colon due to increased oxidative stress and apoptosis, which may play a causative role in the motility disturbances [150].

The extent of the diagnostic assessment in an individual with diabetes with constipation is not substantially different from that in a person without diabetes and depends on the symptom severity. Digital examination, testing of stools for occult blood, proctosigmoidoscopy, barium enema, or colonoscopy should be performed, particularly if there is weight loss or rectal bleeding. There are no pathognomonic radiographic findings on barium enema in people with diabetes. A dilated ahaustral colon, similar to that associated with laxative abuse, may occur in some cases. Megacolon or megasigmoid may be found occasionally. Significant symptoms may be present, however, in the absence of radiographic abnormalities. In other disorders associated with a hypomotile colonic state, such as scleroderma, severe barium impaction has occurred. This should be kept in mind when barium studies are performed on persons with diabetes with severe colonic hypomotility. Thorough cleansing maneuvers should be performed post-examination. The colonic segmental transit time can be examined using radiopaque markers to distinguish between diffuse colonic hypomotility and rectosigmoid dysfunction (outlet obstruction) [142].

Management

The first approach in treating the constipation should be an increase in dietary fiber to reduce the intestinal transit time. Some high-fiber foods may lead to increased gas production, hence the quantity of fiber in the diet should be increased gradually to avoid excessive flatulence and bloating. Supplementation with a hydrophilic mucilloid psyllium preparation is a practical method of increasing stool bulk. Lactulose has been proposed for use in chronic constipation. This non-absorbing carbohydrate is degraded by the colonic bacteria to low molecular weight fatty acids which act as osmotically active particles. The acidic pH and increased osmotic activity stimulate colonic propulsive activity. Periodic use of stool softeners, mineral oil, or enemas may be needed to prevent fecal impaction. Patients should be counseled against chronic laxative use, particularly with the anthraquinone group (senna, cascara, aloes), which may produce progressive toxic damage to the intrinsic nerve plexuses of the colon, thus aggravating an already existing autonomic neuropathy of the gastrointestinal tract.

A small group of individuals with advanced diabetic enteropathy may develop severe constipation or obstipation that is unresponsive to the above measures. These people may benefit from a trial of drugs that stimulate the colonic smooth muscle. Cholinergic agents such as bethanechol (cholinergic agonist) or pyridostigmine (cholinesterase inhibitor) can be tried. Those with recalcitrant constipation may be helped by prokinetic drugs such as metoclopramide. This clinical observation is consistent with the cholinergic-like stimulatory effect of these drugs on colonic smooth muscle [142].

Prucalopride, a 5-hydroxytryptamine receptor-4 agonist, has recently been licensed for the treatment of chronic constipation in women in whom laxatives fail to provide satisfactory relief. A meta-analysis with data from 936 women with chronic constipation reported greater improvements with prucalopride (2 mg/day) than placebo in overall symptom score, abdominal symptoms score, stool symptoms score, and rectal symptoms score after 12 weeks [151]. However, diabetes was an exclusion criterion in these studies. There is a relationship between increased colonic transit time and increased symptom severity in individuals with chronic constipation, and treatment with prucalopride accelerates colonic transit time [152]. Whether prucalopride is effective in chronic constipation in men and people with diabetes remains to be established.

Anorectal dysfunction

Diagnosis

Fecal incontinence may be associated with diabetic diarrhea or constitute an independent disorder of presumably multifactorial etiology. Although a reduction in rectal sensitivity has been reported, most people with diabetes and fecal incontinence are aware of the presence of stool in the rectum but are unable to prevent its passage. Anorectal function can be examined by anorectal manometry and tests of continence for solids and liquids. Some manometric studies have shown reduced internal sphincter tone but normal external sphincter pressures, but others found both to be abnormal. Continence for solids and liquids can be directly assessed by simulating the stress of stools with a solid sphere or with rectally infused saline [153].

Management

As fecal incontinence is usually associated with diarrhea, the most successful treatment strategy is to treat the diarrhea. Several studies evaluated biofeedback conditioning for fecal incontinence related to various medical disorders. A small number of individuals with diabetes were among those studied. Patients were taught to develop reflex transient contraction of the external sphincter in response to rectal distention. Ability to sense rectal distention was a major prerequisite for successful conditioning [153].

Autonomic neuropathy of the urogenital system

Urogenital complications are frequently found in individuals with diabetes. In most, neuropathy and/or angiopathy are the etiologies or most pronounced co-etiologies of micturition or sexual dysfunctions. Since the impairment of bladder storage and emptying and also erectile and ejaculatory dysfunction may have severe organic and psychosocial consequences, their existence (often not apparent to the patient) should be systematically screened in the routine diabetes clinic. Given hints of existence, comprehensive evaluation of the impaired organ system is mandatory. For treatment, a wide range of various approaches is available and can be individually offered following appropriate diagnosis [154] The clinical features, diagnostic work-up, and specific treatment of diabetic autonomic neuropathy involving the urogenital system are summarized in Table 40.7.

Urinary bladder dysfunction

Clinical features and diagnosis

Diabetic bladder dysfunction is mainly due to neurogenic detrusor muscle dysfunction. In the early stages of diabetic autonomic neuropathy, the motor function of the bladder is not impaired, but the sensation of bladder distention may be blunted by selectively reduced afferent autonomic nerve activity from the bladder. Many individuals with mild autonomic neuropathy report diminished urinary frequency, but other symptoms or signs are relatively rare. As the autonomic efferent fibers become damaged, urination is less frequent and the person is no longer able to void completely; dribbling and overflow incontinence are common complaints. Individuals may be aware of prolonged intervals between micturition and also experience a sensation of incomplete bladder voiding [154, 155].

Typically, residual urine volumes are greater than 150 mL, predisposing the person to recurrent urinary tract infections. Residual urine volume increases gradually with time and gross bladder retention with abdominal swelling and sometimes overflow incontinence may occur in severe cases. The bladder is frequently

Table 40.7 Diabetic autonomic neuropathy of the urogenital system: clinical features, diagnostic work-up, and specific treatment.

Organ manifestations/ clinical features	Diagnostic procedures	Treatment
Diabetic cystopathy (bladder emptying dysfunction)	*Basic diagnostic work-up* Micturition diary over 48 h *Extended diagnostic work-up* Questionnaire (e.g. International Prostate Symptom Score [IPSS]) Uroflowmetry Residual urine measurement Digital rectal examination for men Urodynamic testing, as applicable	Behavioral changes Electrical stimulation Biofeedback Anticholinergics α-Rreceptor blockers Antibiotic therapy, as applicable Bladder neck incision Self-catheterization Suprapubic cystostomy
Erectile dysfunction	*Basic diagnostic work-up* Stage 1: Sexual history, IIEF-5 Laboratory tests Total (free) testosterone, prolactin, FSH, LH Stage 2 (optional) Test with a PDE-5 inhibitor (sildenafil, vardenafil, tadalafil) *Extended diagnostic work-up* Stage 3 (only if surgical therapy is planned/indicated): Intracavernosal injection test Doppler/duplex sonography Cavernosometry/cavernosography Nocturnal tumescence measurement	Erectile dysfunction: Avoidance of medication side effects (caused by antihypertensives, tranquilizers, antidepressants) Stage 1: PDE-5 inhibitors (sildenafil, tadalafil, vardenafil) Stage 2: Erection aid system (vacuum pump) Corpus cavernosum auto-injection therapy Stage 3: Corpus cavernosum implant Hypogonadism Testosterone substitution

Source: Modified from Ziegler et al. 2014 [51]. Reproduced with permission. © Georg Thieme Verlag KG.

palpable at the time of presentation, but painful acute urinary retention is rare, as are hydroureter and hydronephrosis [154, 155].

Lower urinary tract symptoms (LUTS) are common age-related complaints that are often attributed to benign prostatic hyperplasia (BPH). LUTS and BPH increase rapidly with age, starting at about 50 years of age. Straining, intermittency, post-void dribbling, and weak stream may signify urethral obstruction from BPH. However, among men with diabetes, similar symptoms may also result from bladder dysfunction due to denervation and poor detrusor contractility. Other complex associations of LUTS and BPH among men with diabetes include symptoms of urgency, frequency, and nocturia that may occur from detrusor overactivity, resulting from BPH, and/or microvascular complications associated with diabetes, increasing hyperactivity of the detrusor. Because previous studies have failed to differentiate LUTS from BPH in men with diabetes, the effect of diabetes on the development or presence of LUTS and BPH remains controversial [154].

Diagnostic assessment should include ultrasound examination before and after emptying. Urodynamic evaluation should be performed to differentiate between people with diabetic cystopathy and those with other causes of bladder outflow obstruction. Cystometry usually shows the presence of residual urine and reduced sensation of bladder filling. The total bladder capacity may exceed 1 L. Voiding is usually at a slow rate (5 mL/s), intermittent, and facilitated by abdominal straining [154, 155].

Management

The principles of treatment are to compensate for the deficient bladder sensation and thereby to prevent the development of a high residual urine volume. Patients should be educated to void every third hour during daytime to compensate for the lack of first desire to void. Repetitive voiding by double- or triple-voiding techniques may replace a deficient detrusor contraction and enable the patient to discharge almost all of the bladder volume. The Credé maneuver (manual suprapubic pressure) may be recommended to those who find it difficult to maintain sufficient straining. This particularly occurs in women without sufficient pelvic support of the bladder. To compensate for the loss of the afferent part of the reflex arc triggering detrusor function, cholinergic agents such as bethanecol (10–20 mg orally three times daily) may be used. However, side effects such as sweating, salivation, tachycardia, and flushing limit daily use. Booster doses of bethanecol with 30–60 mg orally twice per week may be an alternative option. Prazosin, an α_1-adrenergic blocker, may be effective by reducing urethral resistance. Intermittent catheterization may offer an alternative for individuals who do not benefit from education and pharmacological treatment. This method needs to be applied with care to minimize the risk of urinary tract infection. Bladder neck resection or incision of the internal sphincter may be necessary in very severe cases. Such surgery leaves the external sphincter intact, maintaining urinary continence, but can cause premature ejaculation or, in women, cystourethrocele. Moreover, this irreversible step should be approached with caution, since the external sphincter may also be impaired as a result of autonomic neuropathy, and urinary incontinence following bladder neck incision has been reported [154, 155].

Erectile dysfunction

Epidemiology

The term erectile dysfunction describes the persistent or recurrent inability to achieve and maintain a penile erection of sufficient rigidity to permit satisfactory sexual activity for at least 3 months (See Chapter 49) [156]. Erectile dysfunction is more common with advancing age, and since the aged population will increase, its prevalence will continue to rise. Diabetes is the most frequent organic cause of erectile dysfunction, the onset of which starts about 15 years earlier in individuals with diabetes than in those without. Around 50% of men with diabetes report erectile dysfunction, which may be the earliest clinical feature of autonomic neuropathy. Risk factors and clinical correlates include duration of diabetes, glycemic control, the various components of the metabolic syndrome, each of the chronic diabetic complications, and smoking [154].

Pathophysiology

Cholinergic and non-cholinergic non-adrenergic neurotransmitters mediate erectile function by relaxing the smooth muscle of the corpus cavernosum. A principal neural mediator of erection is nitric oxide, which activates guanyl cyclase to form intracellular guanosine monophosphate, a potent second messenger for smooth muscle relaxation. The importance of this pathway is mirrored by the clinical effect of facilitated erection by a selective inhibitor of phosphodiesterase-5 (which breaks down cyclic guanosine monophosphate). *In vivo* studies of isolated corpus cavernosum tissue from men with diabetes have shown functional impairment in autonomic and endothelium-dependent relaxation of corpus cavernosum smooth muscle [154].

Diagnosis

Frequently, a careful history, physical examination, serum glucose or HbA_{1c}, lipid profile, and optional hormonal testing facilitate the diagnosis of erectile dysfunction and effective therapy. Patient history can differentiate erectile dysfunction from other male sexual dysfunctions, including ejaculatory disorders (premature ejaculation and other abnormalities), hypogonadism, disorders of orgasm, and Peyronie disease. Underlying risk factors associated with erectile dysfunction are common to cardiovascular disease in general, and should be identified during evaluation as they may represent the initial clinical sign of generalized endothelial disease (vascular insufficiency). Evaluation of family history, nicotine use, blood pressure, lipid profile, and glucose is required or should be documented if previously performed. Active management of identified cardiac risk factors should be instituted (e.g. smoking cessation, blood pressure treatment) [156].

An interview with the partner is advisable and will confirm the problem but may also reveal other causes of the difficulties, e.g. vaginal dryness. The relative importance of psychological and organic factors may be determined from the history. Drugs that may be associated with erectile dysfunction include tranquilizers (phenothiazines, benzodiazepines), antidepressants (tricyclics, SSRIs), and antihypertensives (β-blockers, vasodilators, central sympathomimetics, ganglion blockers, diuretics). In most men, sophisticated investigation is unnecessary [154].

Management

The initial management should able to advise the man to reduce possible risk factors and to optimize glycemic control. Even if the cause is organic, almost all men with ED will be affected psychologically. Sexual counseling is an important aspect of any treatment, and it is preferable also to involve the partner. Once reversible causes of erectile dysfunction have been ruled out, a trial of oral medication is recommended as first-line therapy, based on treatment efficacy, side-effect profile, and minimal invasiveness (Table 40.7). In a trade-off network meta-analysis of starting dosages of phosphodiesterase-5 (PDE-5) inhibitors, sildenafil 50 mg had the greatest efficacy but also had the highest rate of overall adverse events. Tadalafil 10 mg had intermediate efficacy but had the lowest overall rate of all adverse events. Vardenafil 10 mg had similar overall adverse events to sildenafil 50 mg but a markedly lower global efficacy [157]. However, the majority of men with diabetes will require the maximum dose of each compound. Specialized testing and referral are generally reserved for cases where oral first-line treatments fail or are not appropriate, or if greater insight into the etiology is desired by the patient/physician. Second-line therapies, although more invasive than oral agents, are generally well tolerated and effective. Surgery remains an important option for men refractory to medical management, offering effective and durable erectile dysfunction treatment outcomes [156].

Other sexual problems in men

Diminished or absent testicular pain has been described as an early sign of autonomic neuropathy. Retrograde ejaculation from the prostatic urethra into the bladder may occur occasionally and follows loss of sympathetic innervation of the internal sphincter which normally contracts during ejaculation. Complete loss of ejaculation probably indicates widespread pelvic sympathetic involvement and, like retrograde ejaculation, causes infertility, which may be treated by insemination.

Female sexual dysfunction

Female sexual dysfunction include persistent or recurrent disorders of sexual interest/desire, disorders of subjective and genital arousal, orgasm disorder, and pain and difficulty with attempted or completed intercourse (see Chapter 49). The scientific knowledge on sexual dysfunction in women with diabetes is rudimentary. There is evidence to suggest that in men with diabetes, sexual dysfunction is related to somatic and psychological factors, whereas in women with diabetes, psychological factors are more predominant [158]. The effect of diabetes on women's sexual function is complex; the most consistent finding is a correlation between sexual dysfunction and depression [159]. Sexual dysfunction was observed in 27% of women with T1DM. Female sexual dysfunction was not related to age, body mass index (BMI), HbA_{1c}, duration of diabetes, and diabetic complications. However, female sexual dysfunction was related to depression and the quality of the partner relationship [158]. According to a recent meta-analysis, frequency of female sexual dysfunction was higher in T1DM (OR [95% CI] 2.3 [1.2–4.2]), in T2DM (2.5 [1.6–4.0]), and in women with "any diabetes" (T1DM and T2DM) (2.0 [1.5–2.7]) than in women without diabetes for any duration of diabetes. Depression was significantly more frequent in women with diabetes than in those without diabetes. In meta-regression, only BMI was significantly associated with effect size. In weighted regression, the only significant association was found between age and female sexual function index score [160].

Problems affecting sexuality in women with diabetes include fatigue, changes in premenstrual blood glucose control, vaginitis, decreased sexual desire, decreased vaginal lubrication, and increased time to reach orgasm. Even minor episodes of depression, which is twice as frequent than in men, can result in a loss of libido. The extent to which these symptoms are related to autonomic neuropathy has also been examined in a few studies, the results of which are at variance [161]. The examination of a woman with diabetes with sexual dysfunction should include the duration of symptoms, psychological state, concomitant medications, presence of vaginitis, cystitis, and other infections, frequency of intercourse, blood pressure, BMI, retinal status, pelvic examination, presence of discharge, and glycemic control.

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8 Macrovascular Complications in Diabetes

41 Pathogenesis of Macrovascular Complications in Diabetes

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Key points

- Diabetes accounts for 75–90% of excess coronary artery disease (CAD) risk seen in people with diabetes and enhances the effects of other cardiovascular risk factors.
- A range of hemodynamic and metabolic factors contribute to macrovascular disease in diabetes.
- The link between glucose control and cardiovascular disease (CVD) is not as strong as that seen with microvascular complications of diabetes.
- There is clear *in vitro* and *in vivo* evidence that glucose exerts direct and indirect toxic effects on the vasculature.
- Glycemic memory describes the deferred long-term injurious effects of prior glycemic status; early glycemic control appears to be important to reduce vascular complications in subsequent decades.
- Specific insulin resistance pathways appear to contribute to atherogenesis in diabetes.
- The accumulation of advanced glycation end-products (AGEs) exerts proinflammatory and profibrotic effects on the vasculature via receptor-independent and receptor-dependent effects. The AGE receptor (RAGE) is pivotally involved in the pathogenesis of diabetes-accelerated atherosclerosis.
- The components of the classic renin–angiotensin system (RAS) and in particular more recently discovered components such as angiotensin-converting enzyme 2 appear to contribute to macrovascular disease in diabetes. Inhibitors of the RAS have consistently demonstrated reduced endothelial dysfunction and atherosclerosis in animal models via suppression of inflammation, fibrosis, and oxidative stress. There is also strong clinical evidence for vasculoprotection by RAS blockade.
- Other vasoactive components such as endothelin and urotensin II are also likely to contribute to macrovascular complications in diabetes and interact with the RAS. Furthermore, the role of novel tumor necrosis factor (TNF)-related ligands, such as TNF-related Apoptosis-inducing ligand and osteoprotegerin, and the complement system in atherosclerosis are currently under evaluation.
- Treatments that reduce oxidative stress and inhibit inflammation have been shown to be antiatherosclerotic in experimental studies with some evidence, albeit not uniform, also having been obtained in clinical studies.
- A multifactorial approach treating conventional cardiovascular risk factors in addition to diabetes-specific risk factors is currently viewed as the optimal strategy to reduce the burden of CVD in diabetes.

Epidemiology of diabetic macrovascular complications

Macrovascular complications develop in people with type 1 (T1DM) [1–3] and type 2 diabetes mellitus (T2DM) [4–6]. This is of a particular concern as the increasing prevalence of diabetes now also affects adolescents and younger adults, thus promoting the earlier development of long-term cardiovascular complications. Even after adjusting for concomitant risk factors such as hypertension and hyperlipidemia, there remains an excess risk for cardiovascular disease (CVD) in people with diabetes [7, 8]. Indeed, diabetes itself accounts for 75–90% of the excess coronary artery disease (CAD) risk and enhances the effects of other cardiovascular risk factors. Death from stroke and myocardial infarction (MI) are the leading causes of mortality in T1DM and T2DM [1, 9].

A range of hemodynamic and metabolic factors have been considered responsible for the development and progression of macrovascular disease in diabetes (Figure 41.1) [10]. In terms of hemodynamic factors, in particular the hormonal cascade known as the renin–angiotensin system (RAS) has been shown to have a pivotal role in diabetes-associated atherosclerosis; however, other

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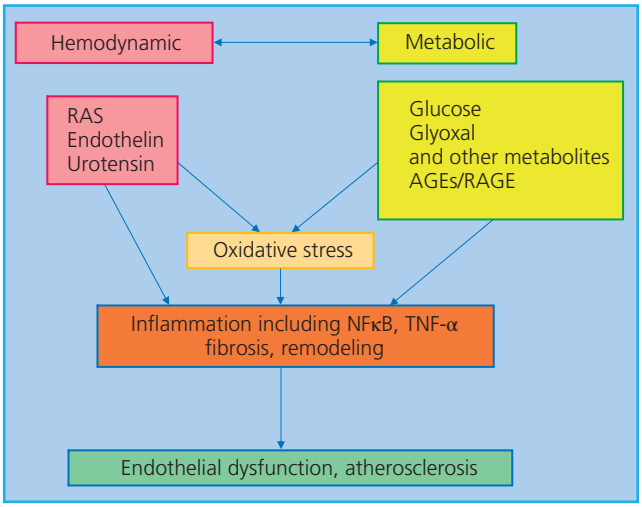

Figure 41.1 Hemodynamic and metabolic mediators contribute to the pathogenesis of diabetic vascular complications. Hemodynamic factors include the renin–angiotensin system (RAS) and other vasoactive factors. Metabolic factors include glucose and glucose metabolites such as the formation of advanced glycation end-products (AGEs). Both pathways interact with each other and lead to oxidative stress and inflammation, thus promoting endothelial dysfunction and atherosclerosis. NFκB, nuclear transcription factor κB; TNF-α, tumor necrosis factor α.

vasoactive hormone systems such as the endothelin (ET) [11] and urotensin systems [12, 13] have also been implicated in diabetic macrovascular disease. Furthermore, oxidative stress and a decrease in antioxidant defense have emerged as critical factors driving many atherogenic processes in diabetes [14], in addition to a host of immune–inflammatory responses involving factors such as tumor necrosis factor (TNF)-related, Apoptosis-inducing ligand (TRAIL) [15] and the complement system [16].

Pathogenesis of diabetic macrovascular disease

Chronic exposure of the vascular endothelium to hyperglycemia induces an inflammatory response involving the adhesion and transmigration of monocytes through the vascular wall into the sub-endothelial space [17]. Furthermore, accelerated generation and vascular deposition of AGEs in addition to interactions with RAGE in diabetes initiate oxidative reactions that promote the oxidation of low-density lipoprotein (LDL) (oxLDL) [18], which enhances the proinflammatory properties of the endothelium [19]. Monocytes differentiate into macrophages, which, via uptake of lipids, transform into foam cells and accumulate in the vascular wall. The early atherosclerotic process results in the formation of fatty streak lesions, which over time develop into more advanced lesions, characterized by infiltration with vascular smooth muscle cells (VSMCs), formation of a necrotic core, and further lipid accumulation [17]. In humans, these lesions can demonstrate features of instability and plaque rupture including intraplaque hemorrhages in addition to heightened thrombogenicity.

Role of hyperglycemia

A pivotal role for glycemic control and duration of diabetes exposure has been well established for microvascular complications in the UK Prospective Diabetes Study (UKPDS) study [6, 20], although the data are not as convincing for macrovascular disease. The importance of glycemic control for macrovascular injury was subsequently extensively investigated in a series of studies. It was suggested that HbA_{1c} acts as an independent and continuous risk factor for macrovascular disease [21–24]; however, this link is not as strong with respect to microvascular complications. For an increase in HbA_{1c} from 5.5% (37 mmol/mol) to 9.5% (80 mmol/mol), there is a 10-fold increase in microvascular disease endpoints, whereas the risk for macrovascular disease endpoints increases only twofold.

Clinical trials and hyperglycemia

Clinical trials such as the Action to Control Cardiovascular Risk in Diabetes trial (ACCORD) [25], Action in Diabetes and Vascular disease: PreterAx and DiamicroN-MR Controlled Evaluation (ADVANCE) trial [26], and the Veterans Affairs Diabetes Trial (VADT) [27], which explored tight glycemic control in people with T2DM with established CVD, investigated the association between tight glycemic control and cardiovascular endpoints. As observed in the initial reports of the Diabetes Control and Complications Trial (DCCT) in people with T1DM and in the UKPDS trial in people with T2DM, tight blood glucose control had little effect on macrovascular outcomes. This was further emphasized by subsequent studies including the ADVANCE [26] and ACCORD trials [25]. Both studies failed to demonstrate significant cardiovascular benefits, with the ACCORD study suggesting possibly deleterious cardiovascular outcomes in association with tight glucose control.

One possible explanation for the lack of a positive effect of tight glycemic control on cardiovascular outcomes may be the short duration of these trials (less than 5 years). Indeed, as best seen with respect to the longer follow-up of the Steno 2 study [28] and a long-term follow-up of the UKPDS [29], the benefits of prior intensified cardiovascular risk management including aggressive glucose control may not appear for up to 10 years after initiation of the studies. Thus, in view of the relative lack of an impact on CVD with intensive glucose control, other risk factor modification strategies need to be emphasized. The recent publication of the ADVANCE-ON trial did not show a benefit of the initially intensive glucose lowering treatment arm in terms of cardiovascular outcomes after 6 years of follow-up, whereas the initially treated blood pressure (BP) arm continued to show cardiovascular protection [30]. Several recent reports of newer glucose-lowering agents such as dipeptidyl peptidase 4 (DPP-4) inhibitors have failed to demonstrate superior protection with respect to macrovascular disease. These findings need to be considered in the context that these studies were aiming for equivalent glucose-lowering efficiency in both arms and therefore the findings do not disprove the potential of glucose lowering ultimately leading to less macrovascular disease [31, 32].

Direct and indirect glycotoxicity

Hyperglycemia is thought to have direct and indirect toxic effects on vascular cells. It has been suggested that increased glucose levels enter the polyol pathway at an increased flux rate leading to heightened formation of diacylglycerol. In addition, an increased flux of glucose into the hexosamine pathway may contribute to glucose-mediated vascular injury in diabetes. To investigate specifically hyperglycemia-mediated atherosclerosis, aldose reductase transgenic mice have been investigated [33]. These mice demonstrated increased glucose delivery via the polyol pathway and also showed early atherosclerosis, but did not develop advanced vascular lesions. It has been suggested that the formation of reactive dicarbonyls is a more reliable marker of glucose toxicity than the conventional measurements of fasting glucose or HbA_{1c} measurements [34], although this is as yet to be proven.

In vitro studies

Studies in cell culture experiments have obtained clear evidence that hyperglycemia induces a range of proatherogenic effects. Glucose directly activates monocytes–macrophages *in vitro,* initiating increased expression of cytokines such as interleukin 1β (IL-1β) and IL-6 [35]. Furthermore, this leads to protein kinase C (PKC) and nuclear factor κB (NFκB) activation resulting in increased production of reactive oxygen species (ROS). Auto-oxidation of glucose can also lead to the formation of ROS and can mediate oxLDL. Scavenger receptors on activated macrophages can mediate the uptake of modified lipids such as the proatherogenic oxidized LDL. The formation of advanced glycation end-products (AGEs) in the hyperglycemic milieu can lead to the formation of modified albumin, which inhibits scavenger receptor class B type 1-mediated efflux of cholesterol to high-density lipoprotein (HDL). Therefore, prolonged hyperglycemia can indirectly lead to a range of secondary changes, including changes in lipid profile, cellular lipid accumulation, and foam cell formation, in addition to AGE-mediated modification of proteins leading to altered cellular structure and function.

Animal models

The study of atherosclerosis in diabetes has long been hampered by the lack of an appropriate animal model. Our group and others have developed a murine model of diabetes-associated macrovascular disease, the ApoE knockout (KO) mouse rendered diabetic by multiple low doses of streptozotocin injections. This model is considered by the National Institutes of Health/Juvenile Diabetes Research Foundation (NIH/JDRF) co-sponsored Animal Models for Diabetes Complications Consortium (AMDCC) to be an appropriate model to study macrovascular disease in diabetes [36].

To address the separate roles of hyperglycemia and dyslipidemia in diabetes-associated atherosclerosis, mice deficient in the LDL receptor were bred with transgenic mice expressing a viral protein under control of the insulin promoter [37]. When infected with the virus, T cells mediate destruction of pancreatic β cells that express the viral protein, thus closely mimicking the autoimmune response in human T1DM. In these animals, atherosclerosis development was accelerated even on a normal diet, suggesting that hyperglycemia was driving atherosclerosis in these mice [37, 38]. When the animals were placed on a high-fat diet, a further acceleration of atherosclerosis occurred, suggesting that glucose and lipids may act through synergistic mechanisms to accelerate atherosclerosis. Furthermore, plaque disruption and intraplaque hemorrhages, features of plaque instability and potential plaque rupture, were observed in this model [37].

Metabolic memory

The concept of "glycemic memory" describes the deferred effects of prior glycemic status on the subsequent development of diabetic complications. Episodes of poor glycemic control during the earlier stages of diabetes can precipitate or accelerate the development of complications later in the course of diabetes even when glycemic control is subsequently improved. Two studies have provided evidence for such a metabolic imprint, the DCCT/EDIC trial in T1DM [1] and the UKPDS in T2DM [29]. Both studies have shown that poor glycemic control was associated with an increased subsequent burden of complications. Another study in people with T2DM, the VADT study, compared intensive with standard glucose control (6.9 vs. 8.4%, 52 vs. 68 mmol/mol), but did not demonstrate significant cardiovascular protection after the participants had been exposed to hyperglycemia for long periods (12–15 years) [27]. Therefore, it appears that early glycemic control is crucial for a long-term beneficial outcome on diabetic complications.

The concept of "metabolic memory" raises two important issues. First, hyperglycemia may expose people with diabetes to its harmful effects years before T2DM is diagnosed. Indeed, 25% of people show complications at the time of diagnosis of T2DM. Therefore, it has been postulated that early diagnosis and strict glycemic control may be pivotal to reduce the induction of this metabolic memory with subsequent development of long-term diabetic vascular complications. Second, glycemic oscillations including peaks and troughs, which are not reflected in the HbA_{1c} levels [39, 40], may have a key role in mediating growth factor and cytokine expression in addition to inducing chromatin remodeling [41].

There are many cellular and molecular processes that may contribute to the mechanisms underlying metabolic memory, with most of them relating to glycotoxicity. These pathways include the formation of AGEs, glycation of DNA, increased flux of glucose metabolism, leading to increased oxidative damage, overproduction of PKC-β and mitochondrial stress. It has been shown that transient hyperglycemia induces long-lasting activation of epigenetic changes in the promoter region of the NFκB subunit p65 in aortic endothelial cells both *in vitro* and *in vivo*. These hyperglycemia-induced epigenetic changes and increased p65 expression were prevented by reducing mitochondrial superoxide production or superoxide-induced generation of α-oxoaldehydes such as methylglyoxal (Figure 41.2) [41]. These studies suggest that transient hyperglycemia causes persistent atherogenic effects

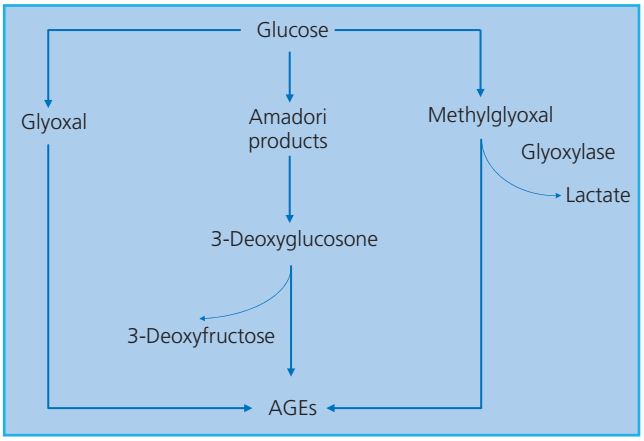

Figure 41.2 The formation of advanced glycation end-products (AGEs) can involve early glucose metabolites such as glyoxal and methylglyoxal, highly reactive dicarbonyls, and key precursors of AGEs.

during subsequent normoglycemia by inducing long-lasting changes in chromatin remodeling and highlight a critical role for ROS in epigenetic modulation of glucose-responsive pathways. Specifically, hyperglycemia results in recruitment of the mobilization of the histone methyl transferase Set7 to the nucleus with increased H3K4 monomethylation of the proximal promoter region of the NFκB subunit p65 gene, leading to increased expression of proatherogenic pathways including monocyte chemotactic protein 1 (MCP-1) and vascular cell adhesion molecule 1 (VCAM-1) [41]. Subsequent studies in mice, which were initially diabetic but returned spontaneously to normoglycemia, have also demonstrated persistent upregulation of proinflammatory genes such as p65 and MCP-1 as a result of prior hyperglycemia. Novel Set7 networks encompassing immune–inflammatory pathways [42] and also antioxidant molecules such as heme oxygenase 1 by H3K4m1-dependent but also H3K4m1-independent pathways have been implicated in the development of macrovascular disease in diabetes [43]. Recent studies by Paneni et al. validated Set7 as an epigenetic regulator of vascular cell inflammation in people with diabetes, which was associated with an increase in the oxidative stress marker 8-isoPGF2α [44]. Furthermore, more detailed epigenetic studies revealed that changes in histone modifications as a result of prior hyperglycemia also included changes in H3K9 methylation of the p65 promoter in addition to effects on various histone methyl transferases and interestingly also demethylases such as LSD-1 [45]. In-depth analysis of the elaborate epigenetic regulatory networks that are altered in diabetes and related metabolic syndromes has recently been reviewed [46].

Insulin resistance

Insulin resistance occurs in T2DM and in people with impaired glucose tolerance, and has been associated with increased cardiovascular risk [47–49]. There is now increasing evidence that insulin resistance promotes atherogenesis as an independent risk factor [50–52]. Furthermore, insulin resistance is often associated with a proatherogenic lipid profile that includes a high very low-density lipoprotein (VLDL) component, a low HDL and small dense LDL.

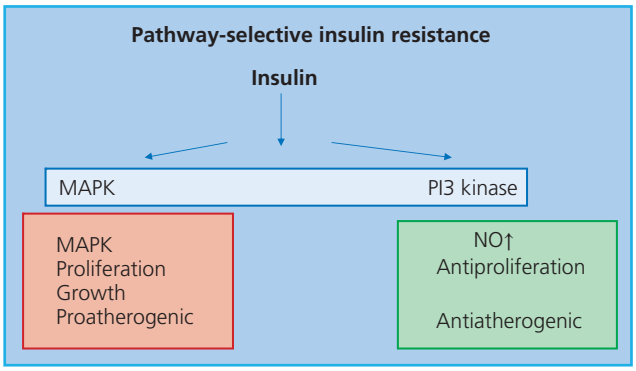

Figure 41.3 Pathway-selective insulin resistance leading to endothelial dysfunction and atherosclerosis. MAPK, mitogen-activated protein kinase; NO, nitric oxide; PI3 kinase, phosphatidylinositol 3 kinase.

In vitro studies have shown that insulin exerts both pro- and antiatherogenic effects [53, 54], which has led to the hypothesis of pathway-specific insulin resistance (Figure 41.3). It has been suggested that insulin resistance towards glucose transport also affects resistance to the antiproliferative effects of insulin, whereas the signaling pathways leading to cellular proliferation remain intact (Figure 41.3). Insulin signaling via phosphatidylinositol-3-kinase (PI3K) has been associated with antiproliferative and antithrombogenic effects with decreased adhesion molecule expression such as MCP-1, VCAM-1, and intercellular adhesion molecule 1 (ICAM-1). Furthermore, nitric oxide (NO) production is mediated via the PI3K signal transduction pathway and therefore is impaired in insulin resistance. NO has been shown to reduce oxLDL and proliferation of VSMCs. In contrast, effects on VSMC proliferation and migration are mediated via the Ras/Raf/MEKK/MAPK signal transduction pathway, which is further stimulated in the context of hyperinsulinemia, suggesting that pathway-specific insulin resistance contributes to the proatherogenic effects of insulin. More recently, it has been shown that IL-6 decreases insulin-stimulated NO production from endothelial cells via decreased activity of insulin signaling mediated by enhanced TNF-α production [55]. Paradoxically, IL-6 increases insulin-stimulated glucose uptake into skeletal muscle and adipose tissue via enhanced insulin signaling, yet IL-6 and insulin have not been linked to increased TNF-α expression in skeletal muscle [55].

Formation of AGE

AGE formation originates from early glycation products, the Schiff bases, which form the more stable Amadori products such as 1-amino-1-deoxyfructose derivatives. The Amadori products undergo further enzymatic modifications resulting in a number of reactive intermediates such as 3-deoxyglucosone and methylglyoxal (Figure 41.2). Methylglyoxal reacts with amino, sulfhydryl and guanidine functional groups in proteins, causing browning, denaturation, and redox-active diamine cross-linking

between lysine residues of the target amino acids. Methylglyoxal also generates hydroimidazolones, N^{ε}- (carboxyethyl)lysine, a homolog of carboxymethyllysine (CML) and methylglyoxal–lysine dimer [56, 57]. The AGE-based cross-links are resistant to enzymatic degradation and therefore very stable [58]. The rate of AGE formation is dependent on multiple factors, including the ambient concentrations of various sugars including glucose, the extent of oxidative stress, and the duration of exposure to these various stimuli [59, 60].

More recently, research has been focused not only on AGE modifications on cellular and short-lived extracellular proteins, lipids, and DNA, but also on the impact of key intermediates including the highly reactive dicarbonylmethylglyoxal [34, 61]. Methylglyoxal (MGO) is 20,000 times more reactive with proteins than glucose itself. The formation of MGO may correlate better with glucose fluctuations observed in diabetes and may explain why postprandial glucose concentrations are independent risk factors for CVD [62]. Impaired glucose metabolism and T2DM have been shown to correlate with higher plasma MGO levels. Furthermore, there is evidence that MGO-derived AGEs are associated with increased risk of CV events in people with T2DM [63].

The detoxifying enzyme glyoxalase-1 (GLO-1), which reduces MGO accumulation, has also been suggested to play a key role in diabetic vascular disease [63]. It is downregulated in diabetes and other states of inflammation, hypoxia, and aging. Genomic studies have shown GLO-1 as the molecular mechanism in the development of CVD [64, 65].

Direct effects of vascular AGE accumulation

There is evidence from experimental studies that AGEs directly influence endothelial function [66] in addition to enhancing the evolution of macrovascular disease [67, 68]. AGEs mediate their effects both directly and via receptor-mediated mechanisms. AGE accumulation in the vascular wall is associated with changes in the structural integrity of proteins, disturbance of their cellular function, and degradation of these proteins [35]. AGEs accumulate on many proteins, including collagen, albumin, and apolipoproteins. Furthermore, the cross-linking of AGEs with matrix molecules can disrupt matrix–matrix and matrix–cell interactions. It has been shown that AGE cross-linking to collagens decreases vascular elasticity and reduces vascular compliance, resulting in increased vascular stiffness [69, 70]. In addition, AGEs are also able to quench NO [66, 71] and generate ROS by stimulating nicotinamide adenine dinucleotide phosphate (NADPH) oxidase activity [72].

AGE-binding proteins

The receptor-mediated effects of AGEs occur via binding to proteins such as RAGE [73], AGE-R1 (p60), AGE-R2 (p90), and AGE-R3 (galectin-3), the ezrin–radixin–moesin (ERM) family of proteins [74], macrophage scavenger receptor ScR-11, and CD-36 [75]. The exact roles of AGE-R1, -R2, and -R3 have not been fully elucidated. Finally, the interaction between AGEs and several macrophage scavenger receptors, such as CD36 [75], has been postulated also to promote atherosclerosis with studies using CD36 KO mice, supporting the view that CD36 promotes atherosclerosis [76].

Receptor for AGE (RAGE)

RAGE is a multiligand signal transduction receptor of the immunoglobulin superfamily of cell surface molecules that acts as a pattern recognition receptor [73]. In addition to binding ligands that actively participate in inflammation and immune responses, RAGE serves as an endothelial adhesion receptor for leukocyte integrins and promotes leukocyte recruitment and extravasation of infiltrating cells. Of direct relevance to diabetic macrovascular complications, RAGE is found on endothelial cells and monocytes–macrophages [68, 77, 78], and has been implicated in inflammatory lesions in many disorders [79].

Downstream effects of RAGE activation

Engagement of RAGE leads to activation of the proinflammatory transcription factor NFκB (Figure 41.4) [80]. AGE binding to RAGE activates various signaling pathways, including NADPH oxidase [72], MAPKs, $p21^{ras}$ [81], extracellular signal-regulated kinases (ERKs) [82], and PKC, causing activation and translocation of NFκB [80]. Furthermore, expression of RAGE

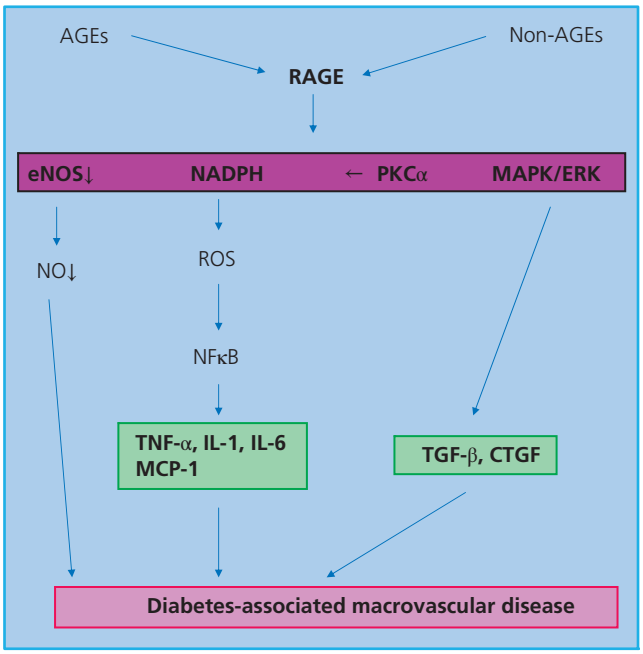

Figure 41.4 Activation of AGE receptor (RAGE) contributes to diabetes-associated macrovascular disease via increased production of reactive oxygen species (ROS), decrease in nitric oxide (NO) availability, activation of the nuclear transcription factor κB (NFκB), and tumor necrosis factor α (TNF-α), in addition to activation of profibrotic growth factors such as transforming growth factor β (TGF-β) and connective tissue growth factor (CTGF) associated with vascular remodeling. eNOS, endothelial nitric oxide synthase; ERK, extracellular signal-regulated kinase; MAPK, mitogen-activated protein kinase; MCP, monocyte chemotactic protein; NADPH, nicotinamide adenine dinucleotide phosphate; PKC, protein kinase C.

itself can be induced by NFκB [83]. RAGE expression within tissues is markedly enhanced in response to metabolic disturbances such as diabetes, dyslipidemia, uremia, and aging, possibly because of accumulation of AGEs in these conditions [77, 79]. In plaques from diabetic ApoE KO mice, upregulation of connective tissue growth factor (CTGF) has been demonstrated to be AGE dependent [67] and may be mediated via RAGE. Intracellular accumulation of AGEs may also promote phenotypic conversion of VSMCs into foam cells within atherosclerotic plaques [84].

Studies reducing vascular AGE accumulation

A variety of pharmacological interventions have been used to reduce the accumulation of AGEs via decreasing the total AGE load or via chemical modification of existing AGEs into inactive forms [85, 86]. Aminoguanidine is a potent inhibitor of the formation of AGEs, scavenges reactive dicarbonyl AGE precursors [85, 86], and decreases oxidative damage to mitochondrial proteins [87]. In experimental and clinical diabetes, aminoguanidine treatment has been shown to reduce microvascular [88] and more recently macrovascular complications in a model of accelerated atherosclerosis, the diabetic ApoE KO mouse [67].

Another potential agent that inhibits AGE accumulation is ALT-711 or alagebrium [89]. Based initially on a range of *in vitro* studies, this thiazolium compound and its original prototype, phenylthiazolium bromide [90], have been shown to cleave preformed AGEs, hence one of the postulated mechanisms of ALT-711 is as an AGE cross-link breaker [89].

The removal of established cross-links in rats with diabetes by ALT-711 has been shown to be associated with reversal of the diabetes-induced increase in large artery stiffness, increased collagen solubility, and reduced vascular and cardiac AGE accumulation [70, 91–93]. In addition, alagebrium prevents the progression of nephropathy [94, 95], possibly via direct inhibition of PKC-α phosphorylation [96], thus reducing renal expression of vascular endothelial growth factor (VEGF). Treatment with ALT-711 in diabetic ApoE KO mice was associated with a significant reduction in atherosclerosis [67]. This antiatherosclerotic effect was associated with reduced vascular AGE accumulation and RAGE expression. Alagebrium treatment was also associated with less inflammation and reduced expression of profibrotic growth factors, in particular CTGF [97, 98]. In the clinical setting, ALT-711 has been shown to reduce pulse pressure and improve vascular compliance in people with systolic hypertension [70].

Soluble RAGE

There are three major splice variants of RAGE [99]: first, the full-length RAGE receptor; second, the N-terminal variant that does not contain the AGE-binding domain; and third, a C-terminal splice variant, soluble RAGE (sRAGE), which does not contain the trans-membrane and effector domains. It remains controversial as to whether the effects of sRAGE are primarily as a decoy to ligands such as AGEs or whether sRAGE acts as a competitive antagonist to the full-length biologically active RAGE [99, 100].

Soluble RAGE and diabetes-associated atherosclerosis

sRAGE has been identified as having therapeutic value in a model of diabetes-associated atherosclerosis, the streptozotocin diabetic ApoE KO mouse [101, 102]. In the original study, Park et al. [102] reported that diabetic ApoE KO mice treated with sRAGE showed a dose-dependent suppression of atherosclerosis and reduced plaque complexity. These beneficial effects were independent of effects on glucose or lipid levels. Furthermore, AGE levels in these diabetic mice were suppressed in a dose-dependent manner by sRAGE to levels similar to those seen in non-diabetic mice. Furthermore, the effect of RAGE blockade with sRAGE was investigated in established atherosclerosis [101]. Administration of sRAGE decreased the expression of RAGE, in addition to reducing the number of infiltrating inflammatory cells and gene expression for transforming growth factor β (TGF-β), fibronectin, and type IV collagen in both the aorta and the kidney in association with reduced plaque area. Therefore, it was concluded by these investigators that RAGE activation contributes not only to lesion formation, but also to the progression of atherosclerosis.

sRAGE treatment has also been reported to be effective in reducing vascular complications in other models of atherosclerosis and diabetes. Atherosclerosis in the LDL receptor –/– mouse made diabetic by streptozotocin injection [103] was significantly attenuated by sRAGE treatment. ApoE KO mice bred onto a *db*/*db* background, a model of T2DM and deficient leptin receptor signaling, showed increased atherosclerosis that was significantly attenuated by daily sRAGE treatment [104].

To understand better the specific role of RAGE in the genesis of vascular lesions, mice selectively deficient in RAGE/ApoE ($RAGE^{-/-}$) have been created [105, 106]. These mice completely lack not only tissue bound full-length RAGE, but also sRAGE. As had been predicted by the pharmacological intervention studies directed towards the RAGE ligands and AGEs, RAGE KO mice bred onto an $ApoE^{-/-}$ background showed a marked reduction in plaque area in the presence and absence of diabetes [105, 106]. More recently, the effect of RAGE deletion on atherosclerosis development has been investigated in streptozotocin diabetic RAGE/ApoE KO mice and showed a significant reduction in atherosclerotic plaque area compared with diabetic ApoE KO mice expressing RAGE. These vascular changes seen in the streptozotocin diabetic double RAGE/ApoE KO mice were associated with reduced inflammation, less accumulation of RAGE ligands such as S100/CML, decreased infiltration by macrophages and T lymphocytes, and a reduction in expression of profibrotic and proinflammatory growth factors and cytokines [105].

These promising results with RAGE antagonism have encouraged the development of RAGE-neutralizing compounds for clinical use. The RAGE-modulating agent TTP488 is currently being considered in phase II clinical trials in people with Alzheimer disease, with some positive results [107]. Another compound, TTP4000, is in phase I clinical trials (www.clinicaltrials.gov and www.vtvtherapeutics.com); however, currently, the major focus of antagonizing RAGE does not appear to involve studies addressing CVD in the absence or presence of diabetes.

Interaction with the renin–angiotensin system

Because diabetic complications appear to be multifactorial in origin and involve interactions between hemodynamic pathways such as the RAS and metabolic pathways such as hyperglycemia and the formation of AGEs, there has been increasing investigation of the potential links between these various pathways (Figure 41.1) [108]. There is increasing evidence that AGE accumulation can induce an upregulation of certain components of the RAS, although these studies have been performed predominantly in the renal context [109]. Furthermore, angiotensin-converting enzyme (ACE) inhibition has been reported to confer its end-organ protective effect partly via a reduction in AGEs and an increase in sRAGE [110]. Therefore, the status of the RAS could represent a key modulator in AGE-induced diseases. More recently, other therapeutic interventions shown to be antiatherosclerotic have been reported to exert part of their vasculoprotective effect via inhibition of the AGE/RAGE pathway. These include angiotensin II receptor blockers (ARBs), peroxisome proliferator-activated receptor α (PPAR-α), and PPAR-γ agonists and statins [111–113].

Role of vasoactive hormones in diabetes-related atherosclerosis

Classic RAS

Renin was described more than 100 years ago by Tigerstedt and Bergman [114]. Nevertheless, our understanding of the RAS is still not complete and has grown increasingly complex over the last decade. The classic pathway is now very well characterized (Figure 41.5). The generation of angiotensin (AT) I and II is not restricted to the systemic circulation and also takes place in vascular and other tissues (Figure 41.5) [115].

Novel aspects of the RAS: ACE2

In 2000, a further enzyme associated with the generation of AT peptides was identified—ACE2, a carboxypeptidase with sequence similarity to ACE [116]. ACE2 does not generate AT II but increases the formation of AT-(1–7) (Figure 41.6). This heptapeptide causes vasodilation and has growth inhibitory effects [117]. Further research, including into specific inhibitors, is needed to elucidate the many functions of ACE2 inside and outside the RAS.

AT receptors

The effects of all AT peptides are mediated through specific cell surface receptors (Figures 41.5 and 41.6). The AT_1 receptor mediates most of the effects usually associated with AT II. The role of the AT_2 receptor subtype remains controversial, but it appears to antagonize certain effects of AT II mediated via the AT_1 receptor [118]. Its role in the macrovasculature remains controversial [119].

Role of the RAS in macrovascular disease

It is now recognized that local RAS activation has an important role in the pathogenesis of diabetes-induced endothelial dysfunction and atherosclerosis [120–122]. As a result, there is a strong rationale for blockade of the RAS to prevent cardiovascular events in individuals with diabetes. In addition, several clinical trials [123–128] have suggested that blockade of the RAS may protect against the development of T2DM in at-risk persons.

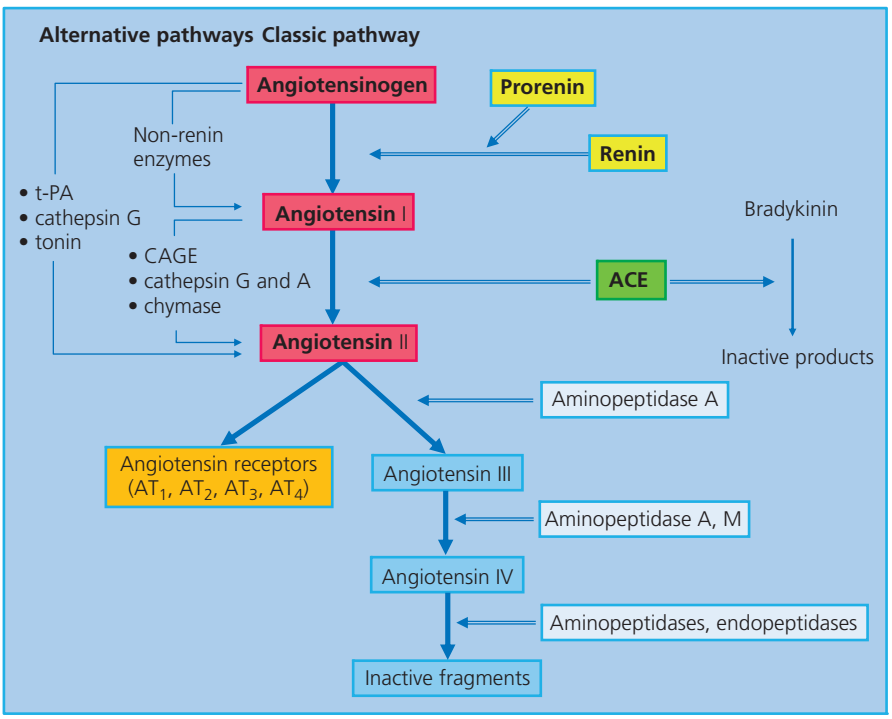

Figure 41.5 Overview of the enzymatic cascade of the renin–angiotensin system (RAS): classic and alternative pathways. In the classic pathway, renin cleaves the decapeptide angiotensin I from angiotensinogen. Angiotensin I is then converted to angiotensin II, which acts through several receptor subtypes, AT_1 and AT_2 receptors being the more relevant in the vasculature. CAGE, chymostatin-sensitive angiotensin II-generated enzyme; t-PA, tissue plasminogen activator.

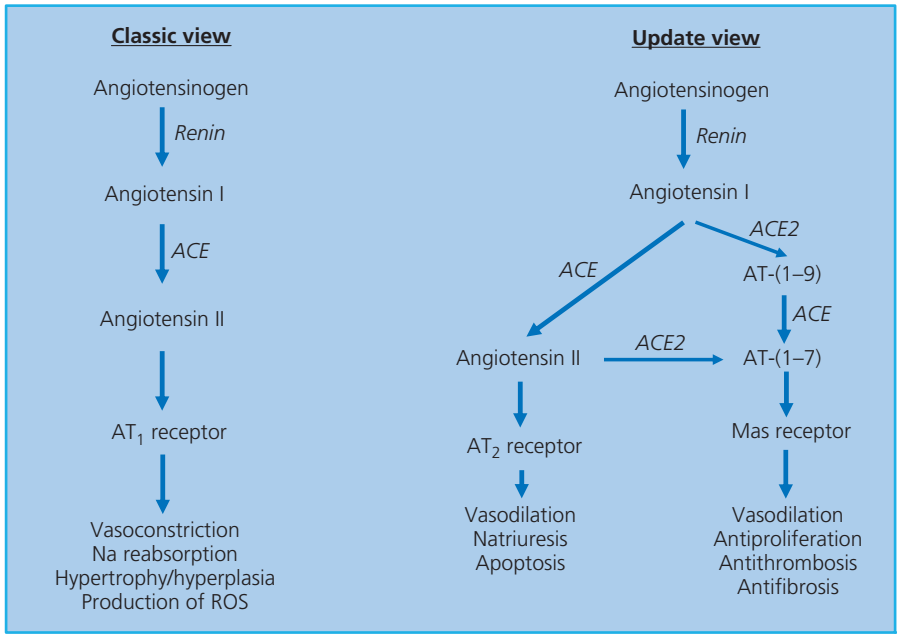

Figure 41.6 New aspects of the renin angiotensin system (RAS) components and its interactions. The classic RAS illustrates the main pathway for angiotensin II (AT II) generation from angiotensin I (AT I) via ACE, with effects being mediated via AT_1 receptor. The updated view illustrates the new components of the RAS in which ACE2 has a role to degrade AT I to AT-(1–9), and AT II to the vasodilator AT-(1–7), which acts through the Mas receptor.

RAS activation and endothelial dysfunction

Endothelial dysfunction has been considered as an imbalance between vasoconstrictors and vasodilators in the vascular tone [129] associated with a decrease in NO activity and increased AT II and ET activity [130]. Endothelial dysfunction is characterized by defective endothelium-dependent vasorelaxation in association with inflammatory cytokine-induced increased interactions with blood leukocytes, in which adhesion molecules such as VCAM-1 and chemoattractants such as MCP-1 are essential [131]. Endothelial dysfunction is strongly associated with atherosclerosis (Figure 41.7) [132, 133].

Crucial to the pathogenesis of diabetes-induced endothelial dysfunction in the early stages, in the absence of structural changes of the vessel wall, is the activation of the RAS. Although measurements of components of the RAS in plasma have, in general, suggested suppression of this system in diabetes, there is increasing evidence for activation of the local cardiovascular RAS in the diabetic context [134, 135]. It has been demonstrated that

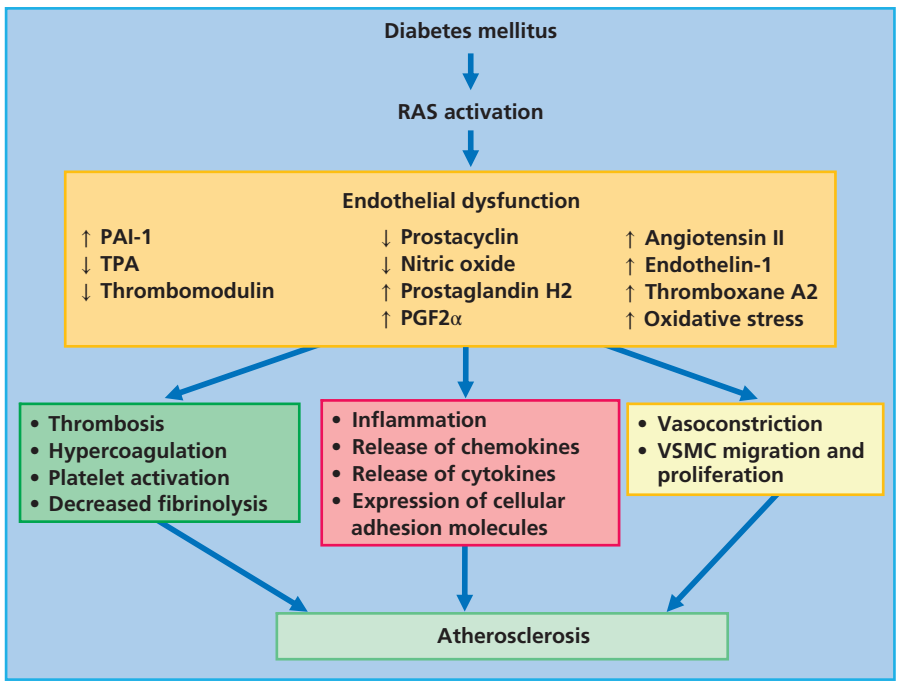

Figure 41.7 Effects of diabetes-induced renin–angiotensin system (RAS) activation on mechanisms associated with endothelial dysfunction and atherosclerosis. In diabetes, activation of RAS induces endothelial dysfunction that is characterized by vasoconstriction, inflammation, cellular growth, and thrombosis. By losing its protective properties, dysfunctional endothelium is a major promoter of atherogenesis and, consequently, cardiovascular events. PAI-1, plasminogen activator inhibitor-1; TPA, tissue plasminogen activator; VSMC, vascular smooth muscle cell.

there is an increase in ACE expression and activity, in AT II expression, and in AT_1 receptor expression in the aortic wall of diabetic ApoE KO mice, suggesting a key role for RAS activation in the pathogenesis of diabetes-associated endothelial dysfunction [120, 136].

RAS and regenerative endothelial cell repair

A role for the RAS has also been demonstrated in affecting the number of regenerative endothelial progenitor cells in individuals with diabetes. An increased concentration of circulating endothelial progenitor cells, which are believed to maintain the integrity of the vascular endothelium, has been associated with a favorable cardiovascular outcome in persons with CAD [137]. A study in individuals with T2DM [138] suggested that treatment with an ARB (olmesartan) increases the number of regenerative endothelial progenitor cells, which could contribute to the beneficial cardiovascular effects seen with AT_1 receptor blockade.

Role of AT-(1–7) and ACE2 in endothelial dysfunction

It has been hypothesized that disruption of the ACE–ACE2 balance may result in abnormal blood pressure, with increased ACE2 expression protecting against hypertension, and ACE2 deficiency causing hypertension (Figure 41.6) [139]. As reported above, it is well established that AT II produces endothelial dysfunction through different pathways, such as increasing oxidative stress and exerting proliferative and prothrombotic activities [140]. It has been observed that AT-(1–7), which is generated by the enzyme ACE2, promotes the release of NO and prostaglandins [141, 142] and potentiates bradykinin effects in different experimental models [141, 143]. In addition, AT-(1–7) inhibits growth of VSMCs [144], platelet aggregation and thrombosis [145], inflammation, fibrosis [146], and oxidative stress [147], which in turn might lead to restoration of endothelial function. It appears that AT-(1–7) can antagonize AT II effects, not only by the stimulation of other vasodilators but also through AT_1 receptor inhibition. In this regard, Kostenis et al. [148] reported that the Mas receptor, which is increasingly considered to be the major receptor conferring the biological effects of AT-(1–7), seems to act as a physiological antagonist of AT_1 receptor, thus counteracting many of the actions of AT II at the endothelial level.

RAS activation and atherosclerosis

Clinical and experimental evidence clearly indicates that activation of the RAS is central to almost all these proatherosclerotic pathways (Figure 41.7) [122, 149]. Diet et al. [121] observed increased ACE protein accumulation within the atherosclerotic plaque in human coronary arteries, suggesting that ACE may contribute to an increased production of local AT II, which may participate in the pathophysiology of artery disease. In addition, there is evidence that AT II and the AT_1 receptor are overexpressed in atherosclerotic plaques [120, 150, 151]. Indeed, blockade of the RAS with an ACE inhibitor or an AT_1 receptor antagonist prevents atherosclerosis by mechanisms involving inhibition of proinflammatory molecules such as VCAM-1 and MCP-1 and prosclerotic and proproliferative cytokines such as CTGF and platelet-derived growth factor. These observations confirm a key role for RAS activation in the development and progression of atherosclerosis.

Production of proinflammatory cytokines, such as IL-1β, TNF-α, and IL-6, have a major role in the pathogenesis of atherosclerosis [152]. IL-6, ACE, and AT_1 receptors have been detected in stable and unstable atherosclerotic plaques [151, 153]. AT II stimulates the redox-sensitive nuclear transcription factor, NFκB, which could serve as a unifying signaling system for inflammatory stimuli in atherogenesis through enhanced expression of adhesion molecules ICAM-1 and VCAM-1, E-selectin, MCP-1, and IL-8. Several clinical and experimental studies have demonstrated that both ACE inhibitors and AT_1 receptor blockers decrease the expression of several adhesion molecules, thus confirming that the chronic inflammatory response associated with atherosclerosis appears to be modulated by AT II at every level and can be targeted therapeutically by RAS inhibition [122, 135, 154].

Moreover, the sustained proinflammatory state seems to play an important part in the transformation of a stable atherosclerotic plaque into a vulnerable plaque prone to rupture. Plaque rupture has been connected with activation of matrix metalloproteinases in the fibrous cap of the atherosclerotic lesion [155], and there is evidence that AT II is implicated in matrix metalloproteinase activation, both through a direct action and through induction of proinflammatory cytokines such as IL-6.

ACE2 and diabetes accelerated atherosclerosis

Although studies on the expression and activity of ACE2 in atherosclerosis are limited, there is increasing evidence that such more recently identified components of the RAS may be involved in the development and progression of atherosclerosis. Zulli et al. [156] have shown very high expression of ACE2 in endothelial cells, macrophages, and α-smooth muscle cells within atherosclerotic plaques in a rabbit model of atherosclerosis. It is not clear whether this increase in ACE2 is in response to injury in an attempt to protect the vessel by increasing levels of AT-(1–7).

In the human context, there is evidence for a significant activation of the cardiac RAS after coronary artery occlusion, and it is well known that RAS blockade reduces remodeling and improves survival in humans after an MI. It has also been reported [157] that cardiac ACE2 expression and activity are also increased with experimental MI. Studies using ACE2 KO mice crossed with the atherosclerosis prone $ApoE^{-/-}$ mouse have shown that ACE2 KO mice develop a similar degree of atherosclerosis to diabetic $ApoE^{-/-}$ mice with a concomitant activation of inflammatory markers [158]. The induction of streptozocin diabetes in ACE2/ApoE KO mice was not associated with a further increase in plaque area, suggesting that the downregulation of ACE2 in diabetes plays a key role in the development of atherosclerosis [159]. All these observations suggest that an imbalance in the RAS plays a central role in the pathogenesis of atherosclerosis and that the preservation and augmentation of ACE2 expression and activity represents a potential therapeutic target for the prevention of CVD in diabetes.

RAS and oxidative stress

There is increasing evidence that the local production of ROS has a pivotal role in atherosclerosis, specifically in the diabetic milieu. Increased vascular superoxide production in aortas from diabetic atherosclerotic ApoE KO mice has been demonstrated [111]. These changes were mediated by increased NAD(P)H oxidase (Nox) activity in the aorta with increased expression of various Nox subunits including p47phox, gp91phox, and rac-1 [111]. Evidence of increased local vascular ROS generation in diabetes is further supported by the demonstration of increased nitrotyrosine staining in these diabetic plaques. Indeed, interventions that reduce vascular superoxide production such as PPAR-α and PPAR-γ agonists have been associated with reduced plaque formation, further emphasizing the link between vascular oxidative stress and atherosclerosis [111, 160]. Furthermore, the deletion of antioxidant enzymes such as glutathione peroxidase, specifically the Gpx1 isoform in the vascular wall, results in an increase in plaque area particularly in the diabetic context via increases in inflammatory mediators including adhesion molecules and chemokines [161]. More recently, it has been shown that treatment of GPx1-deficient mice with the Gpx1 analog ebselen reduced oxidative stress variables and atherosclerosis in diabetic GPx1/ApoE KO mice [162]. Furthermore, in the Gpx1/Apo E double KO mice, there was associated upregulation of RAGE, further linking vascular RAGE expression to increased oxidative stress and accelerated atherosclerosis in settings such as diabetes [161].

Therapeutic implications

RAS blockade and endothelial dysfunction

As a result of previous observations, RAS blockade has emerged as an obvious and attractive therapeutic target. Early evidence for a clinical beneficial effect of inhibition of this system on impaired endothelial function was derived from the Trial on Reversing Endothelial Dysfunction (TREND) [163], which showed that ACE inhibition improves endothelial function in people with CAD. Moreover, O'Driscoll et al. [164] observed that ACE inhibition with enalapril improved both basal and stimulated NO-dependent endothelial function in normotensive people with T2DM.

Data are also available for the role of ARBs in improving endothelial function such as the AT_1 receptor antagonist losartan [165, 166]. Furthermore, in people with T1DM, treatment with the ACE inhibitor ramipril or the ARB losartan for 3 weeks [167] improved endothelial dysfunction potentially mediated by increased bradykinin levels with ACE inhibition or increased levels of AT-(1–7) levels.

RAS inhibition and cardiovascular protection

There is accumulative evidence that pharmacological therapy that interrupts the RAS may afford special benefits in reducing CVD in people with diabetes [125, 168, 169]. In a post hoc subgroup analysis of the Captopril Prevention Project (CAPP) study, the participants with diabetes treated with captopril fared significantly better than those treated with conventional therapy (β-blockers and diuretics) in terms of primary endpoint and also for MI, all cardiac events, and total mortality [169]. These relative beneficial effects of ACE inhibitor therapy were particularly striking in those at highest risk, specifically those with the highest median fasting glucose or those with more elevated blood pressure. This is in contrast to the UKPDS [170], in which there were comparable CVD benefits for people with T2DM who were randomized to captopril or atenolol, perhaps reflecting a lower CVD risk in the newly diagnosed individuals with diabetes studied in the UKPDS.

In a substudy of the Hypertensive Old People in Edinburgh (HOPE) study, the MICRO-HOPE [171], which included 3577 individuals who had diabetes and one other CVD risk factor, there was a risk reduction of 25% for combined CVD events, 37% for CVD mortality, 22% for MI, and 33% for stroke. In the Fosinopril versus Amlodipine Cardiovascular Events Trial (FACET) study, the incidence of CVD events was less in participants with T2DM and hypertension treated with fosinopril than the amlodipine-treated group [172]. The European Trial on Reduction of Cardiac Events with Perindopril in Stable Coronary Artery Disease (EUROPA) [173] showed that ACE inhibition reduced cardiovascular mortality and morbidity in participants with established CAD without left ventricular dysfunction. The data from these trials were pooled with those of the Quinapril Ischemic Event Trial (QUIET) [174] study in a meta-analysis that included a total of 31,555 participants [175]. This analysis showed that, compared with placebo, ACE inhibitor therapy produced a significant 14% reduction in all-cause mortality and MI, a 23% reduction in stroke, and a 7% statistically significant reduction in revascularization procedures. The ADVANCE study [23] showed that the administration of the ACE inhibitor perindopril and the diuretic indapamide in high-risk people with T2DM induced a reduction in macrovascular outcome compared with placebo.

Reports of trials with ARBs indicate that these agents have CVD protection effects in individuals with T2DM similar to those observed with ACE inhibitors. In the Losartan Intervention For Endpoint reduction in hypertension (LIFE) study [125], treatment with losartan in people with T2DM and left ventricular hypertrophy (LVH) resulted in a significant reduction in death from CVD and in particular all-cause mortality. An analysis of the large Reduction of Endpoints in NIDDM with Angiotensin II Antagonist Losartan (RENAAL) study showed that treatment with losartan in participants with T2DM, nephropathy and LVH reduced the cardiovascular risk to levels similar to those observed in individuals without LVH [176]. The Ongoing Telmisartan Alone and in combination with Ramipril Global Endpoint Trial (ONTARGET) showed that the ARB telmisartan provides a benefit similar to that of a proven ACE inhibitor such as ramipril in high-risk people with CVD or those with diabetes who have end-organ damage. This is a population similar to that examined previously in the HOPE study [177]. Furthermore, in the ONTARGET study, the combination of ramipril with telmisartan, despite the further lowering of blood pressure, did not reduce the

risk of cardiovascular events compared with an ACE inhibitor alone, but was associated with additional adverse effects including hypotension and renal dysfunction. Hence an ACE inhibitor, or possibly an ARB, is an initial antihypertensive agent of choice in people with diabetes because these agents have been shown to have the capacity to prevent or retard the development of diabetic macrovascular complications, thus significantly reducing cardiovascular mortality and morbidity.

The endothelin system

Endothelin (ET) was first discovered in 1988 by Yanagisawa et al. [178] and is one of the most potent vasoconstrictors known. There are three distinct ET genes that encode different mature ET sequences, designated ET-1, ET-2, and ET-3. Big ET-1 is converted into mature 21 amino acid ET-1 by ET-converting enzyme. ET-1 is predominantly present in endothelial cells. In 1990, the ET_A and ET_B receptor subtypes [179] were cloned. ET_A receptors are found in VSMCs and mediate vasoconstriction and cell proliferation (Figure 41.8). ET_B receptors are found in endothelial cells (ET_{B1}), where they mediate vasodilation via the release of NO, and on smooth muscle cells, where they may elicit vessel contraction and cell proliferation (Figure 41.8).

Role of ET in diabetic macrovascular complications

Plasma concentrations of ET-1 are increased in people with T2DM complicated with atherosclerosis compared with those without diabetes with atherosclerosis and healthy individuals [180]. Kalogeropoulou et al. [181] demonstrated increased ET-1 levels in people with diabetes and carotid atherosclerosis. ET stimulates the production and release of inflammatory cytokines from monocytes [182] and enhances the uptake of LDL-cholesterol by these cells, promoting a phenotypic change into foam cells [183]. Cytokines released from monocytes–macrophages, in turn, stimulate ET-1 production, providing positive feedback for further cytokine production [184].

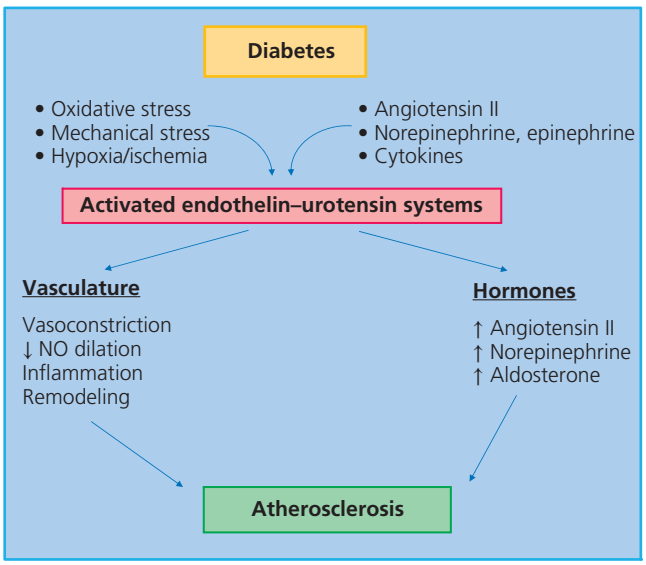

Figure 41.8 Proposed mechanisms of the endothelin and urotensin systems on atherosclerosis in diabetes. In diabetes, activation of the endothelin system induces vasoconstriction, vascular smooth muscle cell proliferation, wall thickening, inflammation, and tissue remodeling, thus leading to the development and progression of atherosclerosis.

In several animal models, both ET_A receptor-selective and non-selective ET_A/ET_B receptor blockade have been shown to inhibit the development of atherosclerotic lesions, suggesting that elevated vascular ET-1 tissue levels promote endothelial dysfunction and vascular structural alterations via the activation of ET_A receptors [183, 185]. Treatment with an ET_A receptor antagonist decreased the atherosclerotic lesion area in the aorta in ApoE KO mice [11]. Similar results have been reported with a non-selective ET_A/ET_B receptor blocker in rabbits. The role of the ET_B receptor in atherosclerosis remains controversial at this stage, although it has been shown to have antiatherosclerotic effects via stimulation of NO production [186].

Finally, some of the beneficial effects of ACE inhibitors in term of cardiovascular protection may be mediated at least in part by ET inhibition. Captopril inhibits the release of ET from cultured human endothelial cells and decreases 24-h urinary ET-1 excretion [187, 188]. Furthermore, ET_A receptor antagonism appears to be beneficial in the treatment of diabetic nephropathy, but there are currently no data to support a protective effect on macrovascular disease in people with diabetes. More recently, ET receptor antagonists have been trialed in T2DM nephropathy. A study using avosentan had to be terminated prematurely owing to off-target effects leading to fluid retention, heart failure, and CV mortality [189]. It is possible that the antidiuretic effect mediated by activation of the ET_B receptor is responsible for this effect. Newer and more ET_A receptor-selective endothelin blockers such as atrasentan have been evaluated and have demonstrated a reduction in the residual albuminuria in people with T2DM [190]. If these renoprotective effects will also translate into cardiovascular protection, as suggested in preclinical studies, it will need to be evaluated in long-term studies with predefined CV endpoints.

Urotensin II

Several reports have revealed the powerful vasocontractile effect of urotensin II (UT II) consistent with a potential importance of this peptide in cardiovascular physiology and diseases (Figure 41.8) [191]. A specific UT II receptor was identified in 1999 [192]. Elevated circulating concentrations of UT II have been detected in persons with various CVD states including heart failure, hypertension [193], carotid atherosclerosis, pre-eclampsia and eclampsia, renal dysfunction, and diabetes mellitus [194]. In addition, upregulation of the UT receptor system has been found in individuals with congestive heart failure and pulmonary hypertension [195].

Role of urotensin II in atherosclerosis

Expression of UT II is upregulated in endothelial, myointimal, and medial smooth muscle cells of atherosclerotic human coronary arteries. Bousette et al. [12] demonstrated that UT II expression is increased in both atherosclerotic carotid arteries and aortas. It has been shown that the plasma UT II level is correlated positively with carotid atherosclerosis in people with essential hypertension [196]. In ApoE KO mice, UT expression was significantly higher than in wild-type control mice [197]. Chronic infusion of UT II enhances atherosclerotic lesions in the aorta of ApoE KO mice by increasing ROS production and acyl-CoA–cholesterol acyl transferase 1 expression. UT II expression in endothelial cells and VSMCs is increased following balloon injury in rat carotid arteries [198]. Furthermore, treatment with a UT II receptor blocker was associated with a 60% reduction in intima lesion development.

UT II is linked to the activation of the redox-sensitive enzyme NADPH oxidase in the vascular wall and increased expression of inflammatory cytokines (Figure 41.8). In human peripheral blood mononuclear cells, inflammatory stimuli including IL-1β and TNF-α strongly enhance UT receptor mRNA and protein expression [199]. Of direct relevance to atherosclerosis, UT II has been shown, predominantly in *in vitro* studies, to enhance LDL-cholesterol and ROS production via NADPH oxidase and to promote monocyte recruitment.

Oxidative stress

Excessive production of ROS, in conjunction with dysfunctional antioxidant defense systems, shifts the redox state of the cellular environment in favor of oxidant species, a state termed "oxidative stress." Clinically, people with diabetes exhibit increased expression of various markers of oxidative stress [200, 201] and reduced antioxidant capacity [202, 203]. Despite a strong theoretical basis, clinical trials of antioxidant treatments for the lowering of cardiovascular disease burden have produced disappointing results [128, 204].

Role of reactive oxygen species in diabetes-accelerated atherosclerosis

Reactive ROS and its products can directly damage vascular endothelial cells leading to apoptosis [205], autophagy [206], and DNA damage [207,208]. Aberrant activation of redox-sensitive signaling molecules including protein kinases and transcription factors also plays a central part in diabetes-mediated vascular pathology [209]. Increased ROS production is associated with the induction of inflammatory gene expression, which occurs via upregulation of redox-sensitive inflammatory gene master regulator NFκB [210].

NADPH oxidase production of ROS

A number of enzymatic and non-enzymatic sources contribute to pathological increases in ROS generation in the diseased vasculature, including Nox, nitric oxide synthetase (NOS), myeloperoxidase (MPO) and xanthine oxidase (XO) [211]. However, the Nox enzymes are widely recognized as the major ROS producers in the vasculature [212] and also represent viable pharmacological targets for the treatment of diabetes-associated vascular disease [213].

The Nox isoforms Nox1, Nox2, Nox4, and Nox5 are differentially expressed in vascular cells, and play unique roles in physiology and disease [212, 214]. A number of groups, including our own, have demonstrated increased gene and protein expression of Nox1 and Nox4 in hyperglycemic conditions associated with increased atherosclerosis [67, 215–218]. Important roles for Nox1-derived superoxide have been described for AGE-mediated VSMC activation [219] and diabetes-associated endothelial dysfunction [220]. Recent evidence has identified a central role for Nox1 in accelerating atherosclerosis in the aorta of diabetic mice [218]. Controversy surrounds the role of Nox4 in vascular disease. Nox4 is constitutively expressed and produces predominantly hydrogen peroxide [214]. Its role in vascular disease appears to be dependent on the disease and experimental model under investigation. More recently, a vasculoprotective role for Nox4 has been demonstrated in a model of long-term diabetes-associated atherosclerosis [221]. Studies focusing on endothelial cell function following ischemia and angiotensin II stimulation have shown protective effects of Nox4 [222–224]. In contrast, Nox4-derived ROS have been shown to promote cardiac hypertrophy [225] and cardiovascular aging [226].

Nox5 is a calcium-dependent Nox isoform expressed in human endothelial and vascular smooth muscle cells [227] and also monocytes and macrophages [228]. The exact function of vascular Nox5 is not yet known, but it has been shown to affect endothelial nitric oxide synthase (eNOS) [229] and VSMC proliferation [230]. In macrophages, Nox5 expression and activity were induced by treatment with proinflammatory cytokine IFNγ [228], suggesting a link between Nox5 and inflammation. However, the lack of Nox5 in mice and rats has hindered investigations.

Inflammation and immune responses

There is an increasing body of evidence to support an altered immune response in diabetes-associated macrovascular disease [105, 231, 232]. In diabetes, elevated ROS upregulates the expression of proinflammatory genes that lead to foam cell formation [233]. Emerging links between Nox-derived ROS and innate-adaptive immune cell responses have provided insight into the potential immunomodulatory role of Nox in diabetes-associated atherosclerosis. Induction of Nox4 in human monocytes and macrophages has been shown to be required for oxLDL-stimulated ROS production and cytotoxicity [234]. Gray et al. also identified an important role for Nox1-derived ROS in monocyte adhesion and macrophage accumulation in the lesions of diabetic ApoE$^{-/-}$ mice [218]. More recently, we described an immunomodulatory role of Nox1- and Nox4-derived ROS in diabetes-associated atherosclerosis in the aortic sinus of ApoE$^{-/-}$ mice [235]. In humans, T cells isolated from atherosclerotic plaques have been shown to recognize and respond to oxLDL [236].

TNF-related apoptosis-inducing ligand and osteoprotegerin

TNF-related apoptosis inducing ligand (TRAIL) is a member of the TNF ligand family [237] and is expressed across all cell types of the vasculature, including macrophages of atherosclerotic plaques [238]. Both the membrane-bound and soluble forms of TRAIL rapidly induce apoptosis in multiple transformed cell lines and tumor cells, but not in normal cells [237, 239].

Osteoprotegerin (OPG) is a member of the TNF-receptor superfamily [240] that is produced by a variety of tissues, including the cardiovascular system. OPG has two known TNF family ligands: receptor activator of NFκB ligand (RANKL) [241] and TRAIL [242]. Increasing experimental evidence suggests that both TRAIL and OPG are involved in vascular pathophysiology.

The potential role of soluble recombinant (sr) TRAIL in the pathogenesis and/or treatment of diabetes-induced atherosclerosis has been investigated *in vivo* in streptozotocin diabetic ApoE KO mice [243]. Repeated intraperitoneal injections of srTRAIL significantly attenuated plaque development and contributed to the stabilization of atherosclerotic lesions by selectively decreasing the number of infiltrating macrophages and increasing the VSMCs within the atherosclerotic plaques [243]. Also, diabetic rats treated with srTRAIL had improved endothelial function and suppressed ROS generation [244]. Knockdown of Nox4 in VSMCs significantly reduced TRAIL-induced activity of the NFκB reporter gene and ICAM expression [245]. The potential clinical relevance of these results was corroborated by animal-based studies, which identified that TRAIL can be regulated by insulin levels and may be involved in regulating vascular tone [246], and two studies in people with acute coronary syndrome, revealing significantly lower srTRAIL serum levels in these individuals compared with those with stable angina or normal coronary arteries [247, 248]. Furthermore, individuals with untreated diabetes had lower concentrations of circulating TRAIL than healthy people in association with reduced flow-mediated endothelium-dependent arterial dilation (FMD). Diabetes treatment resulted in an increase in TRAIL concentrations and an improvement in FMD, but still lower than those without diabetes [249].

OPG-deficient mice demonstrated calcifications of the aorta and renal arteries [250], suggesting that OPG might have a role in protecting against vascular calcification. Interestingly, a study in elderly women found a significant correlation between elevated OPG serum levels and cardiovascular mortality [251]. The potential links between OPG and vascular disease in humans have been further supported by the detection of a single nucleotide polymorphism in the promoter region of the human gene for OPG related to vascular morphology and function [252]. Several independent studies have reported elevated serum and/or plasma OPG levels in people with diabetes, and in particular in people with diabetes and vascular complications [253–256]. Although some authors have proposed that the increase in OPG levels may represent a defense mechanism against other factors that promote vascular pathologies, other studies support a proatherosclerotic role for OPG in the vasculature [257].

Complement activation

The complement system consists of ~30 proteins that provide an important component of the innate immune system. The complement system is activated through three different pathways: the classic, the alternative and the mannose-binding lectin (MBL) complement pathway, respectively. These three pathways merge and stimulate the formation of a C3 convertase (Figure 41.9).

An increasing amount of evidence indicates that complement system activation may have a role in the development of diabetic macrovascular complications [16], in particular the MBL pathway as the initiating pathway of complement activation in people with diabetes [16]. Individuals with T1DM with nephropathy and CVD have significantly higher circulating levels of MBL than people with normoalbuminuria [258]. Furthermore, there is evidence that MBL levels may have prognostic relevance in people with diabetes. Several observations have suggested that MBL may be involved in the pathogenesis of microvascular and macrovascular complications in T1DM and that determination of MBL status might be useful in identifying individuals at increased risk of developing these complications [258, 259]. High levels of MBL early in the course of T1DM are significantly associated with later development of persistent microalbuminuria and macroalbuminuria [260]. In addition, in persons with T2DM, measurement of MBL has been shown to provide prognostic information on mortality and development of microalbuminuria [261]. The mechanism responsible for this potential activation of the complement system in individuals with diabetes is still

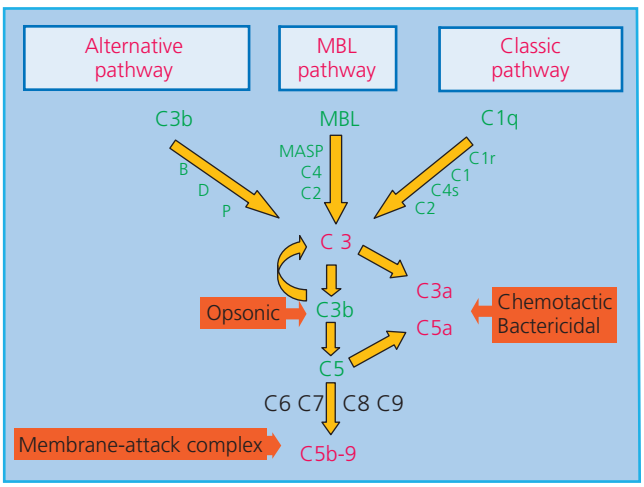

Figure 41.9 Schematic representation of the complement system. The complement cascade is activated by either of the three pathways: the classic, the mannose-binding lectin (MBL) pathway, or the alternative pathway. Activation leads to formation of the membrane-attack complex and also formation of opsonic, chemotactic, and bactericidal factors.

unknown. It has been hypothesized that hyperglycemia in people with diabetes may activate the complement system via mitochondrial ROS production or enhanced RAGE activation.

Clinical studies using pexelizumab, an inhibitor of C5, have recently demonstrated a significant reduction in mortality following acute MI in addition to reductions in the incidence of death or MI in people after coronary artery bypass graft surgery [262]. Further studies are needed to determine in particular if manipulation of the complement system may represent a promising target in the treatment and prevention of diabetes-associated macrovascular disease.

Interventions to reduce diabetes-associated macrovascular complications

A range of interventions have been proposed for reducing the macrovascular complications of diabetes, including lifestyle modification, weight reduction, dietary changes, and regular exercise.

Glucose control

Optimal glucose control is pivotal for the prevention and treatment of microvascular complications of diabetes; however, based on clinical trials [25, 26], the evidence for beneficial effects on macrovascular outcomes is less clear. Nevertheless, it has been suggested to aim for $HbA_{1c} < 7\%$ (53 mmol/mol), but to be more cautious in those with underlying and pre-existing CVD. Recently, a range of novel glucose-lowering interventions have entered the clinic arena, including DPP-4 inhibitors, GLP-1 receptor agonists, and SGLT-2 inhibitors. As yet, no clear superiority of these classes of drugs with respect to diabetes-associated macrovascular disease has been identified. Recent studies with newer classes of glucose-lowering drugs have demonstrated cardiovascular protection. For example, the SGLT-2 inhibitor Empagliflozin acts on sodium balance and has been shown to reduce the cardiovascular and total mortality in the EMPA-REG study [263]. Furthermore, there was an associated benefit on renal endpoints including end-stage renal failure, doubling of serum creatinine and albuminuria [264]. Recently, the LEADER study was completed using the GLP-1 receptor agonist Liraglutide, which also showed clear benefits on CV and renal disease [265]. These positive findings emphasize the importance of drug choice in individuals with type 2 diabetes.

Hypertension

Epidemiological studies have shown that the risk for cardiovascular events and mortality starts at blood pressure values as low as 115/75 mmHg for the general population and doubles for every increase of 20 mmHg in systolic and 10 mmHg in diastolic blood pressure (see Chapter 42). The question of what systolic or diastolic blood pressure level should be targeted has not been completely answered by currently available outcome trials. Based on studies such as the Hypertension Optimal Treatment (HOT) study [266], UKPDS [267], and the Appropriate Blood Pressure Control in type 2 Diabetes (ABCD) trial [268], a maximum systolic BP of 130–135 mmHg should be the goal for people with diabetes.

The more recently completed ADVANCE trial [26] evaluated the effect of a fixed dose of perindopril and indapamide on macrovascular and microvascular outcomes in participants with T2DM. The treatment group showed a mean reduction in systolic and diastolic BP of 5.6 and 2.2 mmHg, respectively, which was associated with an 18% reduction in cardiovascular deaths and a 14% reduction in coronary events in comparison with the control group. No lower limit for BP reduction appears to exist at which benefits related to cardiovascular outcomes are not observed, with a similar pattern reported subsequently for renal disease [269]. The later ACCORD trial tested the effects of lowering BP below 140/90 mmHg on cardiovascular outcomes. Specifically, it aimed to evaluate if a BP reduction to 120 mmHg systolic would further reduce the cardiovascular event rate. In the ADVANCE-ON trial, after 6 years of follow-up, benefits on CV outcomes were still present among those originally assigned to BP-lowering therapy but there was no evidence that glucose lowering had long-term benefits with respect to mortality of macrovascular events [30].

Choice of antihypertensive treatment

Experimental studies have clearly demonstrated a reduction in atherosclerosis with RAS inhibitors with a possible superiority of ACE inhibitors compared with ARBs in T2DM; however, in the human setting, there are no conclusive studies as yet to show clear superiority of one class of antihypertensive drugs over another. The majority of the beneficial effects on cardiovascular events appear to be related to the antihypertensive actions of these agents. The ONTARGET study was the first to evaluate the effect of combined RAS blockade in comparison with full-dose ramipril and telmisartan alone [270]. There was no superiority of the ACE inhibitor over the ARB in terms of cardiovascular events, and dual blockade did not confer greater cardiovascular protection and indeed was associated with more adverse events; however, only 30% of all participants in this study had diabetes, and no specific subgroup analysis has been reported so far. Therefore, this study cannot conclusively answer the question of the superiority of different blockers of the RAS and combination RAS–blockade on microvascular and macrovascular outcomes in diabetes.

Plasma aldosterone levels have been shown to correlate with the progression of atherosclerosis as assessed in the carotid plaque area [271]. Mineralocorticoid receptor antagonists have been evaluated with respect to CV outcomes. The RALES study initially showed a beneficial effect of the non-specific aldosterone antagonist spironolactone on mortality [272], but in the more recent EPHESUS trial [273] a 15% relative risk reduction in all-cause mortality and a 13% relative risk reduction in cardiovascular mortality/complications compared with participants on current standard therapy was demonstrated [274]. Although there is experimental evidence for eplerenone attenuating endothelial dysfunction [275] and early lesion size in experimental models of atherosclerosis [276], the evidence for a direct vasculoprotective effect of these newer agents awaits to be forthcoming, particularly in the context of diabetes.

Inhibitors of neutral endopeptidase (NEP) were associated with unwanted off-target effects, including angioedema [277, 278].

However, more recently the first-in-class combined angiotensin receptor blocker combined with a neprilysin inhibitor (ARNi) was evaluated for heart failure in the PARADIGM-HF trial [279]. Simultaneous inhibition of neprilysin enhanced the NEP system and blockade of the AT1 receptor with valsartan reduced cardiovascular death and heart failure by 20% and all-cause mortality by 16%. This new class of drugs is a potential new and effective treatment for heart failure but the effects in CVD and atherosclerosis need to be further elucidated.

Renal denervation

Initial encouraging results attenuating the overactivity of the sympathetic nervous system in hypertension using renal denervation (RDN) demonstrated substantial and sustained reductions in blood pressure in people with resistant hypertension [280, 281]. Furthermore, additional beneficial effects were observed, including reductions in serum glucose, insulin and C-peptide levels 3 months after denervation [282].

Surprisingly, a randomized clinical trial including a sham control arm (Symplicity HTN3) did not find superiority of the RDN arm compared with the sham control group [283]. Many reasons for the failure of this trial have been discussed, including ineffective denervation, inexperience of the operators, and suboptimal compliance with medication. Currently more than 100 randomized controlled trials are designed to confirm or reject further the initial findings in various chronic diseases, including CVD, heart failure, kidney disease, and diabetes [284].

Dyslipidemia

The lipid profile is usually altered in the diabetic milieu and further altered in the context of liver or renal disease. Dyslipidemia further accelerates atherosclerosis development and progression (see Chapter 43). At any given level of cholesterol, a person with diabetes has a 2–3-fold increased cardiovascular risk than a person without diabetes.

Current guidelines based on numerous studies particularly with statins (Heart Protective Study [HPS] [285], the Collaborative Atorvastatin Diabetes Study [CARDS] [286]) suggest reducing LDL levels below 2.5 mmol/L with some more recent evidence suggesting enhanced benefits if LDL is lowered to <2 mmol/L, triglycerides to <1 mmol/L, and HDL to >1 mmol/L according to pre-existing CVD and risk [287]. This area of research will significantly change with the recent advent of monoclonal antibodies against proprotein convertase subtilisin kexin 9 (PCSK9). These drugs are powerful agents that lower LDL levels by >60%. Furthermore, there have been early reports about beneficial effects on cardiovascular events [288, 289]. Whether there are antiatherosclerotic effects of these drugs beyond cholesterol lowering, as has been postulated for statins, and efficacy in diabetes needs to be shown in future trials.

Hypercoagulability

Diabetes is associated with prothrombotic changes and enhanced coagulability, thus increasing cardiovascular risk [290, 291]. Although not studied in detail, agents such as aspirin may be useful in people with diabetes, with increasing evidence that higher doses of these agents are often required in individuals with diabetes to confer cardiovascular benefits. Other drugs to consider in diabetes are clopidogrel and also agents such as abciximab [292], which has been reported to be particularly effective in people with diabetes.

Novel therapies

Several approaches have been used to intervene in diabetes-associated complications, including aldose reductase inhibitors and PKC isoform inhibitors, in particular PKCβ, but most of the evidence for a potential role for these agents has been obtained in the context of microvascular complications. Furthermore, inhibitors of glucose-induced ROS formation, such as benfotiamine, have been investigated in clinical trials with variable results. AGE inhibitors and RAGE antagonism have also been employed, mainly in the context of diabetic nephropathy. The cross-link breaker alagebrium has been shown to reduce arterial stiffness in people with hypertension and to improve left ventricular function. Direct antagonists of RAGE and human chimeric sRAGE are also currently being investigated in early clinical trials, but so far not with respect to macrovascular disease.

The role of PPAR-α and PPAR-γ agonists has also been investigated with modest or no effects on cardiovascular outcomes [293–295]. The dual PPAR-α/γ agonists such as muraglitazar do not appear to be likely to be introduced as a result of adverse side effects and the possibility of adverse cardiovascular events [296]. As outlined earlier, the landscape of novel therapies has changed with the advent of GLP-1 receptor agonists, DPP-4 inhibitors, and SGLT-2 inhibitors for diabetes control with positive effects on cardiovascular endpoints recently reported [263, 265].

Multifactorial approaches

The Steno 2 study, using a multifactorial approach addressing lipids, blood pressure, and hyperglycemia, demonstrated significant improvements on cardiovascular outcomes [28]. Thus, a synergistic multifactorial approach addressing glycemic control in the context of additional strategies to reduce concomitant cardiovascular risk factors remains the best approach to be currently considered. Furthermore, strategies directed towards a reduction in activation of vasoactive systems such as the RAS, the ET and UT systems, the AGE/RAGE axis, novel proteins such as TRAIL, and the complement system in addition to oxidative stress and inflammation may represent additional promising approaches to prevent and minimize macrovascular disease in diabetes.

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42 Cardiovascular Risk Factors: Hypertension

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Key points

- Hypertension in diabetes is a prevalent and treatable risk factor for cardiovascular complications and retinopathy.
- Evaluation by use of ambulatory blood pressure monitoring should be offered to all people with type 1 and type 2 diabetes.
- Most antihypertensive drugs can be used for treatment, but blockers of the renin–angiotensin system (RAS) may confer special clinical benefits for target organ protection.
- Drug combination therapy is needed for most people to achieve reasonable blood pressure control.
- Encouragement of home blood pressure measurements will make it possible to achieve better blood pressure control while also supporting the involvement and empowerment of the person with diabetes.
- The blood pressure goal for people with type 2 diabetes is <140/85 mmHg in the European Guidelines.

Introduction

Hypertension often accompanies both type 1 diabetes mellitus (T1DM) and type 2 diabetes (T2DM). The association between the two conditions has long been recognized. In 1923, the Swedish physician Eskil Kylin described a syndrome of diabetes, hypertension, and hyperuricemia [1], which are now regarded as aspects of the broader "metabolic syndrome" that has been linked to insulin resistance [2, 3]. The relationship between diabetes and hypertension is complex. Both are common and so are likely to be associated by chance, but in some instances they may have a common cause, even programmed in early life; moreover, hypertension can develop as a consequence of diabetic nephropathy, and some drugs used to treat hypertension can induce diabetes in susceptible individuals, at least at higher dosages.

Hypertension is important because, like diabetes, it is a major cardiovascular risk factor and one that synergizes with the deleterious effects of diabetes. It is also a risk factor for microvascular complications, namely nephropathy and retinopathy. The management of hypertension in diabetes has been widely debated, and there is still a need to agree on treatment targets and strategies. The current blood pressure goal for therapy is <140/80–90 mmHg in general, but lower in newly detected patients with shorter diabetes duration and fewer comorbidities. During the last two decades, several well-constructed trials have added considerably to the evidence base [4–8], demonstrating convincingly the benefits of lowering blood pressure, but also highlighting how difficult this can be to achieve in practice.

Size of the problem

Hypertension is widely defined according to the World Health Organization/International Society of Hypertension (WHO/ISH) criteria (Table 42.1). People with diabetes are still at risk of macrovascular and microvascular complications at blood pressure levels below these thresholds, and the treatment target range is therefore lower (in the range 130–140/80–90 mmHg).

Overall, hypertension (according to the WHO criteria) is up to twice as common in people with diabetes as in the general population [9]. In white Europeans, 10–30% of people with T1DM and 60–80% of those with newly diagnosed T2DM are hypertensive [10]. There are racial and ethnic differences in the prevalence of hypertension, which presumably are at least partly genetically determined. For example, hypertension (and macrovascular disease) is less frequent among the Pima Indians and Mexican Americans [11]. Impaired glucose tolerance (IGT) is also associated with hypertension (20–40% of cases), perhaps reflecting the common origins of these aspects of the metabolic syndrome [12].

There is evidence that the true prevalence of hypertension is increasing in the population with diabetes (especially T2DM) after allowing for the greater number of cases identified through improved screening and the lowering of thresholds for treatment of blood pressure [13]. The causes probably include the rising

Textbook of Diabetes, Fifth Edition. Edited by R. Holt, C. Cockram, A. Flyvbjerg and B. Goldstein.

Table 42.1 Criteria for hypertension and related tissue damage, defined by the World Health Organization (WHO) and the International Society for Hypertension, 1999 [40].

Category	Systolic (mmHg)	Diastolic (mmHg)
WHO criteria for the general population[a]		
Optimal	<120	<80
Normal	<130	<85
High normal	130–139	85–89
Grade 1 hypertension (mild)	140–159	90–99
Subgroup: borderline	140–149	90–94
Grade 2 hypertension (moderate)	160–179	100–109
Grade 3 hypertension (severe)	≥180	≥110
Isolated systolic hypertension	≥140	<90
Subgroup: borderline	140–149	<90
Hypertension-related tissue damage (WHO criteria)		
Grade I: none		
Grade II: subclinical damage (e.g. retinopathy, proteinuria)		
Grade III: clinical damage (e.g. heart failure, ischemia)		
Degree of proteinuria		
Microalbuminuria: 30–300 mg/24 h (20–200 mg/min)		
Macroalbuminuria: >300 mg/24 h (>300 mg/min)		

[a]Desirable blood pressure limits in people with diabetes are suggested in Figure 42.5.

Table 42.2 Associations between hypertension and diabetes.

Hypertension associated with T2DM, (insulin resistance or metabolic syndrome)
Hypertension associated with nephropathy in T1DM
Coincidental hypertension in people with diabetes
Essential hypertension
Isolated systolic hypertension
Renal scarring (e.g. from recurrent pyelonephritis)
Diabetogenic antihypertensive drugs
Potassium-losing diuretics (chlortalidone, high-dose thiazides)
β-Blockers (high dose)
Combined diuretics and beta-blockers
Drugs causing obesity, hypertension, and glucose intolerance
Glucocorticoids
Combined oral contraceptive pills
Antipsychotics
Endocrine disorders causing hypertension and glucose intolerance
Acromegaly
Cushing syndrome
Conn syndrome
Pheochromocytoma

prevalence of obesity and longer survival of older people with diabetes.

Causes of hypertension in diabetes

Associations between hypertension and diabetes are listed in Table 42.2. Essential hypertension and isolated systolic hypertension are both common in people without diabetes, especially in the elderly. It is estimated that essential hypertension accounts for about 10% of cases in people with diabetes. Other important causes are the hypertension that coexists with insulin resistance, obesity, and IGT in the metabolic syndrome, and hypertension secondary to diabetic nephropathy, as discussed in detail below.

Hypertension in the metabolic syndrome

This syndrome consists of insulin resistance, impaired fasting glycemia (including T2DM), a characteristic dyslipidemia—hypertriglyceridemia, low high-density lipoprotein (HDL) cholesterol, and somewhat raised low-density lipoprotein (LDL), with a clear excess of small, dense LDL particles—truncal obesity, procoagulant changes (raised plasminogen activator inhibitor 1 and fibrinogen levels) and hyperuricemia [2, 14, 15]. As these abnormalities are all risk factors for atherogenesis, the syndrome is completed by a marked tendency for early vascular aging, leading to macrovascular disease, especially coronary heart disease (CHD) and stroke (Figure 42.1). As discussed in Chapter 13, insulin resistance has been proposed by Reaven [2], DeFronzo and Ferrannini [14], and others [15] to be a fundamental cause of hypertension and cardiovascular disease (CVD) in addition to T2DM. Insulin resistance is partly genetically determined, while acquired factors such as obesity, physical inactivity, and perhaps malnutrition *in utero* and during early infancy may also contribute [16]. In support of the latter, family studies have revealed a correlation between the blood pressure of the mother and her offspring that appears to be non-hereditary in origin; early growth retardation is suggested to program abnormal development of the vasculature and also the tissues that regulate glucose homeostasis.

Insulin resistance is closely associated with high blood pressure in both humans and animals. Experimental induction of insulin resistance (e.g. feeding rats with fructose) is accompanied by a rise in blood pressure. More persuasively, an inverse relationship has been demonstrated in humans between blood pressure and insulin sensitivity [17] (Figure 42.2). Various mechanisms have been proposed to explain how insulin resistance and/or the accompanying hyperinsulinemia could increase blood pressure (Figure 42.3). First, there is some evidence that insulin is an endothelium-dependent vasodilator, releasing nitric oxide (NO) from the endothelium, which relaxes vascular smooth muscle [18, 19]; blunting of this effect, caused by insensitivity to the action of insulin on the endothelium and also on metabolically important tissues, could contribute to the increased peripheral resistance that is the hallmark of hypertension in obesity and T2DM. Impaired endothelium-mediated vasodilation is associated with insulin resistant states and may have a key role in the initiation and progression of atherosclerosis [20], further negatively influenced by smoking.

By contrast, insulin also has several actions that tend to raise blood pressure, and there is some evidence that these are accentuated in insulin resistant states, presumably because sensitivity

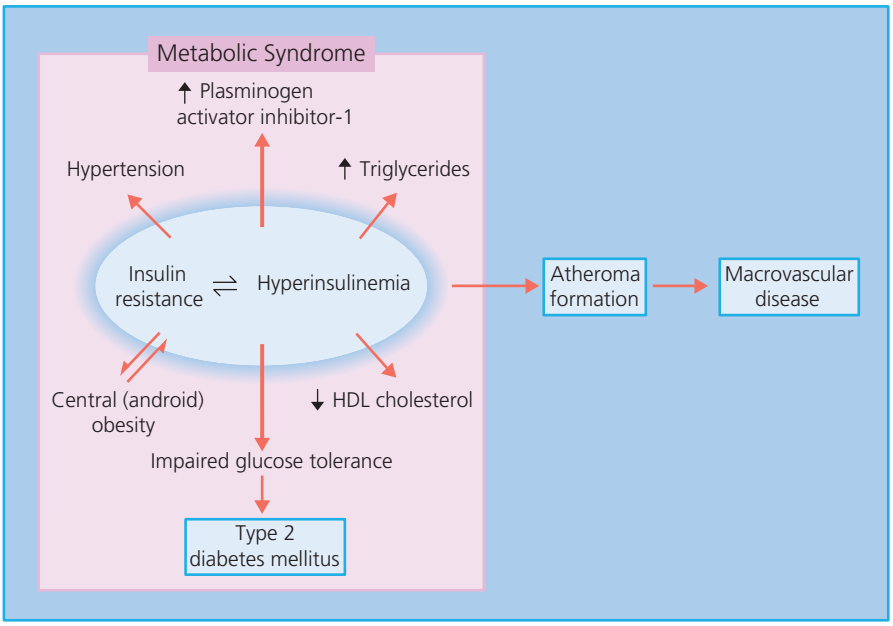

Figure 42.1 The metabolic syndrome. HDL, high-density lipoprotein.

to the effects of the raised insulin levels is preserved. Insulin acts on the distal renal tubule to retain Na^+ ions and water [20, 21], an effect that still operates in people with insulin resistance [22], and so could contribute to the rise in total body Na^+ content that occurs in obesity and T2DM [23]. Insulin also stimulates the cell membrane Na^+–K^+ ATPase, which would raise intracellular Na^+ concentrations in vascular smooth muscle and, by increasing systolic Ca^{2+} levels, would enhance contractility and increase peripheral resistance [22, 23]. Through its effects on the central nervous system (CNS), insulin may stimulate the sympathetic outflow. Theoretically, this could also increase blood pressure, although direct evidence in humans is lacking [22, 24]. Finally, insulin may stimulate the proliferation of vascular smooth muscle cells, which could lead to medial hypertrophy and increased peripheral resistance [22, 25].

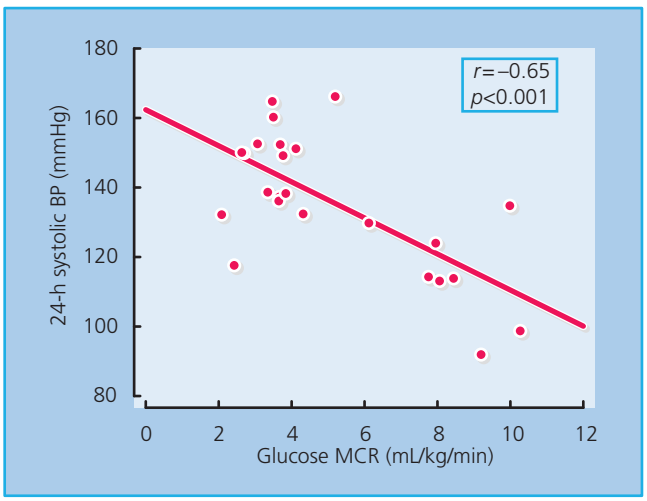

Figure 42.2 Hypertension is associated with insulin resistance. Insulin sensitivity, measured as the metabolic clearance rate (MCR) of glucose during an insulin clamp study, is inversely related to the mean 24-h systolic and ambulatory blood pressure (BP). Source: Pinkney et al. 1994 [17]. Reproduced with permission from Wolters Kluwer Health.

Hypertension and diabetic nephropathy

This association is most obvious in young people with T1DM, in whom the presence of hypertension is strikingly related to renal damage and even minor degrees of proteinuria. Blood pressure begins to rise when the urinary albumin excretion (UAE) enters the microalbuminuric range (>30 mg/24 h) and is usually over the WHO threshold when UAE reaches the macroalbuminuric stage (>300 mg/24 h) [26]. The association may be partly genetically determined: people with diabetes and microalbuminuria commonly have parents with hypertension and may also inherit overactivity of the cell-membrane Na^+–H^+ pump (indicated by increased Na^+–Li^+ counter-transport in red blood cells), which would tend to raise intracellular Na^+ concentrations and thus increase vascular smooth muscle tone [27].

The basic mechanisms of hypertension include decreased Na^+ excretion with Na^+ and water retention. Peripheral resistance is increased, to which raised intracellular Na^+ will contribute. The role of the renin–angiotensin aldosterone system (RAS) is uncertain, as both increased and decreased activity has been reported [28, 29]. These discrepancies may be explained by differences in diet, treatment, metabolic control, and the type and duration of diabetes. Na^+ retention and hypertension would be predicted to suppress the RAS, whereas renin levels may be influenced by other complications of diabetes: renal tubular acidosis type 4 causes hyporeninemic hypoaldosteronism and neuropathy can also lower plasma renin, while renin may be raised in retinopathy and advanced nephropathy. Individuals with microalbuminuria who are insulin resistant appear to be particularly susceptible to hypertension [30].

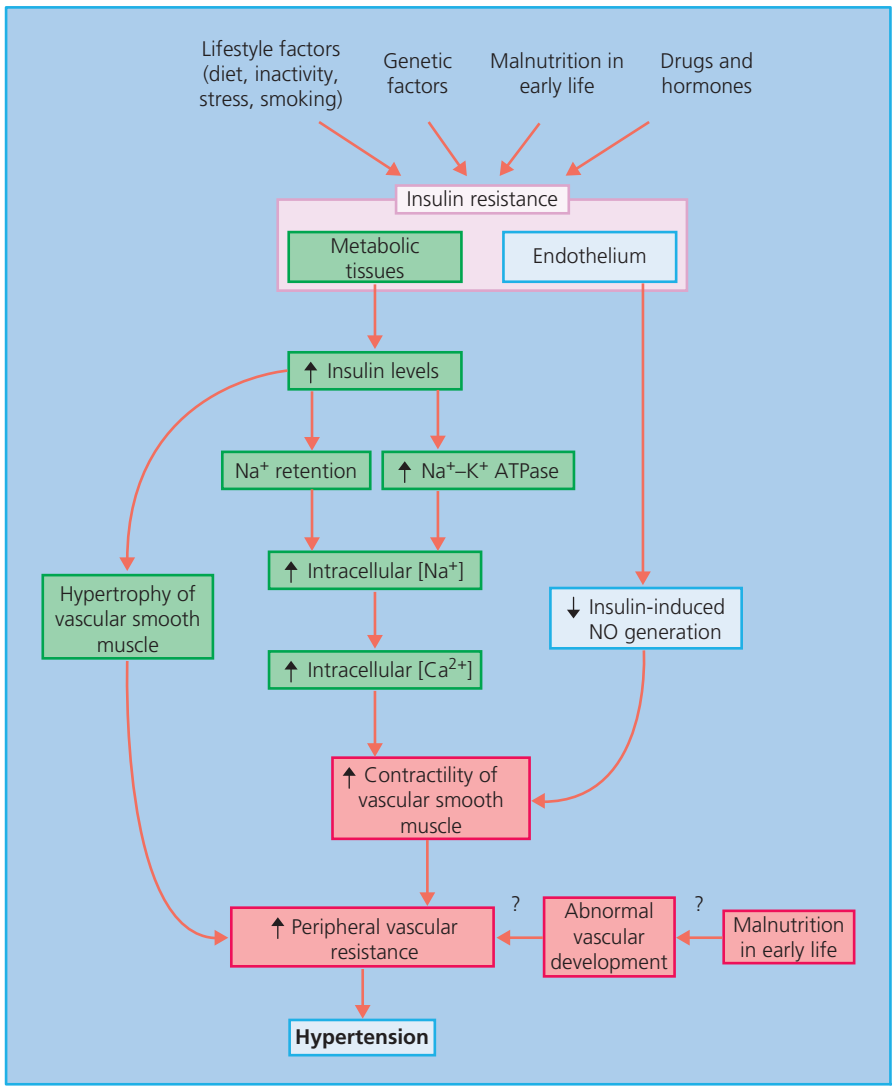

Figure 42.3 Possible mechanisms of hypertension in conditions of insulin resistance.

Impact of hypertension in diabetes

A large proportion of people with hypertension and diabetes show signs of cardiovascular aging and target-organ damage [10]. Hypertension, as an independent risk factor for atherogenesis, synergizes with the effects of diabetes and significantly increases the development and progression of CHD and cerebrovascular and peripheral vascular disease. Overall, the effects of hypertension on deaths from CHD are increased 2–5-fold in people with diabetes, with the greatest increase occurring at the lowest blood pressure levels (Figure 42.4).

The deleterious effects of hypertension on left ventricular function are also accentuated by the presence of diabetes. These include impaired left ventricular relaxation [31] and increased left ventricular mass [32], the latter being an independent predictor of premature death from CHD.

Hypertension also predisposes to the development of certain microvascular complications, particularly nephropathy and end-stage renal disease, for which the risk is increased 2–3-fold (see Chapter 39). Hypertension is also a risk factor for retinopathy, as has been confirmed by the beneficial effects of improved blood pressure control in people with T2DM, reported by the UK Prospective Diabetes Study (UKPDS) [4].

In recent years, interest in arterial stiffness (arteriosclerosis) has increased and it has been shown that arterial stiffness is a characteristic of people with the metabolic syndrome and T2DM [33]. It is believed that increased aortic pulse wave velocity (aPWV) is a marker of the arterial stiffness that is supposed to precede, but later also to interact with, atherosclerosis [34]. A threshold of aPWV >10 m/s [35] is a marker of increased arterial stiffness that can also independently predict cardiovascular risk and total mortality [36]. At early stages, the degree of hyperglycemia and dyslipidemia increases arterial stiffness also in people with normoglycemia or impaired glucose metabolism [37], resulting in early vascular aging (EVA) [38].

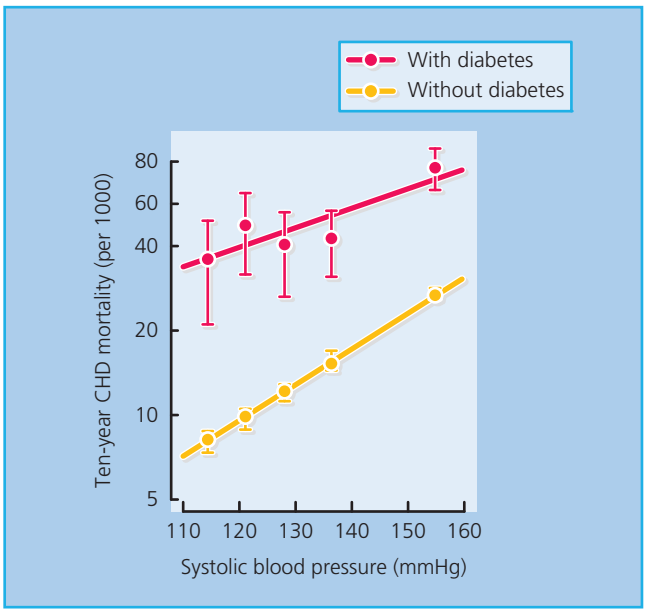

Figure 42.4 Synergistic effects of diabetes and hypertension on deaths from coronary heart disease (CHD). Data from 342,815 people without diabetes and 5163 people with diabetes aged 35–57 years, free from myocardial infarction at entry. Source: Reproduced with permission from O. Vaccaro, paper presented at the 26th Annual Meeting of the European Diabetes Epidemiology Group, Lund, 1991.

Screening for hypertension in diabetes

As the two conditions are so commonly associated, people with diabetes must be regularly screened for hypertension and vice versa. People with hypertension, especially if obese or receiving treatment with potentially diabetogenic drugs, should be screened for diabetes at diagnosis and during follow-up. Should hyperglycemia be detected, potentially diabetogenic antihypertensive drugs should be reduced or changed to others or used in combinations that do not impair glucose tolerance; normoglycemia can then often be restored when lifestyle improvements are also supported.

All people with diabetes should have their blood pressure checked at diagnosis and at least annually thereafter. This is especially important in those with other cardiovascular risk factors, such as nephropathy (which is associated with a substantial increase in the cardiovascular mortality rate), obesity, dyslipidemia, smoking, or poor glycemic control, or with a positive family history of cardiovascular disease.

Measurement of blood pressure

Blood pressure should be measured with the patient in the supine or sitting position, with an accurate sphygmomanometer and a cuff of appropriate size (i.e. wider for obese people with an arm circumference of >32 cm). Systolic and diastolic blood pressure should be recorded, to the nearest 2 mmHg if using a manual sphygmomanometer, from phases I and V (i.e. appearance and final disappearance of the sounds of Korotkoff). Usual precautions should be taken to ensure reliability and avoid "white coat" stress effects, which can acutely raise blood pressure. Conditions should be quiet and relaxed, and at least two readings should be taken initially and then repeated at intervals over weeks or months to determine the person's typical values and any trend to change. Office blood pressure could be complemented by repeated home blood pressure recordings.

Blood pressure should also be checked with the patient in the upright position (1 min after standing), because there may be a significant postural fall (>20 mmHg systolic) in people with diabetic autonomic neuropathy, the elderly, or those treated with vasodilators or diuretics. Marked postural hypotension, which can coexist with supine hypertension, may indicate the need to change or reduce antihypertensive medication, especially if symptoms are provoked.

Ambulatory blood pressure monitoring over 24 h may be useful in some cases to exclude "white coat" effects, and in people with early nephropathy who have nearly normal blood pressure during the day, but who may be at risk of hypertensive tissue damage because they fail to show the physiological blood pressure dip during sleep. Masked hypertension is also a common phenomenon in about 20–30% of all individuals with T2DM [39].

Diagnosis of hypertension in diabetes

The criteria issued in 1999 by the WHO and ISH [40] define hypertension as an office blood pressure exceeding 140/90 mmHg (Korotkoff I–V) and borderline hypertension as being below these limits but above 130 mmHg systolic and/or 85 mmHg diastolic (Figure 42.5) [40]. Established hypertension is diagnosed when readings consistently exceed 140/90 mmHg over several weeks, or when the blood pressure is very high (diastolic blood pressure >110 mmHg), or when there are clinical signs of tissue organ damage from long-standing hypertension.

It is clear from numerous epidemiological studies that the WHO/ISH threshold is sometimes too high in people with diabetes because of their additional risk of both macrovascular and microvascular disease, and that there are definite benefits from treating people with microalbuminuria whose diastolic blood pressure is <90 mmHg [41]. Various other expert bodies have suggested alternative, generally lower target levels (Figure 42.5). A consensus would be to aim for a blood pressure in the range 130–140 mmHg systolic and below 80–85 mmHg diastolic, and to treat any one whose blood pressure is consistently above one or both of these thresholds, supported by modern guidelines [42–45].

Investigation of hypertension in diabetes

Initial investigation of the person with diabetes and hypertension aims to exclude rare causes of secondary hypertension (Table 42.2), to assess the extent of tissue organ damage caused by hypertension and diabetes (Table 42.1), and to identify other

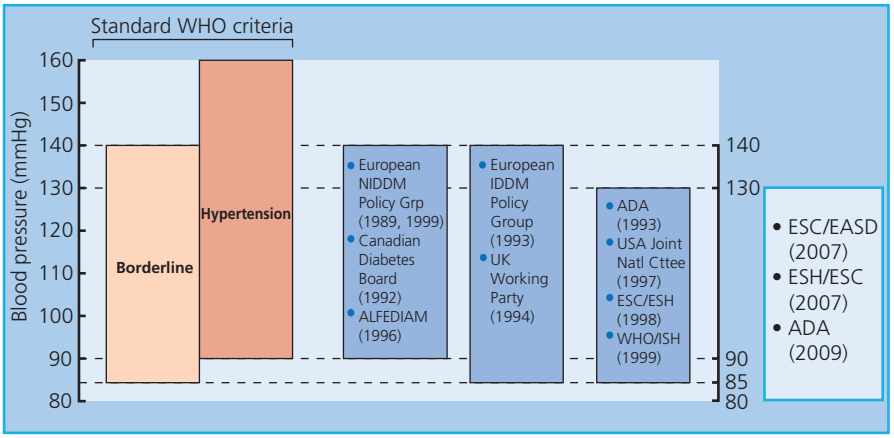

Figure 42.5 Previous blood pressure treatment targets suggested for people with diabetes, compared with the World Health Organization/International Society of Hypertension definition of hypertension and borderline hypertension [40]. ALFEDIAM, Association de langue française pour l'étude du diabète et des maladies métaboliques; ADA, American Diabetes Association; ESC, European Society of Cardiology; EASD, European Association for the Study of Diabetes; ESH, Europe Society of Hypertension.

potentially treatable risk factors for vascular disease. The major points in the medical history and examination are shown in Table 42.3.

- *Cardiac function.* A standard 12-lead electrocardiogram may show obvious ischemia, arrhythmia, or left ventricular hypertrophy; the last is more accurately demonstrated by echocardiography, which will also reveal left ventricular dysfunction and decreased ejection fraction. Exercise testing (or stress-echo) testing and 24-h Holter monitoring may also be appropriate.
- *Renal function.* A fresh urine sample should be tested for microalbuminuria (see Chapter 39) and another examined microscopically for red and white blood cells, casts, and other signs of renal disease. Microscopic hematuria can occasionally occur in people with T1DM (particularly children) in the apparent absence of significant renal dysfunction, but coexisting renal disease must always be excluded. Serum urea, creatinine, and electrolytes should be checked. If the serum creatinine concentration is raised, measurement of the glomerular filtration rate (GFR) should be considered, ideally using a specific clearance method such as using chromium–ethylenediaminetetraacetic acid complex (Cr-EDTA), iohexol, or cystatin C. Further specialist investigations needed include an isotope renogram and other tests for renal artery stenosis (Figure 42.6). This complication of renal arterial atherosclerosis may affect up to 20% of older people with T2DM and, if bilateral, can lead to severe and sometimes permanent renal impairment if angiotensin-converting enzyme (ACE) inhibitors are given.
- *Lipid profile.* Fasting serum lipid concentrations should be checked. If total cholesterol or triglyceride levels are found to be elevated after repeated measurements, further investigation of lipoprotein subclasses—very low-density lipoprotein (VLDL), LDL, HDL, and also the apo-B : apo-A1 lipoprotein ratio—is recommended. Treatment for hyperlipidemia should be considered if the total cholesterol is >4.0 mmol/L, the LDL cholesterol level is >2.5 mmol/L, or the LDL : HDL cholesterol ratio is >4 [43]. This is discussed in more detail in Chapters 43, 44, and 46.

Other forms of secondary hypertension may be indicated by clinical findings of endocrine or renal disease, significant hypokalemia (plasma potassium <3.5 mmol/L without previous

Table 42.3 Investigation of the person with diabetes and hypertension.

Investigations	
History	Is hypertension significant?
Cardiovascular symptoms	Does hypertension have an underlying cause?
Previous urinary disease	• Renal
Smoking and alcohol use	• Endocrine
Medication	• Drug-induced
Family history of hypertension or cardiovascular disease	Has hypertension caused tissue damage?
Examination	• Left ventricular hypertrophy
Blood pressure erect and supine	• Ischemic heart disease
Left ventricular hypertrophy	• Cardiac failure
Cardiac failure	• Peripheral vascular disease
Peripheral pulses (including renal bruits and radiofemoral delay)	• Renal impairment
Ankle–brachial index	• Fundal changes
Fundal changes of hypertension	Are other cardiovascular risk factors present?
Evidence of underlying endocrine or renal disease	• Smoking
Electrocardiography	• Hyperlipidemia
Left ventricular hypertrophy	• Poor glycemic control
Ischemic changes	• Positive family history of cardiovascular disease
Rhythm	
Chest radiography	
Cardiac shadow size	
Left ventricular failure	
Echocardiography	
Left ventricular hypertrophy	
Dyskinesia related to ischemia	
Blood tests	
Urea, creatinine, electrolytes	
Fasting lipids	
Urinary tests	
(Micro-)albuminuria	

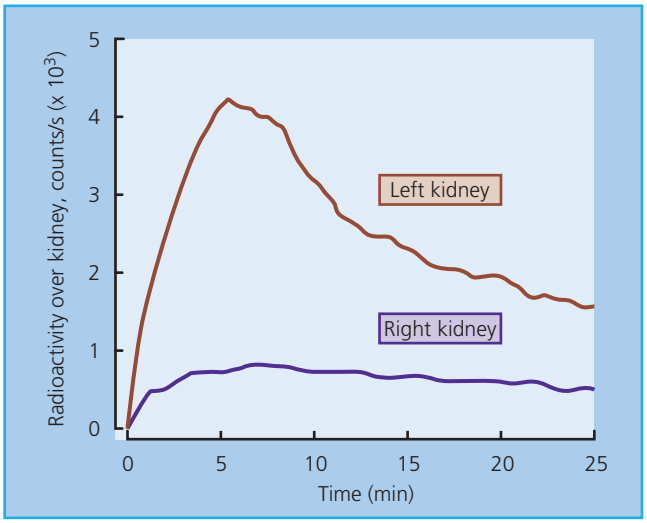

Figure 42.6 Renal artery stenosis affecting the right kidney in a person with diabetes and hypertension. Uptake of the isotope on this side is markedly reduced and delayed.

diuretic treatment), failure of hypertension to respond to standard treatment, or a sudden decline in GFR after starting treatment with ACE inhibitors (suggestive of renal artery stenosis).

Management of hypertension in diabetes

Strict blood pressure control is the primary goal of treatment. In recent years, target treatment levels have declined progressively to the current recommendation of a mean office blood pressure in the range 130–140/80–85 mmHg for all people who can tolerate this without side effects such as orthostatic reactions or compromising arterial circulation in critical vascular beds. Recent observations indicate that there may be subgroups of susceptible individuals who will not tolerate a dramatic reduction below 130 mmHg systolic blood pressure, so caution should be exercised, especially when comorbidities are present.

Management begins with lifestyle modification, but few people respond to this alone, and most will require more than one antihypertensive drug to control blood pressure adequately [4, 5], a fact that new guidelines emphasize [42–45].

Non-pharmacological treatment

The treatment of hypertension in people with diabetes must be based on structured lifestyle intervention. This means weight reduction or weight stabilization in the obese, sodium restriction, diet modification, and regular physical exercise (moderate intensity, 40–60 min, 2–3 times weekly). Dietary intake of saturated fat has been associated with impaired insulin sensitivity and should therefore be reduced [46]. Alcohol should be restricted to 2–3 units/day in men and 2 units/day in women, but omitted altogether if hypertension proves difficult to control. It should be remembered that the Look-AHEAD study in the United States provided no evidence for benefits of weight loss per se as a strategy to lower cardiovascular risk in obese individuals with T2DM of long duration, even though metabolic and risk factor control may improve [47]. This is therefore a rationale to aim for control of risk factors in these persons in the first place, not weight loss itself, with drugs based on evidence and guidelines [42–45].

Smoking causes an acute increase in blood pressure and greater variability overall [48]. Smoking cessation is especially important, as smoking not only accelerates the progression of atherosclerosis and vascular aging, but also impairs insulin sensitivity [49] and worsens albuminuria [50]. Treatment with nicotine supplementation for 4–6 weeks (chewing gum or patches), bupropion, or varenicline may be useful.

When adopted in full lifestyle modification can be effective for blood pressure control itself, and is believed to benefit cardiovascular risk in general even if the evidence is scanty. The above measures can lower systolic and diastolic blood pressure by 11 and 8 mmHg, respectively [51]—as much as many antihypertensive drugs—and sometimes enough to lessen the need for drug therapy. Weight reduction in those with obesity can similarly reduce blood pressure, but not cardiovascular events, according to the Look-AHEAD Study, which is why more research is needed [47].

Antihypertensive drug therapy

Numerous drugs are available to lower blood pressure, but some are better suited than others to the particular needs of people with diabetes because of their favorable or neutral effects on glucose metabolism and other factors. Most people with diabetes (at least two-thirds) will require combinations of antihypertensive drugs to control blood pressure—an average of around three different drugs in two large studies [4, 5]. Accordingly, the clinician must be able to use a wide variety of antihypertensive drugs and to choose combinations that exploit pharmacological synergy. Combination therapy usually means that lower dosages of individual drugs can often be used, thus reducing the risk of their adverse effects.

Diuretics

Diuretics are often effective antihypertensive agents for people with diabetes, in whom the total body sodium load is increased and the extracellular fluid volume expanded [52]; however, diuretics that increase urinary potassium and magnesium losses can worsen hyperglycemia, as insulin secretion is impaired by potassium depletion, and insulin sensitivity in peripheral tissues may also be decreased [53]. The use of high-dose thiazide diuretics, equivalent to ≥5 mg/day bendroflumethiazide (bendrofluazide), is reported to increase the risk of people with hypertension developing diabetes by up to threefold; this does not seem to occur with low dosages (up to 2.5 mg/day bendroflumethiazide) [54]. Potassium depletion is particularly severe with high-dose chlortalidone (chlorthalidone), less so with furosemide (frusemide) and bendroflumethiazide, and apparently negligible with indapamide. This mechanism is irrelevant to those with C-peptide-negative T1DM who are totally dependent on exogenous insulin. Thiazides may also aggravate dyslipidemia [55], although

low dosages probably carry a small risk. Thiazides have also been associated with gout and erectile dysfunction and are generally avoided in middle-aged men with diabetes and hyperuricemia or erectile dysfunction; nevertheless, some evidence suggests that the risk of erectile failure may have been overstated. Diuretics may precipitate hyperosmolar hyperglycemia syndrome and should be avoided or used at the lowest effective dose in people with a history of this complication.

Diuretics have been shown to prevent CVD successfully in elderly people with T2DM and systolic hypertension [56], but one observational study suggested that the use of diuretics increased cardiovascular mortality in people with hypertension and T2DM who were still hyperglycemic in spite of treatment [57]. Overall, these drugs are effective and safe when used appropriately in people with diabetes.

Diuretics suitable for use in diabetic hypertension include furosemide, bendroflumethiazide (≤2.5 mg/day), hydrochlorothiazide, spironolactone, and indapamide. Low dosages should be used, sometimes in combination with potassium supplements or potassium-sparing drugs, such as amiloride. If ineffective, diuretics should be combined with another first-line drug (e.g. an ACE inhibitor or an angiotensin II receptor blocker [ARB]), rather than given at increased dosage. Spironolactone is best not combined with an ACE inhibitor, as this increases the risk of hyperkalemia. Furosemide is useful in people with renal impairment (serum creatinine >150 μmol/L) or edema.

Serum urea, creatinine, and potassium should be checked when starting diuretic therapy and every 6–12 months thereafter, as dangerous disturbances in plasma potassium levels can develop, especially in individuals with diabetes and renal impairment.

β-Adrenergic blocking agents

β-Blockers may significantly lower blood pressure levels in people with diabetes and hypertension, even though renin release (a major target for these drugs) is commonly reduced in diabetes because of Na^+ and fluid retention. These drugs are often ineffective in Afro-Caribbean people, who commonly have low renin hypertension. Other mechanisms of action that reduce blood pressure include reductions in heart rate and cardiac output via interaction with β_1- and β_2-receptors in the myocardium and in the vessel wall.

Like diuretics, β-receptor blockers may aggravate both hyperglycemia and dyslipidemia [58]. These effects depend on both the dosage and the degree of selectivity of the individual drug. The hyperglycemic effect is attributed to inhibition of β_2-adrenergic-mediated insulin release and decreased insulin action in peripheral tissues; the long-term risk for a person without diabetes developing the disease may be increased sixfold [59], and even more if given together with thiazides. Some studies suggest that the hazards of both hyperglycemia and hyperlipidemia have been exaggerated and may be both dose dependent and secondary to weight gain [60]. The metabolic side effects of β-blockers can be reduced by using low dosages combined with other agents, particularly dihydropyridine calcium-channel antagonists, or by intensifying non-pharmacological efforts to decrease weight and improve physical activity.

β-Blockers have other side effects relevant to diabetes. They may interfere with the counter-regulatory effects of catecholamines released during hypoglycemia, thereby blunting manifestations such as tachycardia and tremor and delaying recovery from hypoglycemia [61]. In clinical practice, however, this rarely presents a serious problem, especially when cardioselective β_1-blockers are used. β-Blockers may also aggravate erectile dysfunction, and are generally contraindicated in second- or third-degree atrioventricular (AV) heart block, severe peripheral vascular disease, asthma, and chronic airway obstruction. Some studies have shown that certain β-blockers such as metoprolol and carvedilol [62, 63] can be used favorably in cardiac failure in people with diabetes, as shown in the Metoprolol CR/XL Randomized Intervention Trial in Congestive Heart Failure (MERIT-HF) study, in which 25% of the participants had diabetes [62].

Atenolol is a commonly used drug, as it is cardioselective and water soluble, which reduces CNS side effects and renders its metabolism and dosage more predictable. It is mostly effective as a single daily dose, which probably encourages medication adherence. In the UKPDS, its effect was comparable to that of the ACE inhibitor captopril [64]; however, it should be kept in mind that the stroke-preventive effect of atenolol is 16% less than that of other antihypertensive drugs, based on data from meta-analyses. Metoprolol is an alternative, in moderate dosages. Both non-selective and selective β-blockers are effective in the secondary prevention of myocardial infarction (MI) after an initial event in people with diabetes [65]. Metoprolol or carvedilol may be indicated in those who also have heart failure [62, 63], and β-blockers in general are useful in individuals who also have angina or tachyarrhythmias.

Calcium-channel antagonists

These useful vasodilator agents do not generally worsen metabolic control when used at conventional dosages, although sporadic cases of hyperglycemia have been reported after starting a calcium-channel antagonist of the dihydropyridine class [66]. This may be caused by inhibition of insulin secretion (a calcium-dependent process) in susceptible persons, or a compensatory sympathetic nervous activation, which antagonizes both insulin secretion and action, following vasodilation.

Calcium-channel antagonists have a slight negative inotropic effect and are contraindicated in significant cardiac failure; they often cause mild ankle edema, but this is caused by relaxation of the peripheral precapillary sphincters and raised capillary pressure rather than by right ventricular failure. Because of their potent vasodilator properties, these drugs can cause postural hypotension and can aggravate that brought about by autonomic neuropathy. Non-dihydropyridine calcium-channel antagonists (e.g. verapamil) reduce proteinuria in diabetic nephropathy, but this effect is not seen with dihydropyridine derivatives such as nifedipine, amlodipine, felodipine, and isradipine [67].

Because of their other cardiac actions, these drugs are particularly indicated in people with hypertension who also have angina (e.g. sustained-release nifedipine and diltiazem) or supraventricular tachycardia (e.g. verapamil). Their vasodilator properties may also be beneficial in peripheral vascular disease. Calcium-channel antagonists are ideally combined with selective β_1-blockers, but the specific combination of verapamil and β-blockers (especially together with digoxin) must be avoided because of the risk of conduction block and asystole. Overall, calcium-channel antagonists appear less or similarly cardioprotective but better at preventing stroke than either β-blockers or thiazide diuretics [68, 69].

Amlodipine given once daily is an evidence-based and convenient preparation for general use, and felodipine, isradipine, and sustained-release nifedipine are suitable alternatives.

Angiotensin-converting enzyme inhibitors

ACE inhibitors may be used in diabetic hypertension, even in cases where the general RAS is not activated as the drugs may interfere with local angiotensin action in specific target tissues. When used alone, however, these agents have a limited hypotensive action in many Afro-Caribbean persons, who tend to have suppressed RAS activity.

ACE inhibitors have no adverse metabolic effects and may even improve insulin sensitivity [70]; hypoglycemia has rarely been reported [71]. These drugs are particularly beneficial in diabetic nephropathy by reducing albuminuria and possibly delaying progression of renal damage [72]. Their antiproteinuric effect may be caused specifically by relaxation of the efferent arterioles in the glomerulus, which are highly sensitive to vasoconstriction by angiotensin II, thus reducing the intraglomerular hypertension that is postulated to favor albumin filtration; however, the importance of this mechanism remains controversial [73]. ACE inhibitors are also indicated in cardiac failure, in combination with relatively low dosages of diuretics.

A dry cough is reported by 10–15% of people treated with ACE inhibitors, because these drugs also interfere with the breakdown of kinins in the bronchial epithelium. Changing to another ACE inhibitor or an ARB may avoid this problem. ACE inhibitors occasionally precipitate acute renal failure, particularly in the elderly and in individuals taking non-steroidal anti-inflammatory drugs (NSAIDs), or who have bilateral renal artery stenosis. Other side effects (rashes, neutropenia, taste disturbance) are unusual with the low dosages currently recommended, but become more prominent in renal failure. Because ACE inhibitors cause potassium retention, they should not generally be taken concurrently with potassium-sparing diuretics (spironolactone and amiloride) or potassium supplements. Serum creatinine and potassium levels should be monitored regularly, especially in individuals with renal failure or type 4 renal tubular acidosis, in whom hyperkalemia can rapidly reach dangerous levels.

Ramipril, enalapril, lisinopril, and perindopril, given once daily for hypertension, are all established ACE inhibitors that are suitable for use in people with diabetes. The first dose of an ACE inhibitor should be small and taken just before bedtime to minimize postural hypotension, which may be marked in people receiving diuretics or on a strict sodium-restricted diet. The same problem may arise in those with autonomic neuropathy. ACE inhibitors are now recommended in people with left ventricular dysfunction following MI (see Chapters 44 and 45). Ramipril has been shown to prevent cardiovascular morbidity and mortality in high-risk people with diabetes, with or without pre-existing ischemic heart disease [74].

Angiotensin II type 1 receptor blockers

This class includes losartan, irbesartan, valsartan, candesartan, and telmisartan, which act on the AT1 receptor to decrease blood pressure. They are metabolically neutral [75] and, unlike the ACE inhibitors, do not cause cough. They are effective antihypertensive drugs in people with diabetes [76] and have been shown to slow the progression of nephropathy in those with diabetes and varying degrees of albuminuria (in the RENAAL, IDNT, and PRIME-2 studies) [77–79]. Losartan has also been shown (in a subgroup of the LIFE study) to be better than atenolol in reducing both cardiovascular endpoints (by 25%) and total mortality (by 40%) in high-risk people with T2DM with hypertension and left ventricular hypertrophy [80]. Interestingly, the combination of an ACE inhibitor (lisinopril) with an AT1 antagonist (candesartan) was more effective than either agent alone in lowering blood pressure and UAE in people with T2DM [81]; however, in the ONTARGET study, no extra benefits were recorded for the combination of telmisartan and ramipril on cardiovascular endpoints compared with monotherapy [82]. The combination of an ACE inhibitor and an AT1 receptor blocker for treatment of hypertension is discouraged owing to the negative interaction and risk of adverse renal effects, as evident from the ONTARGET study [83].

Direct renin inhibitor

Another approach to block RAS is via direct renin inhibition. In the ALTITUDE study, this strategy was not successful when the renin inhibitor aliskiren was combined with either an ACE inhibitor or an AT1 receptor blocker versus placebo for cardiovascular and renal protection [84]. As a result, this combination is not recommended for people with T2DM, hypertension, and microalbuminuria in current guidelines [42–45].

α1-Adrenoceptor antagonists

α_1-Blockers can lower blood pressure effectively and also improve dyslipidemia and insulin sensitivity. Doxazosin is normally well tolerated, especially in combination therapy; side effects include nasal congestion and postural hypotension. Doxazosin has been reported to be inferior to the diuretic chlortalidone in the prevention of stroke and heart failure [85].

Treatment strategies

In general, lifestyle modification should be tried initially for ~3 months. If moderate hypertension (systolic blood pressure >160 mmHg or diastolic blood pressure >100 mmHg) or signs of

hypertensive tissue damage are present, then drug therapy should be started at the outset. Initially, monotherapy with one of the first-line drugs suggested above should be used, the choice being influenced by other factors such as coexistence of angina, heart failure, or nephropathy. All drug treatment should aim at being evidence based and cost-effective in the individual. A move to combination drug treatment is recommended for many people owing to the high prevalence of target organ damage when early blood pressure control is mandatory [42–45].

Hypertension in T1DM

ACE inhibitors are especially suitable if the person has albuminuria or more advanced stages of diabetic nephropathy. Diuretics, β_1-selective blockers, and calcium-channel antagonists are equally valid alternatives with regard to blood pressure reduction.

If renal function is moderately impaired (serum creatinine values >150 μmol/L), thiazide diuretics become less effective, and furosemide or other loop diuretics should be used instead; however, in established end stage renal disease (serum creatinine >500 μmol/L), furosemide may be toxic, and dialysis must be started. In some people, hypoglycemia attacks may be masked by the use of β-blockers.

Hypertension in T2DM

Blood pressure control is generally more important than the choice of individual drugs. First-line agents, according to evidence from clinical studies, are ACE inhibitors, ARBs, β-blockers, low-dose thiazide diuretics (in the elderly), furosemide, and calcium-channel antagonists [4–8, 42–45].

Ramipril has evidence-based support for its use in individuals with T2DM because of their high cardiovascular risk [74]. β-Blockers (in combination with low-dose aspirin) are indicated as secondary prevention for those who have had an MI, provided that no serious contraindications are present. Low doses of thiazide diuretics are useful in older people with diabetes, as this class of drugs has proven efficacy in preventing stroke and all-cause mortality in older people with hypertension [8].

α_1-Blockers may be used as part of combination therapy, especially in those with dyslipidemia (high triglycerides and low HDL-cholesterol levels) and prostatic hyperplasia. Indapamide is well tolerated and has no metabolic side effects. Spironolactone may also be of value, especially for elderly obese women with hypertension and hypervolemia with a low renin profile, even though evidence from large-scale randomized studies is so far lacking.

Combination therapy

Combination therapy is needed in most people with diabetes (especially those with T2DM) to achieve satisfactory blood pressure control [42–45]. It is often better to use low-dose combinations than to increase dosages of single agents, as side effects are commonly dose dependent. Potassium-sparing agents (spironolactone and amiloride) should not be combined with an ACE inhibitor, because of the increased risk for hyperkalemia.

Certain combinations of antihypertensive drugs have proved very safe and effective in low to moderate doses, e.g. ACE inhibitor plus diuretic, for example in the ADVANCE study [86]; calcium-channel antagonists plus ACE inhibitor, for example in the ACCOMPLISH study [87]; selective β_1-blocker plus calcium-channel antagonist; or β_1-blocker plus α_1-blocker. In many high-risk patients, a combination treatment could also be considered as initial therapy, especially when signs of target organ damage are present.

Special considerations in ethnic groups

Hypertension in diabetes represents a serious medical problem in many ethnic groups, such as African Americans [88]. In non-white European individuals, β-blockers and ACE inhibitors are often less effective at lowering blood pressure because the RAS is already underactive. Diuretics and calcium-channel antagonists are often drugs to be preferred, particularly in African Americans [89].

Outcome of treating hypertension in diabetes

It has long been recognized that effective treatment of hypertension can slow the progression of diabetic nephropathy, lowering UAE and decreasing the rate of fall of the GFR [90]. The assumptions that improved blood pressure control would improve cardiovascular and other prognoses in T2DM have been confirmed by the UKPDS [4]. In this study, tighter blood pressure control (averaging 144/82 mmHg) for over 8 years led to significant improvements in several outcomes, compared with less strict control that averaged 154/87 mmHg (Table 42.4). Interestingly, the most powerful effects were related to microvascular complications (retinopathy and nephropathy), although significant reductions were also seen in the risk of stroke (44%) and heart failure (56%). MI and peripheral vascular disease showed non-significant reductions (Table 42.4; Figures 42.7 and 42.8).

Table 42.4 Impact of stricter control of hypertension on diabetic complications, macrovascular disease, and diabetes-related deaths in T2DM.

Measure	Relative risk with tight control (mean, 95% confidence intervals)	*p*-Value
Diabetes-related deaths	0.76 (0.62–0.92)	0.19
All-cause mortality	0.82 (0.63–1.08)	0.17
Myocardial infarction	0.79 (0.59–1.07)	0.13
Stroke	0.56 (0.35–0.89)	0.013
Peripheral vascular disease	0.51 (0.19–1.37)	0.17
Microvascular disease	0.63 (0.44–0.89)	0.009

Source: Data from the UKPDS [4].

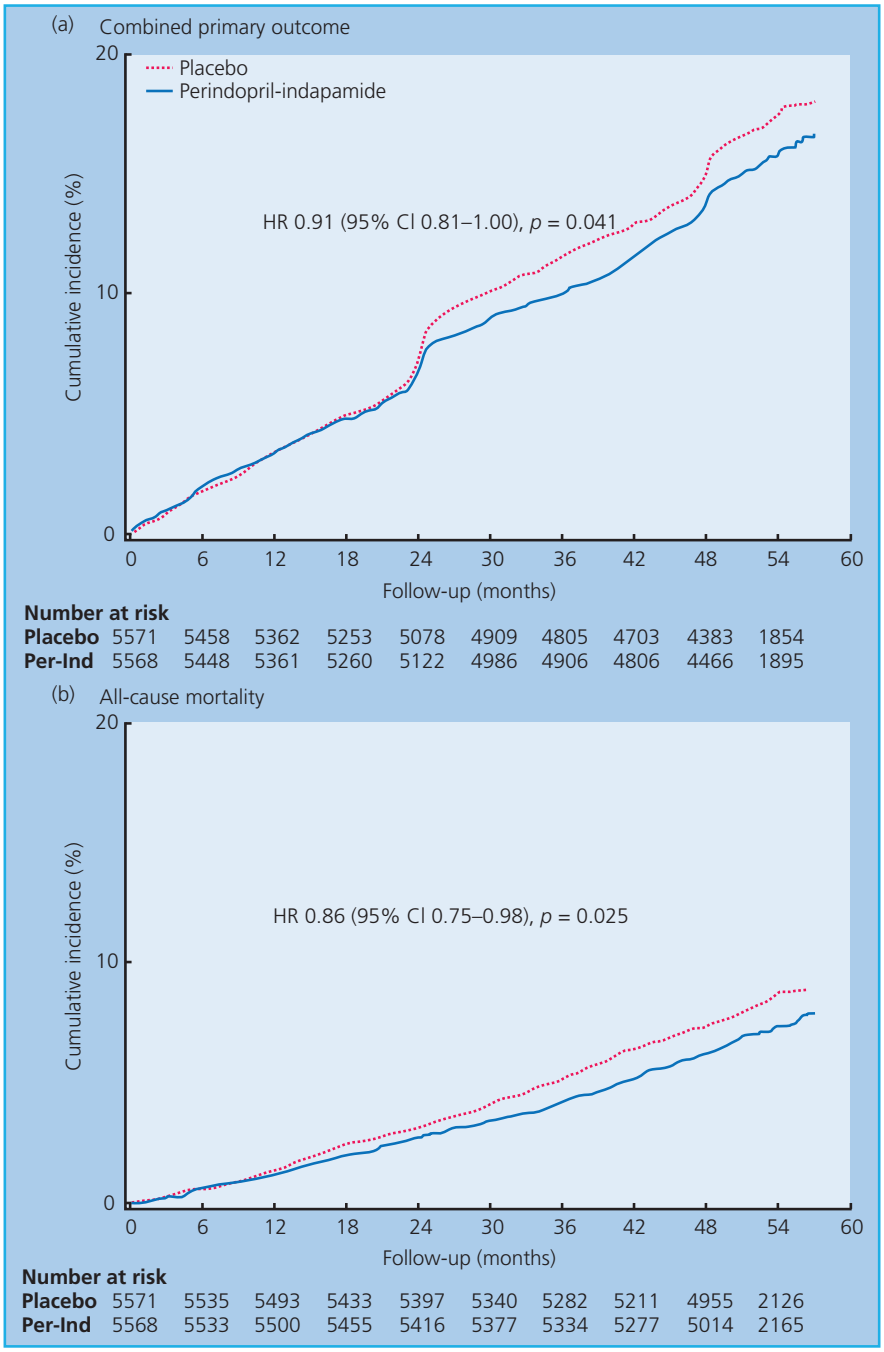

Figure 42.7 Kaplan–Meier curves for the primary outcome and all-cause mortality in the two study groups in the ADVANCE Trial [86]. The combined primary outcome were composites of major macrovascular and microvascular events. Major macrovascular events were cardiovascular death, non-fatal MI, or non-fatal stroke. Major microvascular events were new or worsening nephropathy or retinopathy.

Overall, therefore, tight blood pressure control has been proven to provide substantial benefits for people with hypertension and diabetes. Moreover, this treatment strategy seems to be cost-effective, at least according to the health economics analyses in the UKPDS [91]; however, it must be kept in mind that these benefits will not last if a continuous blood pressure reduction cannot be achieved long term, as shown by the 10-year follow-up of the UKPDS [92]. Antihypertensive treatment therefore has to be continued and not interrupted.

Conclusions

The diagnosis and treatment of hypertension are of great importance for the person with diabetes [42–45]. The treatment targets are demanding and require considerable effort from both people with diabetes and physicians, but the benefits are now undisputed.

New antihypertensive drugs are being introduced [93], but fewer now than previously. They have to prove themselves with

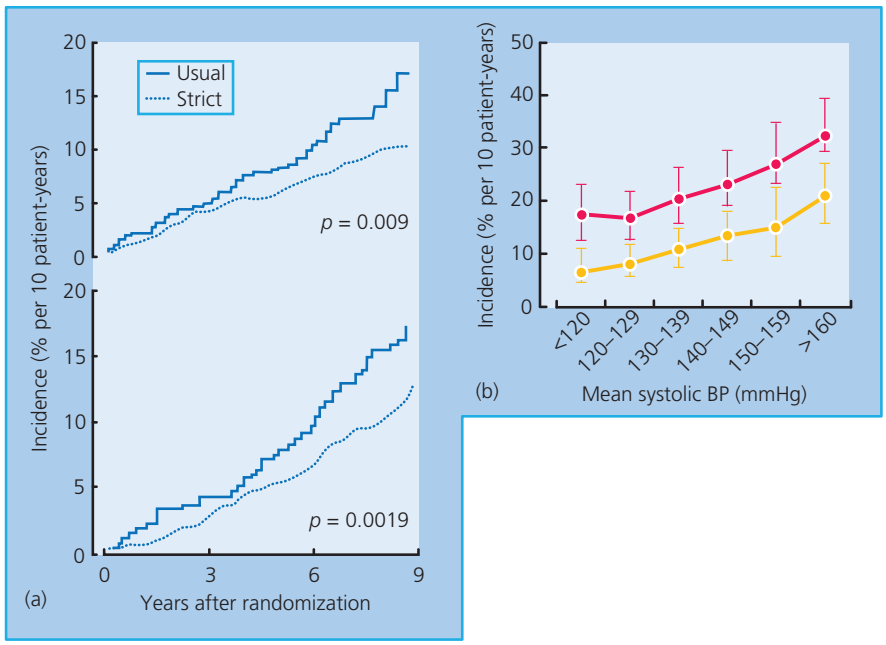

Figure 42.8 Treating hypertension improves the prognosis in T2DM. (a) Stricter blood pressure (BP) control (mean pressure 144/82 mmHg) significantly reduced the risks of both microvascular complications (top) and diabetes-related death (bottom), compared with less strict control (mean 154/82 mmHg). (b) Relationship between BP and rates of microvascular disease and MI. Lowering the BP progressively reduced the risk of microvascular complications, but there was no significant effect on MI. The red line represents MI and the yellow line represents microvascular complications. Source: UKPDS 1998 [4, 91]. Reproduced with permission from BMJ Publishing Group Ltd.

Blood pressure in mm-Hg	NICE 2011(2)	ESH/ESC 2013(3)	ASH/ISH 2014(4)	GoA. et al. AHA/ ACC/CDC 2013(5)	2014 Hypertension guidelines, US 'JNC8' (6)
Definition of hypertension	≥140/90 and daytime ABPM or home BP) ≥135/85	≥140/90	≥140/90	≥140/90	Not addressed
Drug therapy in low risk patients after non-pharmacologic treatment	≥160/100 or day-time ABPM ≥150/95	≥140/90	≥140/90	≥140/90	<60y. ≥140/90 ≥60y. ≥150/90
Beta-blockers as first line drug	No	Yes	No	No	No
Diuretic	(Step 4) chlorthalidon, indapamide	Thiazides chlorthalidon, indapamide	Thiazides chlorthalidon, indapamide	(Step 3) thiazides	(Step 4) thiazides chlorthalidon, indapamide
Initiate drug therapy with two drugs	Not mentioned	In people with markedly elevated BP	≥160/100	≥160/100	≥160/100
Blood pressure targets	<140/90 ≥80y. <150/90	<140/90 Elderly <80y. SBP 140–150 SBP <140 in fit patients Elderly ≥ 80y. SBP 140–150	<140/90 ≥80 y. <150/90	<140/90 Lower targets may be appropriate in some individuals, including the elderly	<60y. <140/90 ≥60y. <150/90
Blood pressure target in patients with diabetes mellitus	Not addressed	<140/85	<140/90	<140/90 Lower targets may be considered	<140/90

Figure 42.9 Comparison of hypertension guidelines 2010–2014 (references as in the original article ABPM, ambulatory blood pressure monitoring; SBP, systolic blood pressure.). Source: Lindholm and Carlberg 2014. ISH Hypertension News 2014, Opus 35 (International Society of Hypertension quarterly newsletter). Reproduced with permission.

regard to both efficacy and tolerability. Even some antidiabetes drugs appear to lower blood pressure in addition to blood glucose [94, 95], but safety concerns are important.

In the future, the application of cardiovascular genomics may substantially change the approach to treating hypertension in diabetes [96], aiming at tailoring treatment according to the genotype of the individual.

In the recent ACCORD blood pressure study [97, 98], there was no significant difference in the primary composite outcome of cardiovascular events between participants randomized to achieve a systolic blood pressure goal below 120 mmHg versus below 140 mmHg, even though a reduction in stroke was noticed (secondary end-point) in the intensive arm. This means that the optimal blood pressure goal for people with hypertension and T2DM is still not fully established (Figure 42.9). According to the most recent meta-analysis, it was concluded that among people with T2DM, blood pressure lowering was associated with improved mortality and other clinical outcomes among those with baseline blood pressure of 140 mmHg and greater, but increased in those with baseline blood pressure below 140 mmHg. In younger people with shorter diabetes duration, fewer comorbidities, and higher estimated risk for stroke and renal events, the blood pressure goal could be at the lower range 130–140/80–90 mmHg [99].

Finally, it takes a multifactorial approach to address and to treat all major cardiovascular risk factors, not only blood pressure, to achieve lasting cardiovascular protection, as evidenced by the Steno 2 trial [100].

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43 Diabetic Dyslipidemia and Risk of Cardiovascular Disease

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Key points

- The greatest long-term risk in diabetes is cardiovascular disease (CVD), with macrovascular disease being the cause of 80% of mortality.
- Epidemiological studies have established that glycemic control, nephropathy, and lipids are risk factors for CVD in type 1 diabetes mellitus (T1DM).
- Low-density lipoprotein cholesterol (LDL-C), high-density lipoprotein cholesterol (HDL-C), smoking, and hypertension are the principal risk factors in type 2 diabetes mellitus (T2DM).
- In T2DM, optimized glycemic control has modest effects in reducing CVD endpoints.
- Reduction of LDL-C with statins has consistently shown cardiovascular event reductions of 20% per 1 mmol/L LDL-C (or non-HDL-C) reduction.
- The dyslipidemia of T2DM is associated with elevated triglycerides, reduced HDL-C, and small, dense particles.
- Fibrates have shown a modest reduction in events in T2DM with monotherapy.
- Optimal control of all risk factors can reduce cardiovascular events and mortality in people with diabetes by 50%.

Introduction

An association between diabetes mellitus and heart disease was described more than a century ago. Two decades later, in 1906, it was hypothesized that this association was due to atherosclerosis. The importance of diabetes as a cardiovascular disease (CVD) risk factor became established following the Framingham Study, and was subsequently confirmed by other landmark studies [1, 2]. The magnitude of diabetes mellitus as a CVD risk factor is substantial, with the increase in cardiovascular risk being 2–4-fold. Many guidelines regard diabetes as a coronary heart disease (CHD) risk equivalent [3–5]. This concept is based originally on a Finnish cohort [6], which showed comparable risk of CVD outcomes such as myocardial infarction (MI) and CVD death, between those with type 2 diabetes mellitus (T2DM) for >10 years and people with established CVD. This was still apparent after adjusting for known risk factors such as age, sex, hypertension, total cholesterol, and smoking. The OASIS (Organization to Assess Strategies for Ischemic Syndromes) study showed that persons with diabetes with no previous CVD have the same long-term morbidity and mortality as those without diabetes with established CVD after hospitalization for unstable coronary artery disease [7]. However, there is wide variation in the rate of CVD in diabetes, which depends on the population studied, duration of diabetes, and existing risk factors [8, 9]. This equivalence has not been confirmed by a subsequent study and it also seems less valid in older people where those with existing CVD have a greater risk than individuals with diabetes but no CVD [9, 10] (Figure 43.1). Most of the literature that reports on CVD risk and diabetes considers only T2DM. However, people with type 1 diabetes mellitus (T1DM) are clearly at increased risk for CVD [11, 12]. In T1DM, the risk of premature CVD was increased with a cohort of 292 people with T1DM followed for 20–40 years; the cumulative mortality rate due to CHD was 35% by age 55 years [11]. A cohort study that examined 7479 individuals with T1DM registered in the UK General Practice research database showed that CVD occurred at a much younger age (10–15 years earlier) in persons with T1DM compared with the general population, the differences being greater in women [13, 14]. Hyperglycemia, hypertension, and microalbuminuria are the strongest risk factors associated with the development of CVD in T1DM, in addition to cigarette smoking, inflammation, and dyslipidemia. As T1DM mostly presents at an earlier age, it remains more difficult to assess and compare this, but rates of CVD are increased at all ages with prevalences being stated to be increased by 7.6-fold in women and 4.0-fold in men [13, 14]. Concomitant CVD risk factors also differ according to the type of diabetes [14]. The

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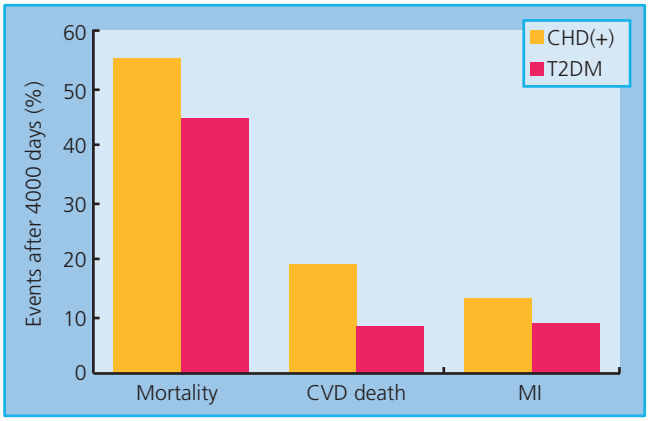

Figure 43.1 Cardiovascular risk in people with new-onset coronary heart disease ($n = 7414$) and those with new-onset diabetes ($n = 3477$) after 7 years' follow-up of the Tayside cohort study. Source: Data from Evans et al. 2002 [9].

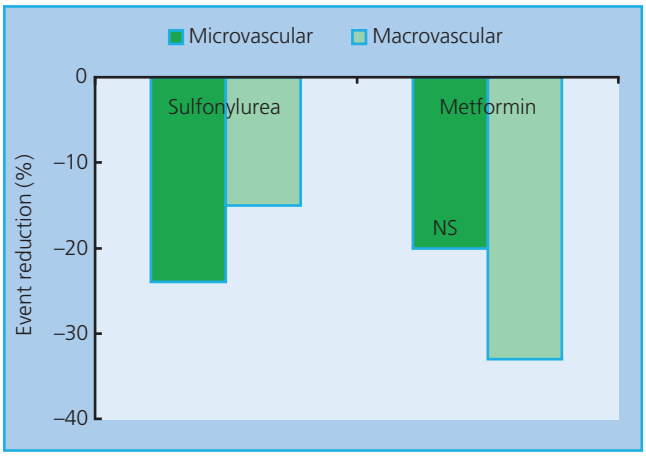

Figure 43.2 Results of the UK Prospective Diabetes Study (UKPDS) at 10 years' follow-up.

risk of CVD is notably increased in those developing diabetic nephropathy in T1DM. However, although the incidence of diabetic nephropathy has declined significantly, this has not been accompanied by a corresponding fall in CHD, indicating that other factors may be at play in the development of CHD in this population. Other markers of CVD risk in people with diabetes include diabetic retinopathy, autonomic neuropathy, erectile dysfunction, microalbuminuria, and proteinuria [15].

Most guidelines do not recommend formal CVD risk estimation in people with diabetes owing to the significant risk already present and term them to be a CVD-risk equivalent, i.e. a similar event risk to normoglycemic individuals with established CVD [16, 17]. This is an exaggeration for most persons with T2DM [9, 18]. Epidemiological or trial-based CVD risk calculators previously showed failures of calibration in individuals with diabetes. The Framingham algorithm underestimates risk in this group, while the UK Prospective Diabetes Study (UKPDS) overestimates CVD events [19, 20]. Recently, the UK QRISK2 calculator system has been updated with formally validated CVD risk tools based on 11,438 CVD events occurring in 48,889 persons with T2DM and 9724 persons with T1DM followed for 15 years [21]. QRISK2 is the only CVD risk calculation system available for T1DM. The NICE cardiovascular risk assessment guidelines (CG181) in the United Kingdom recommend the use of QRISK2 in T2DM but not T1DM, which they consider automatically high CVD risk after age 40 [22].

CVD risk factors in diabetes

Glucose

A risk continuum exists across a broad concentration range that incorporates individuals without diabetes, with the risk of CVD being the lowest when the fasting blood glucose is between 4 and 4.9 mmol/L [23–25]. Despite the well-established association between blood glucose and atherosclerosis, surprisingly few studies have been able to show an improvement in cardiovascular outcome by reduction in blood glucose. In T1DM, the Epidemiology of Diabetes Interventions and Complications (EDIC) [26] follow-up from the Diabetes Control and Complications Trial showed that glucose lowering was associated with a long-term benefit with regard to cardiovascular complications that became apparent only years after recruitment. In T2DM, 10-year follow-up data from the UKPDS with intensive glucose therapy showed long-term beneficial effects on macrovascular outcomes [27]. However, unlike the microvascular benefits, risk reductions for MI and death from any cause were observed only with extended post-trial follow-up (Figure 43.2). These results suggested that improved glucose control may result in a larger cardiovascular risk reduction in persons with T1DM than among those with T2DM, which is consistent with the results of one meta-analysis. Furthermore, neither the recent Action in Diabetes and Vascular Disease: Preterax and Diamicron Modified Release Controlled Evaluation (ADVANCE) [28] nor the Action to Control Cardiovascular Risk in Diabetes (ACCORD) [29] trials, each including in excess of 10,000 participants, could not show a significant beneficial effect on CVD outcome when targeting near-normal glucose levels in T2DM using an HbA_{1c} <48 mmol/mol (<6.5%) (Figure 43.3). More worrying was the finding in the ACCORD trial that near-normal glucose control was actually associated with a significantly increased risk of death from any cause and death from CVD [30].

Differential effects on CVD outcomes in recent meta-analyses have recently been reported with different members of the thiazolidinedione class of oral hypoglycemic drugs. The PROspective pioglitAzone Clinical Trial In macroVascular Events (PROACTIVE) study with pioglitazone in 5138 people with T2DM showed no effect on the primary composite CVD endpoint ($p = 0.10$) but did show a 16% reduction ($p = 0.03$) in the secondary CVD outcomes endpoint but an increase in heart failure admissions [31]. Analyses of the RECORD (Rosiglitazone Evaluated for Cardiac Outcomes and Regulation of Glycemia in Diabetes) trial

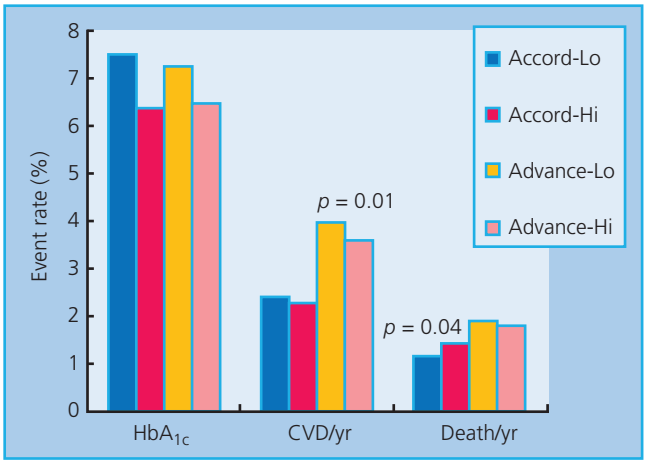

Figure 43.3 Effects of improved diabetes control to an HbA_{1c} <48 mmol/mol (<6.5%) in the ACCORD and ADVANCE studies. Hi refers to conventional treatment and lo refers to intensive glycemic control with lower achieved HbA_{1c}. Source: Data from ACCORD Group et al. 2008 [29]; ADVANCE Collaborative Group et al. 2008 [28].

in 4447 participants with T2DM eventually found no evidence for an increased CVD event rate with rosiglitazone [32]. The final conclusion has been that thiazolidinediones do not increase CVD events but do have adverse effects on heart failure admissions [33] and bone metabolism [34]. The controversy prompted by thiazolidinediones has led to all new hypoglycemic therapies having to be assessed in CVD outcomes trials to demonstrate no increase in CVD events. Recently, the EMPA-REG outcome study of the sodium-glucose-lithium transporter type 2 inhibitor empagliflozin in 7034 people with type 2 diabetes and established CVD showed a 14% reduction ($p<0.001$) in CVD events and a 32% reduction in overall mortality in the context of an overall 2 mmol/mol (0.35%) reduction in HbA_{1c} [35]. Multiple other outcomes trials are under way that should improve our understanding of the problem of glycemic control and CVD [36].

Dyslipidemia

As opposed to hyperglycemia, targeting dyslipidemia has proven much more effective in preventing the macrovascular complications of diabetes. However, for many years the benefits of intervention on lipoproteins as CVD factors in diabetes were uncertain. The principal reason was that people with diabetes were excluded from trials of lipid-lowering therapies. Hence virtually no data exist from early studies with bile acid sequestrants, fibrates, or nicotinic acid.

The reasons for excess CVD risk in diabetes are numerous and varied and in part relate to the lipid abnormalities seen in diabetes. Enhanced glycation of lipoproteins has direct effects on lipoprotein metabolism as these glycated lipoproteins are handled differently by lipoprotein receptors, particularly of the scavenger group, thus promoting atherogenesis [37]. Enhanced glycation also amplifies the effects of oxidative stress on lipoproteins, a feature of both T1DM and T2DM [38]. The term diabetic dyslipidemia refers to the lipid abnormalities typically seen in persons with T2DM and is synonymous with atherogenic dyslipidemia [39, 40]. It is characterized by elevated triglyceride-rich remnant lipoproteins (routinely measured as hypertriglyceridemia), small, dense LDL (sdLDL) particles, and low HDL cholesterol (HDL-C) concentrations. Guidelines have begun to recognize that errors in the calculation of LDL-C concentrations are significant especially in people with T2DM [41], fasting is often difficult for these individuals, and that even directly-measured LDL-C underestimates CVD risk in T2DM [42]. Hence they increasing favor the use of non-HDL-C (difference between total cholesterol and HDL-C) in people with diabetes as this has better predictive value and is less subject to error [16, 17, 22]. Several factors are likely to be responsible for diabetic dyslipidemia, including insulin effects on liver apolipoprotein (Apo) production, downregulation of lipoprotein lipase (LPL) as opposed to hepatic lipase, increased cholesteryl ester transfer protein (CETP) activity, and peripheral actions of insulin on adipose and muscle.

LDL cholesterol

LDL-C is identified as the primary target of lipid-lowering therapy. Analysis of the UKPDS showed that LDL-C was the strongest risk factor for CHD in this population and HDL-C was the second strongest [43]. Until relatively recently, the recruitment of people with diabetes to randomized controlled trials of lipid-lowering therapy was rare or they were specifically excluded. Only recently have studies been performed that recruited large groups of individuals with T2DM. There have still been no specifically designed randomized controlled CVD outcome studies of lipid-lowering drugs in T1DM.

Statins

The first study with statins to demonstrate their potential effectiveness was the Scandinavian Simvastatin Survival Study (4S) [44].The 4S included only 202 participants with T2DM out of 4444 yet simvastatin therapy was associated with a 55% reduction in major CHD (fatal and non-fatal CHD) ($p = 0.002$) compared with 32% in those without diabetes [45]. It was suggested that the absolute benefit of cholesterol lowering in people with diabetes may be greater than that in those without diabetes because of their higher absolute risk of CVD. This notion was later confirmed in several other studies that also recruited subgroups with T2DM [46].

A number of studies have subsequently been specifically designed to investigate the effects of statins in persons with T2DM. The Collaborative Atorvastatin Diabetes Study(CARDS) [47] randomized participants to atorvastatin 10 mg, which reduced LDL-C by 40%. It included persons with T2DM allied with one or more other CVD risk factors (e.g. uncontrolled hypertension and/or microalbuminuria) but without prior overt CVD. The study was terminated 2 years prematurely, showing unexpected early benefit of a 37% reduction in CVD events. However, the similarly designed Atorvastatin Study for Prevention of Coronary Heart Disease Endpoints in Non-Insulin-Dependent Diabetes Mellitus

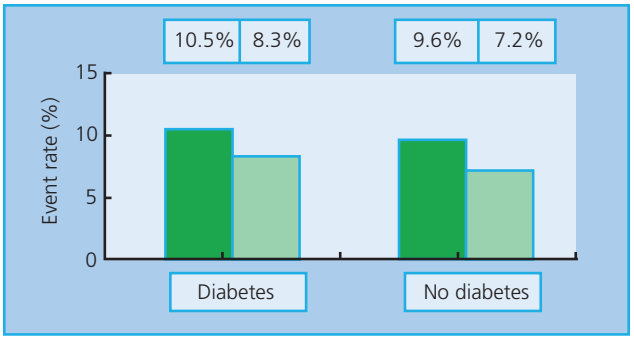

Figure 43.4 Comparison of the effects of reducing LDL-C with statins on CVD events in people with or without T2DM [51].

(ASPEN) study, also using atorvastatin 10 mg predominantly in people without CVD, showed only a non-significant 15% reduction in CVD events [48].

The Heart Protection Study (HPS) had a prespecified subgroup analysis for 5963 people with diabetes (29%) [49] and used simvastatin 40 mg. This reduced LDL-C by 33%, resulting in a 31% reduction in CVD endpoints. Further studies explored other populations with T2DM. However, treatment with atorvastatin 20 mg in people with T2DM and end-stage renal disease requiring dialysis (4D study) reduced LDL-C by 41% but showed a non-significant 8% reduction in CVD endpoints [50]. Hence the benefits of statin therapy seem to occur early in disease in diabetes. Overall, the accumulated evidence therefore supports the use of statin therapy to reduce CVD risk in individuals with diabetes. The Cholesterol Treatment Trialists' individual patient-based meta-analysis evaluated the efficacy of cholesterol-lowering therapy in 18,686 people with diabetes in 14 randomized trials of statins, including a small subgroup of 600 patients with T1DM. It reported a 9% proportional reduction in all-cause mortality and a 21% proportional reduction in major vascular events per 1 mmol/L reduction in LDL-C [51], similar to that in people without diabetes (Figure 43.4).

Other LDL-C-reducing drugs

There are only a few studies examining CVD outcome in people with diabetes for other drugs that reduce LDL-C. The effects of colesevelam on lipids and diabetes have been assessed in three randomized trials. All three trials showed that colesevelam reduced LDL-C by 12–16% and improved HbA_{1c} by 0.5%, sufficient for it to gain a US license as an oral antidiabetes agent [52].

Ezetimibe, which reduces gut cholesterol absorption through the Niemann-Pick-C-1-like protein-1 (NPC1L1) system, reduces LDL-C by 20–25% but has little effect on other lipid fractions. The IMProved Reduction of Outcomes: Vytorin Efficacy International Trial (IMPROVE-IT) study recruited 18,144 individuals with acute coronary syndromes of whom 27% had T2DM [53]. After initiation on baseline simvastatin 40 mg therapy, participants were randomized to ezetimibe or placebo. Further temporary up-titration to 80 mg simvastatin to achieve an LDL-C <2 mmol/L occurred in 27% of the statin-only group and 6% of the statin–ezetimibe group. Ezetimibe therapy reduced LDL-C by a net 0.41 mmol/L, resulting in a 6% reduction in CVD events after 7 years ($p = 0.02$) [53]. The overall absolute reduction in risk over 7 years was 2.0% (34.7 vs. 32.7%), but better results were seen in the T2DM subgroup, where the risk reduction was 5.5% (45.5 vs. 40%). Hence ezetimibe therapy is likely to be effective in persons with T2DM.

A number of studies have used ezetimibe in combination with statins. People with diabetes were excluded from the Simvastatin Ezetimibe Aortic Stenosis (SEAS) study [54]. The Simvastatin Heart and Renal Protection (SHARP) study examined primary prevention in 9270 people with chronic kidney disease (3023 on dialysis), of whom 23% had T2DM [55], randomized to a combination of simvastatin 20 mg and ezetimibe 10 mg or placebo. Combination therapy reduced LDL-C by 0.85 mmol/L, reducing CVD outcomes by 17% after a median follow-up of 4.9 years. Results were similar in the diabetes and non-diabetes subgroups.

Non-HDL-C and ApoB

Although the association of LDL-C with CVD risk is well known, measurement of LDL-C does not include all the atherogenic lipoproteins [56]. Non-HDL-C is calculated by subtracting HDL-C from total cholesterol. It does not require fasting samples as it is not dependent on the measurement of triglyceride levels. Non-HDL-C content and ApoB are indices of total atherogenic particle burden. They are better markers of CVD risk than LDL-C alone, especially in patients receiving statin therapy [57], although controversy exists about which is better [58]. The Emerging Risk Factors Collaboration (ERFC) analyzed data from 302,430 participants without CVD from 68 studies with 18,368 CVD outcomes over a median follow-up of 10.4 years and found that non-HDL-C was a better predictor of CVD risk than directly measured LDL-C [42]. However, in a subset of 37 studies containing 165,544 patients, adding ApoB to LDL-C added little to risk prediction [59].

LDL subfractions

The LDL class comprises a heterogeneous population of particles [60]. LDL is heterogeneous with respect to lipid composition, charge, density, and particle size and shape [61]. sdLDL particles may be more atherogenic than large particles as they are more readily oxidized and glycated [62]. Large numbers of studies, including the Quebec Cardiovascular study [63], have confirmed the association of sdLDL with CVD independent of LDL-C, triglyceride, and the total cholesterol : HDL-C ratio. Biochemical assays exist for sdLDL using either precipitation allied with spectrophotometric detection or nuclear magnetic resonance spectroscopic measurement of particle size and number [64]. However, no prospective studies have specifically examined whether altering particle size profiles results in benefits on CVD events although analysis of the VA-HIT study does suggest some role for this mechanism [65], although particle numbers (analogs of non-HDL-C, ApoB) are better. Even with effective LDL-C treatment,

the residual risk of further CVD remains high, emphasizing the potential importance of improving other lipid abnormalities commonly observed in these individuals [56, 66].

Triglycerides

Triglycerides (also referred to as triacylglycerols) are formed from a single molecule of glycerol combined with three fatty acids and represent a heterogeneous group of molecules that are measured collectively [67]. The two main sources of plasma triglycerides are exogenous (i.e. from dietary fat) carried in chylomicrons produced by the gut and endogenous sources carried in very low-density lipoprotein (VLDL) particles produced by the liver. These particles are hydrolyzed by LPL to release free fatty acids under the control of an activator, apolipoprotein C-2 (ApoC-2), or inhibited by the action of ApoC-3 [68]. The reason for the elevated triglycerides in diabetes is complex [69]. Defects in insulin action and hyperglycemia can lead to parallel changes in plasma lipoproteins in persons with diabetes, as is seen in acute-presenting poorly controlled T1DM. Alternatively, as often occurs in T2DM, obesity and insulin resistance lead to secondary lipid abnormalities [70, 71]. Hepatic VLDL particle and hence its ApoB core component production are increased in T2DM [56], secondary to increased free fatty acid flux to the liver as a consequence of increased adipose tissue lipolysis occurring a result of insulin resistance and/or insulin deficiency. Several meta-analyses have found, however, that triglycerides are an independent risk factor for CHD [72–74]. As high serum triglyceride levels are associated with abnormal lipoprotein metabolism, and co-segregate with other CVD factors including obesity, insulin resistance, diabetes, and low levels of HDL-C, it is difficult to establish them as an independent CVD risk factor, and studies can give conflicting results [42, 72]. Some causes of hypertriglyceridemia have no apparent effect on atherosclerotic vascular disease, making it difficult to prove that elevated triglycerides are a risk factor for it [75].

Statins and triglycerides

Statins form the mainstay of lipid management based their efficacy in lowering LDL-C. Statins upregulate LDL receptor (LDLR) expression. The LDLR can act as a receptor for ApoE at low affinity and for apolipoprotein B-100 (ApoB) at high affinity. Triglyceride-rich particles contain many molecules of ApoE but only one ApoB. Thus statins can reduce triglyceride levels through their effect on LDLR expression and its ApoE action in clearing triglyceride-rich particles. This effect on triglycerides can be quantified as being related to the efficacy of the statin in reducing LDL-C and to the baseline triglyceride level [76].

Fibrates

Fibrates act on the nuclear receptor peroxisome proliferator-activated receptor alpha (PPAR-α) to increase lipoprotein lipase activity and reduce ApoC-3 and may, in a drug-specific manner, also increase HDL-C or decrease fibrinogen [77]. They reduce non-HDL-C but either have no effect on LDL-C levels (gemfibrozil) or produce a slight reduction (fenofibrate). Clinical trials of these drugs have reported mixed results in general and most early trials recruited only a few individuals with diabetes [78, 79].

The Veterans Affairs High Density Lipoprotein Cholesterol Intervention Trial (VA-HIT) recruited 2531 men with established CVD with low HDL-C (0.95 mmol/L) and moderate LDL-C (2.90 mmol/L), of whom 25% had T2DM. Gemfibrozil treatment had no effect on LDL-C, decreased triglycerides by 31%, and increased HDL-C by 8%, leading to a 22% reduction in CVD events [80]. The effects of gemfibrozil correlated with changes in HDL-C in the trial but not triglycerides [81]. Gemfibrozil therapy was more effective in people with T2DM as they showed a 32% relative risk reduction versus 18% in the non-diabetes group [82]. However, the enthusiasm for fibrate use has been considerably damped by results of the Fenofibrate Intervention and Event Lowering in Diabetes (FIELD) study [83]. This trial randomized 9795 people with T2DM, mostly without existing CVD, to fenofibrate (200 mg daily) or placebo. Fenofibrate produced a 12% LDL-C reduction, a 29% triglycerides reduction, and a 5% increase in HDL-C, resulting in a non-significant 11% reduction in the primary end-point of CHD events ($p = 0.16$). However, the similar 11% reduction in the secondary CVD events was significant ($p = 0.04$). The study was confounded by asymmetric statin drop-in with many more participants in the placebo arm being initiated on statin therapy during the trial (17%) than those in the fenofibrate arm (8%) [78]. Further analysis of the FIELD study showed benefits of fibrate therapy on microvascular endpoints, including reduced retinopathy complications and treatments, amelioration of diabetic proteinuria, and a reduction in amputation rates for peripheral arterial disease.

As statins are accepted first-line therapy for lipids in T2DM, the secondary role of fibrates is unclear. The ACCORD lipid study recruited 5518 participants with T2DM already treated with simvastatin 20 mg with moderate dyslipidemia. Fenofibrate therapy was associated with a 19% reduction (0.5 mmol/L) in LDL-C, a 26% reduction in triglycerides, and an 8% increase in HDL-C. These lipid changes were associated with an overall non-significant 8% reduction in CVD events. Subgroup analysis of the high triglyceride (>2.3 mmol/L), low HDL-C (<0.80 mmol/l) suggested a 29% reduction in CVD events with fibrate therapy. As in FIELD, fibrate therapy in ACCORD was associated with a reversible 13% rise in creatinine (with no increase in renal adverse outcomes and benefits on diabetic retinopathy). It is difficult to compare fibrate trials as they seem to give heterogeneous results depending on the compound used, with the greatest benefits with gemfibrozil. However, gemfibrozil interacts with statins to increase rates of myositis, so is not commonly used. Fibrates have not been shown to reduce all-cause or CVD mortality, but meta-analyses suggest that they do reduce non-fatal MI [84, 85] (Figure 43.5).

Omega-3 fatty acids

Omega-3 fatty acids reduce triglycerides in a dose–proportional manner [86] through actions at the GP120 receptor that links to both anti-inflammation and PPAR-γ pathways [87]. They have little effect on HDL-C and may increase LDL-C through a

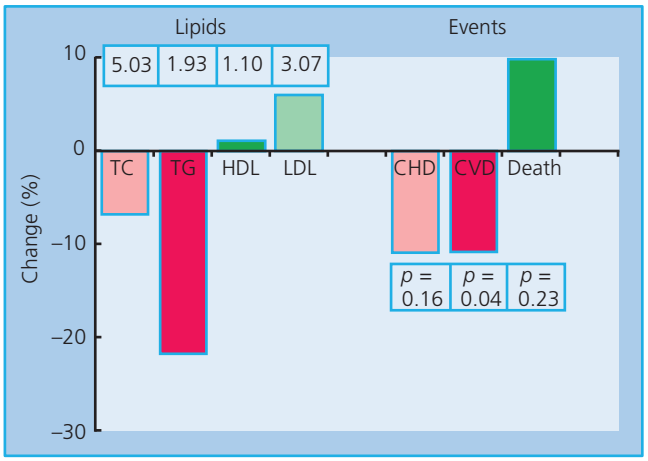

Figure 43.5 Reductions in mortality, CHD, and cardiovascular events with fibrate therapy [84, 85].

redistribution effect. Early dietary and intervention trials of low-dose omega-3 fatty acid acids suggested that they might have CVD benefits in some cases but the results could not be reproduced [88]. More recent clinical trials of omega-3 fatty acid therapy in 12,536 people with impaired glucose tolerance and T2DM failed to show any benefits for this intervention [89], and meta-analyses continue to find no evidence for their CVD benefit [88, 90].

Other triglyceride-reducing agents

Hypoglycemic agents may also have an effect on triglyceride concentrations due to the peripheral actions of insulin on adipose and muscle or via their action on LPL. In poorly controlled T1DM and even ketoacidosis, hypertriglyceridemia and reduced HDL-C are seen to occur and this is most often corrected with insulin therapy. In T2DM, metformin [91], sulfonylureas, acarbose, thiazolidinediones, dipeptidylpeptidase inhibitors [92], and glucagon-like peptide-1 (GLP-1) receptor agonists [93] all show modest reductions in triglycerides that correlate with glycemic control [94, 95]. However, pioglitazone and rosiglitazone have distinctly different effects on PPARs and lipid profiles [77, 96]. Pioglitazone is associated with a reduction in triglycerides, unlike rosiglitazone. Efforts have been made to unite the lipid- and glucose-lowering effects of PPARs in one molecule. Aleglitazar, a dual PPAR agonist (PPAR-α/γ), reduced HbA_{1c} (PPAR-γ), but also reduced triglycerides and LDL-C and increased HDL-C (PPAR-α). However, the AleCardio study in 7226 people with T2DM and acute coronary syndrome was stopped early as it failed to show any benefit of aleglitazar despite reductions in HbA_{1c} and benefits in lipid profiles [97]. None of the PPAR-α/γ class have shown an adequate safety or efficacy profile. Other new diabetes drugs are currently being assessed in CVD outcomes studies [98].

A number of other interventions exist that reduce triglycerides secondary to their action in reducing weight [99]. Orlistat has been shown to prevent progression to diabetes by 37% in the 3305 patients in the XENical in the Prevention of Diabetes in Obese Subjects (XENDOS) study [100]. Other weight-loss interventions, including sibutramine [101] and rimonabant [102], have shown adverse effects on CVD outcomes or on mental health and have been withdrawn. High-dose GLP-1 receptor agonists have recently been approved for weight reduction.

HDL-C

Analogous to LDL, the HDL class also comprises a heterogeneous population of particles [56, 103]. The inverse relationship between HDL-C levels and atherosclerotic CVD provides the epidemiological basis for the widely accepted hypothesis that HDL is atheroprotective, as it has several distinct but potentially overlapping atheroprotective functions. [104]. These include reverse cholesterol transport and reductions in oxidative stress and innate immune inflammation. More HDL-associated proteins are involved in immune/inflammatory functions than in lipid transport and metabolism, suggesting the fundamental role for HDL in innate immunity [105]. Reductions in HDL-C levels occur in T2DM secondary to insulin resistance and an increase in renal clearance of small dense HDL (sdHDL) particles as a consequence of overactivity of cholesterol ester transfer protein and hepatic lipase allied with inhibition of lipoprotein lipase activity and reduced LDLR uptake of triglyceride-rich lipoproteins [56]. In contrast, in T1DM HDL-C levels are normal or even increased [106]. However, HDL reverse cholesterol transport function is impaired in both T2DM [107] and T1DM [108]. The role of intervention in HDL-C levels to improve CVD outcomes is far from clear, although many drugs are under development for this indication [109].

HDL infusion studies

Some HDL therapies may reduce CVD without actually changing plasma HDL-C concentrations although they accelerate HDL particle and cholesterol turnover [110]. A pilot study of five infusions at weekly intervals of a hyperfunctional ApoA-I Milano produced significant regression of coronary atherosclerosis after 3 months in an intravascular ultrasound study in normoglycemic individuals [110]. However, infusion of similar quantities of exogenous native HDL particles failed to show any benefit [111].

Niacin

Niacin (nicotinic acid) raises HDL-C, reduces triglycerides and LDL-C, and has been referred to as the "broad-spectrum" lipid drug [112] through actions on adipose tissue receptors, inhibition of hepatic diacylglycerol acyl transferase, and HDL holoparticle receptors [113]. Niacin has been hampered by its side effects, particularly flushing and hyperglycemia. Niacin was the first lipid-lowering agent to show a significant reduction in CVD events but not mortality. The Coronary Drug Project (CDP) randomized 3908 men with previous MI to either 3 g niacin or placebo [114]. Niacin therapy reduced CVD events by 22% but there was no effect on mortality. However, in the 15-year post-trial follow-up, mortality was reduced by 11% in the niacin-treated group [115]. The CDP showed that niacin was equally effective in reducing CVD outcomes in participants with hyperglycemia

Table 43.1 Effects of different cardiovascular therapies on lipids and other cardiovascular risk factors and endpoint trial evidence of effects in prevention of diabetes and CVD.

	Component of the cardio-metabolic syndrome change (%)						
Drug/treatment group	**LDL-C decrease**	**HDL-C increase**	**TG decrease**	**SBP decrease**	**Glucose decrease**	**DM risk reduction (%)**	**CVD risk reduction (%)**
Metformin	0–10	15	15	0–5	10	45–48	35
Sulfonylurea	0–5	0	0	3	0	?	20
Thazolidinedione	–5 to 10	9	12	5	8	51–58	0 to –16
Statin	20–55	0–15	15–25	0	0	0–14	20–55
Fibrate	0–10	2–16	15–24	0–8	0–6	0–23	11
Orlistat	0–5	3	1	1	4	43	?

CVD, cardiovascular disease; DM, diabetes mellitus; SBP, systolic blood pressure; TG, triglycerides.

(now classified as T2DM) as normoglycemia [116] but also that it increased new-onset T2DM by 16% [117]. Large outcome studies have now reported on the efficacy of niacin in the context of background statin therapy. The Atherothrombosis Intervention in Metabolic Syndrome with Low HDL/High Triglycerides: Impact on Global Health Outcomes (AIM-HIGH) trial recruited 3414 dyslipidemic high-risk individuals, including 34% with T2DM. The trial protocol allowed adjustment in-trial of LDL-C-lowering therapy including (unbalanced) addition of ezetimibe. Niacin treatment reduced LDL-C by 7% (0.14 mmol/L) and triglycerides by 20% and increased HDL-C by 16% with no effect on CVD outcomes, which led to the termination of the trial after 3 years [118]. The Heart Protection Study 2—Treatment of HDL to Reduce the Incidence of Vascular Events (HPS2-THRIVE) trial recruited 25,673 high-risk persons with prior CVD or diabetes (32%) with prior adjustment of LDL-C to <2 mmol/L with ezetimibe. Niacin–laropiprant reduced LDL-C by 16% (0.25 mmol/L) and increased HDL-C by 14% (0.16 mmol/L) but had no effect on CVD events [119]. Niacin therapy increased the risk of serious adverse events, including myositis, bleeding, infection, and increased rate of diabetes [119, 120]. Niacin–laropiprant has been withdrawn and guidelines discourage the use of niacin in diabetes.

CETP inhibition

CETP transfers cholesterol in exchange for triglyceride from HDL particles to VLDL particles. Individuals with CETP deficiency show very high plasma HDL-C and low plasma LDL-C and may have a reduced risk of CVD [56]. A number of therapies have been developed to inhibit CETP activity. The first CETP inhibitor, torcetrapib, increased HDL-C by 72% and decreased LDL-C by 25% in the Investigation of Lipid Level Management to Understand Its Impact in Atherosclerotic Events (ILLUMINATE) trial, which had recruited 15,067 participants at high risk of CVD [121]. This trial was terminated early owing to a 25% increase in CVD events and a 40% increase in CVD deaths in the torcetrapib arm, likely related to the hypertensive off-target effects of this particular molecule [121]. Another CETP inhibitor, dalcetrapib, had lesser effects on lipid profiles, increasing HDL-C by 30% and with no effect on LDL-C. The dal-OUTCOMES study, which recruited 15,871 individuals with acute coronary syndrome, showed no benefit of this drug and was terminated early on grounds of futility [122]. There was a slight reduction in triglyceride levels but no change in LDL-C levels. Two other CETP inhibitors, anacetrapib and evacetrapib, with HDL-C-increasing effects similar to that of torcetrapib but no blood pressure effects, remain in development [109].

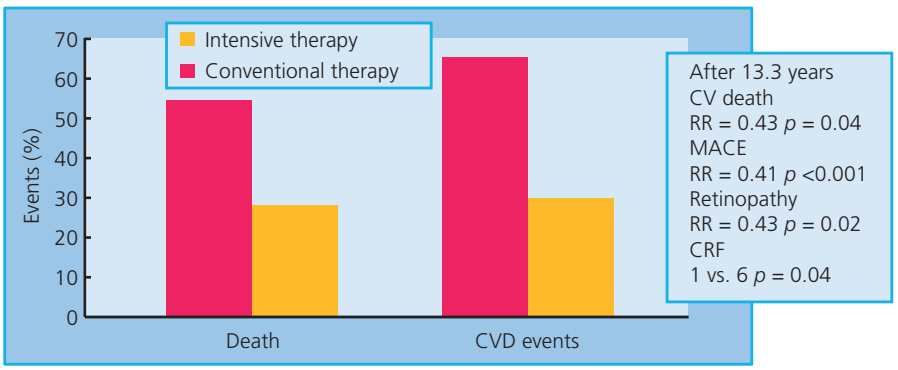

Figure 43.6 Effects of improved multiple risk factor intervention on mortality and cardiovascular events in diabetes. Steno 2: composite endpoint of death from CV causes, non-fatal MI, CABG, PCI, non-fatal stroke, amputation, or surgery for PAD. MACE, major adverse cardiovascular event; RR, relative risk. Source: Adapted from Gæde et al. 2003 [128] and 2008 [129].

Guidelines and lipids in diabetes

The major guidelines agree that diabetes is a major risk factor for CVD but differ in whether they classify diabetes as a CVD risk equivalent, thus mandating early lipid-lowering treatment. Most state or imply treatment from the age of 40 years [16] or after a 10-year history of diabetes if microvascular complications are present [17]. The UK NICE guidelines suggest the use of the QRISK2 calculator in T2DM with a 10% 10-year risk threshold similar to that for persons without diabetes [22].

All guidelines agree that LDL-C reduction is the first priority for reducing CVD risk in diabetes and that this should be done through high-intensity statin therapy [16, 17, 22]. The newest guidelines do not have LDL-C targets but recommend treatment with high-intensity statin (e.g. atorvastatin 20 mg or more) based on other underlying CVD risk factors [16, 22], while the European guidelines still suggest an LDL-C target of 2.0–2.5 mmol/L [17]. Guidelines do not recommend treatment to address triglycerides or HDL-C apart from statins based on current trial evidence, but comment that both hypertriglyceridemia and low HDL-C increase underlying CVD risk.

Future drug developments and drug targets

Drugs that target the exogenous and or the endogenous pathways of cholesterol metabolism may prove to be useful in the future [109]. These include additional therapeutics for LDL-C, for example, proprotein convertase subtilisin kexin type 9 (PCSK-9) inhibitors [123], thyroid mimetics (thyroid receptor β-agonists, e.g. eprotirome or derivatives), antisense oligonucleotides to ApoB (e.g. mipomersen), or microsomal transfer protein inhibitors (MTPIs) (e.g. lomiptapide); and triglycerides, for example, antisense oligonucleotides to ApoC-3, novel PPAR agonists, MTPIs, diacylglycerol acyl transferase-1 inhibitors, and HDL-C, for example, mimetic peptides; HDL delipidation strategies; or CETP inhibitors. Gene therapy using alipogene tiparvovec for lipoprotein lipase deficiency, a rare lipid disorder associated with T2DM caused by chronic pancreatitis, has now been licensed [124].

The most likely innovation in lipid management in diabetes is likely to be the introduction of the injectable anti-PCSK-9 antibody therapies. PCSK-9 is a recently discovered protein that regulates LDL receptor expression. Autosomal dominant activating mutations in PCSK-9 cause familial hypercholesterolemia (and thus increased CVD events) whereas inactivating mutations have been shown to be associated with 0.3–0.5 mmol/L reductions in plasma LDL-C and 70–80% lifetime reduced risks of CHD events [123]. Polymorphisms in PCSK-9 are associated with CVD risk in T2DM [125]. Antibodies to PCSK-9 reduce plasma LDL-C by 50–65% including in people with T2DM [126].

Given the importance of atherosclerosis as a cause of morbidity and mortality in diabetes, numerous therapeutic approaches are under development, but all will require systematic evaluation through endpoint clinical trials to validate their effects in animal models or on surrogate markers [127].

Conclusions

CVD is a very common complication of diabetes, with up to 80% of all people with diabetes dying from macrovascular complications. Lifestyle intervention is both effective and paramount to prevent and treat diabetes and its dyslipidemia. Statins have revolutionized preventive cardiovascular medicine and this has formed the foundation of therapeutic lipid intervention. The abnormalities in lipids and lipoproteins represent only one factor among several that are responsible for the increased risk in persons with diabetes (Table 43.1) and therefore multifactorial intervention is required. Trials suggest that multifactorial approaches to CVD risk in diabetes can reduce events and mortality by 50% [128, 129] (Figure 43.6).

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44 Ischemic Heart Disease in Diabetes

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Key points

- Ischemic heart disease (IHD) is the most common cause of death in people with diabetes.
- Glucose lowering is important for the prevention of microvascular disease in diabetes; its impact on IHD is less clear.
- Lowering low-density lipoprotein (LDL) cholesterol is highly effective in lowering cardiovascular event risk in persons with diabetes; the LDL cholesterol goal in persons with type 2 diabetes mellitus (T2DM) and also in those with type 1 diabetes mellitus (T1DM) who have end-organ damage is <70 mg/dL.
- Treating arterial hypertension also is important; currently a blood pressure <140/90 mmHg is recommended for people with diabetes, with <130/80 mmHg as an optional target especially for younger individuals.
- Aspirin is recommended in people with diabetes who already have established cardiovascular disease (CVD) or otherwise are at a >10% risk of atherosclerotic CVD over 10 years.
- Screening for coronary heart disease in asymptomatic individuals with diabetes is not generally recommended.

Epidemiology

Ischemic heart disease (IHD) is by far the leading cause of death in people with diabetes; about half of them will eventually die from IHD [1]. Understanding the pathophysiological links between diabetes and coronary heart disease and gaining a thorough knowledge of the therapeutic options to prevent IHD in persons with diabetes are therefore of the utmost importance.

The close link between diabetes and IHD has long been recognized. In a 1998 landmark study [2], Haffner et al. reported that individuals with diabetes who had not had a previous acute myocardial infarction (MI) were at the same risk of future IHD events as persons who had a prior MI but not diabetes. This observation, together with others, led to the concept of diabetes as a coronary heart disease risk equivalent [3].

This concept has been extremely important in establishing awareness of the very high-risk status of people with diabetes. Indeed, in current European prevention guidelines, the same aggressive approach to lipid lowering is recommended for persons with type 2 diabetes mellitus (T2DM) as is recommended for those with established cardiovascular disease (CVD) [4]. More recent research, however, including our own, revealed that the concept of diabetes as an IHD risk equivalent is an oversimplification [3, 5–7]. Not all people with diabetes are at the same risk of IHD. There are persons with diabetes, especially those with brief diabetes duration, who are at a much lower risk of future cardiovascular events than persons with established coronary heart disease, whereas other people with diabetes, in particular those with long diabetes duration and multiple other cardiovascular risk factors, are at a very much higher risk of cardiovascular events.

In this context, it is also important to consider that in persons with diabetes without a history of previous cardiovascular events, the prevalence of atherosclerotic disease is high [8]; subclinical atherosclerotic disease therefore may account for a large proportion of cardiovascular risk that has been falsely attributed to diabetes per se. When we characterized angiographically the coronary artery state both in people with and without T2DM, we found that those with diabetes who did not yet have significant coronary atherosclerosis were at a much lower risk of future cardiovascular events than those with established significant coronary artery disease (CAD) at angiography [5–7]. Importantly, cardiovascular risk in our investigation was extremely high in individuals with a combination of T2DM and significant coronary atherosclerosis at angiography.

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This is a common result of all investigations addressing the individual and combined effects of diabetes and previous coronary IHD on future cardiovascular event risk: the cardiovascular prognosis of people with a combination of diabetes and CAD is extremely unfavorable [3]. An important difference between the moderate risk individual with diabetes who did not have significant CAD and the very high-risk patients with a combination of diabetes and CAD in our investigations and also in other was the longer diabetes duration of the latter. CAD typically appears to be present in individuals with long-standing diabetes and is responsible for a dismal cardiovascular prognosis in these subjects. This stresses the utmost importance of efficacious intervention to reduce the development of IHD in persons with diabetes to keep their cardiovascular risk moderate.

Not only diabetes is associated with an increased risk of IHD, but prediabetes is also closely linked to increased cardiovascular risk. Research at our institution showed that individuals with impaired glucose tolerance have a higher prevalence of coronary atherosclerosis at angiography [9] and that their risk of future cardiovascular events is significantly higher than that in persons with normal glucose tolerance [10]. Indeed, cardiovascular risk in people with impaired glucose tolerance is intermediate between those with normal glucose tolerance and those with T2DM [10].

From a clinical point of view, it is desirable to obtain objective risk estimations in persons with diabetes. For example, the recently published pooled cohort equations can also be used for estimating cardiovascular risk in persons with diabetes [11]. Using these equations, one could estimate a 20% 10-year risk of atherosclerotic CVD in a 58-year-old white man with a total cholesterol level of 190 mg/dL and high-density lipoprotein (HDL) cholesterol of 38 mg/dL, who receives treatment for high blood pressure and has a systolic blood pressure of 135 mmHg and no smoking history. This compares with a 4.8% 10-year risk in a similar man with optimal risk factors. Even more dramatically, the lifetime risk of atherosclerotic CVD in this person is 69%. These numbers demonstrate the paramount importance of cardiovascular risk modification in patients with diabetes.

An important consequence of IHD is congestive heart failure, hence heart failure is a very important problem in individuals with T2DM [12]. This issue is discussed in Chapter 45.

Pathophysiological perspective

It is not surprising that prediabetes is associated with IHD. Diabetes as a clinical entity is diagnosed when fasting plasma glucose is ≥126 mg/dL or when glucose by 2 h after a 75-g oral glucose load is ≥200 mg/dL [13]. However, metabolic abnormalities that are associated with atherosclerosis in general and with IHD in particular typically exist for years or decades before diabetes becomes manifest [14, 15]. In particular, in the sequence of events that eventually leads to the development of diabetes, insulin resistance is a very early feature. This in turn is the key pathophysiological mechanism behind the metabolic syndrome, a cluster of metabolic abnormalities including elevated glucose, dyslipidemia, visceral obesity, and elevated blood pressure, all of which are independently linked to the development of atherosclerotic disease [14, 15].

T2DM becomes manifest only when β-cell failure develops on the background of pre-existing insulin resistance, i.e. when the demand for insulin supply caused by insulin resistance can no longer be fulfilled [14]. The atherogenic environment of multiple cardiovascular risk factors associated with the metabolic syndrome then typically has existed for years or decades. From this, it is clear that cardiovascular prevention must not be started at the stage of established diabetes but should take place much earlier.

When glucose levels increase in the case of transition from the metabolic syndrome to T2DM, the cardiovascular risk becomes even greater. In addition to the atherogenic metabolic syndrome stigmata mentioned below, glucose, through oxidative stress, can cause additional harm to the endothelium [16]. Importantly, however, glucose even in the stage of established diabetes is not the only and not even the main driving force of IHD disease risk. This is an important difference in comparison with the paramount role of elevated glucose for diabetic microangiopathy. In contrast to diabetic macroangiopathy (i.e. atherosclerotic disease, of which IHD is the most important manifestation), diabetic microangiopathy is directly caused by elevated glucose and therefore is diabetes specific. The risk of macroangiography is strongly elevated in persons with diabetes, but of course atherosclerosis also occurs in individuals who do not have diabetes.

The above-mentioned pathophysiology applies to T2DM, which is particularly closely linked to CVD. Type 1 diabetes mellitus (T1DM) also is associated with an increased cardiovascular risk [17]. However, the time span between diabetes manifestation and the development of IHD is longer in T1DM than in T2DM. In addition to direct glucotoxicity, impairment of kidney function is an important mechanism linking T1DM to IHD risk. Indeed, once chronic kidney disease has developed, the cardiovascular risk strongly increases. In fact, we have found that albuminuria, a hallmark of diabetic nephropathy, is an MI risk equivalent [18].

How can cardiovascular risk be reduced in persons with diabetes?

Glucose lowering

Given that diabetes is diagnosed when glucose is elevated, at first sight lowering glucose would appear to be an attractive approach to reduce the increased cardiovascular risk in people with diabetes. Unfortunately, however, the results of numerous intervention trials addressing cardiovascular risk modification by lowering of glucose are disappointing.

The classical United Kingdom Perspective Diabetes Study (UKPDS) enrolled more than 4000 individuals with newly diagnosed T2DM [19]. Among other interventions, intensified glucose lowering was compared with conventional treatment;

participants were followed up over 10 years. Although the incidence of microvascular diabetes complications was significantly reduced with intensive glucose lowering, macrovascular events, in particular MI, stroke, and peripheral arterial disease, were not significantly reduced. There was a non-significant trend towards a lower MI incidence in people with intensive glucose control. One objection was that glucose lowering in the intervention arm might not have been aggressive enough in the UKPDS. However, three further trials, Action to Control Cardiovascular Risk in Diabetes (ACCORD), Action in Diabetes and Vascular Disease: Preterax and Diamicron Controlled Evaluation (ADVANCE), and the Veterans Affairs Diabetes Trial (VADT), also did not show a reduction in macrovascular diabetes events with more aggressive glucose lowering [20–22].

For example, in ADVANCE [21], more than 11,000 participants with T2DM were randomized to intensive glucose control, aiming at an HbA_{1c} of <6.5% versus standard glucose control according to country guidelines. During a follow-up period of 5 years, a combined macro- plus microvascular endpoint was significantly reduced by 14%; macrovascular events were not reduced at all.

Interestingly, however, when longer time periods were observed, a benefit of more intense glucose lowering appeared to emerge. For example, in the UKPDS trial, a 10-year post-trial follow-up revealed significant reductions in MI among individuals whose glucose was lowered more aggressively [23]. In ADVANCE, a long-term follow-up did not show a benefit with regard to major vascular events [24], whereas in the VADT [25], similarly to the UKPDS, a significant reduction in macrovascular events was observed with more aggressive treatment of glucose over 10 years.

In people with T1DM, the Diabetes Control and Complications (DCCT) trial failed to show a significant reduction in macrovascular events during the original study period [26], but a long-term follow-up suggested a significant reduction in macrovascular events over a long period of 17 years [27]; the pattern of a long-term benefit in the absence of a short-term benefit of glucose lowering with regard to cardiovascular event risk is therefore the same in T1DM as in T2DM.

Overall, glucose lowering appears to provide a long-term benefit with regard to IHD in persons with T2DM and T1DM. However, this must be treated with some caution because the analyses showing long-term benefit were not the primary study results but post hoc extension analyses of existing clinical trials.

Discomfortingly, in the ACCORD trial [20], mortality and cardiovascular event risk were higher in participants receiving more intense glucose lowering. This suggests that overly aggressive glucose lowering in people with diabetes in fact may do harm with respect to cardiovascular event risk. Indeed, more intensive glucose lowering is associated with more weight gain and, probably more important, with more hypoglycemia.

Hypoglycemia is associated with an increased risk of cardiovascular events [28]. Considering that hypoglycemia both prolongs the action potential and leads to myocyte calcium overload, this is not surprising: both diabetes itself and pre-existing CAD already lead to these electrophysiological abnormalities, which are then even more severely pronounced in the case of hypoglycemia. Prolongation of the action potential and myocyte calcium overload are the most important triggers of arrhythmia [29].

Because there currently is no clear evidence for the reduction of IHD events by aggressive glucose lowering, the American Diabetes Association (ADA) recommends an HbA_{1c} of <7.0% for the prevention of microvascular complications [13]. The above-mentioned results from long-term observations following clinical intervention trials for glucose lowering suggest that more aggressive glucose lowering may be favorable in the long term, especially for those individuals in whom lowering glucose values can be achieved without an increase in hypoglycemia. These are mainly relatively healthy individuals who do not have a long-standing history of diabetes and do not have severe comorbidities.

An important question is whether any particular antidiabetes drug has a benefit with regard to IHD in patients with T2DM. For insulin, the Outcome Reduction with Initial Glargine Intervention (ORIGIN) trial randomizing people to insulin glargine versus standard care did neither show a decrease or an increase in total cardiovascular events or IHD events with insulin glargine [30]. Metformin, in a small subset of 342 among a total of 1704 overweight individuals in the UKPDS, trial led to a 36% reduction in total mortality [31]. However, the small sample size makes it difficult to draw definite conclusions. In the STOP-Noninsulin-Dependent Diabetes Mellitus (STOP-NIDDM) trial, acarbose led to a reduced incidence of cardiovascular events among those with impaired glucose tolerance [32]; no corresponding data for people with diabetes are available.

Somewhat better evidence for cardiovascular risk reduction is available for pioglitazone. In the Prospective Pioglitazone Clinical Trial in Macrovascular Events (PROACTIVE), 5238 people with T2DM and macrovascular disease were randomized to either pioglitazone 45 mg daily or placebo [33], and followed up for 3 years. The primary endpoint of PROACTIVE was very broad, including, in addition to death, non-fatal MI, stroke, acute coronary syndrome, leg amputation, coronary revascularization, and revascularization of peripheral arteries. With regard to the primary endpoint, the risk reduction with pioglitazone was non-significant; however, when the clinically more relevant secondary endpoint, including death, non-fatal MI, and stroke, was considered, a significant 16% event reduction was observed with pioglitazone compared with placebo. This result was confirmed by a subsequent meta-analysis that showed a decreased risk of death, MI, and stroke with pioglitazone [34]. The Pioglitazone Effect on Regression of Intravascular Sonographic Coronary Obstruction Prospective Evaluation (PERISCOPE) trial [35] additionally showed a reduction in CAD progression as visualized by intravascular ultrasound with pioglitazone, and the Carotid Intima-Media Thickness in Atherosclerosis Using Pioglitazone (CHICAGO) trial [36] demonstrated a favorable impact of pioglitazone on the progression of the carotid intima media thickness compared with the sulfonylurea glimepiride.

A similar favorable cardioprotective effect was not observed for another peroxisome proliferator-activated receptor gamma (PPAR-γ) agonist, rosiglitazone. On the contrary, meta-analyses suggested that rosiglitazone even increased cardiovascular risk [37]. Based on the disappointing results for rosiglitazone, the US Food and Drug Administration (FDA) in 2008 demanded that for all new antidiabetes drugs an increase in cardiovascular risk must be excluded in cardiovascular safety trials [38].

Subsequently, several such cardiovascular safety trials were published. For example, the Cardiovascular Outcomes Study of Alogliptin in Patients with Type 2 Diabetes and Acute Coronary Syndrome (EXAMINE) trial [39] enrolled 5380 people with T2DM who had acute coronary syndrome between 15 and 90 days before randomization; individuals were randomized to alogliptin versus placebo and then followed up for a median of 18 months. A primary endpoint of cardiovascular death, MI, and ischemic stroke occurred with similar frequency in alogliptin-treated and placebo-treated individuals based on prespecified power calculations. From this it was concluded that alogliptin is safe with respect to IHD. Analogously, the Saxagliptin Assessment of Vascular Outcomes Recorded in Patients with Diabetes Mellitus (SAVOR-TIMI 53) trial [40] demonstrated safety of saxagliptin with regard to the incidence of cardiovascular endpoints, and the recent TECOS trial [41] demonstrated safety of sitagliptin with respect to cardiovascular events, in particular the incidence of IHD.

Most recently, the Empagliflozin Cardiovascular Outcome Event Trial in Type 2 Diabetes Mellitus Patients (EMPAREG-OUTCOME) [42] was published; this was a cardiovascular safety study for the sodium–glucose co-transporter-2 (SGLT-2) inhibitor empagliflozin. Here, 7020 participants with T2DM and established CVD who had a baseline HbA_{1c} between 7.0 and 9.0% were randomized to receive either empagliflozin (in dosages of 10 or 25 mg/day) or placebo; follow-up was 3.1 years and the primary endpoint was a total of cardiovascular death, MI, and stroke. The primary endpoint was significantly reduced by 14% in participants receiving empagliflozin versus those receiving placebo; the absolute risk reduction was 1.6%, corresponding to a number needed to treat of 63. Further, cardiovascular death was significantly reduced by 38% and all-cause death by 32%. Whereas hospitalizations for heart failure were strongly reduced by 35% with empagliflozin, the incidence of MI was not significantly affected; also, unstable angina and stroke events were not reduced. This may suggest that the main beneficial effect of empagliflozin was achieved by mechanisms other than the inhibition of atherosclerosis progression. Nevertheless, empagliflozin has a very interesting profile with regard to cardiovascular risk management: it not only lowers blood glucose but also blood pressure and leads to a moderate weight reduction [42].

Lipid management

Lipids play an essential role in the development of IHD, and therefore are a central target in preventive cardiology, in particular also in people with diabetes (see Chapter 43). Lipoprotein metabolism in T2DM typically is altered in a specific manner [43]: owing to insulin resistance, an increased amount of free fatty acids is set free from adipose tissue in persons with T2DM, which are used to synthesize triglycerides in the liver. These triglycerides are packed into very low-density (VLDL) particles, which consequently are secreted in the blood. Therefore, triglycerides are elevated in persons with T2DM. Lipases hydrolyze triglycerides from these VLDL particles, which through intermediate-density lipoprotein (IDL) particles finally turn into low-density lipoprotein (LDL) particles, which, mediated by LDL receptors, are taken up in the liver where cholesterol is degraded into bile acids and secreted into the bowel as such.

Elevated triglycerides have a profound impact on both LDL and HDL particles. Mediated by the enzyme cholesteryl ester transfer protein (CETP), triglyceride-rich lipoproteins are exchanged for cholesterol from LDL and HDL particles. LDL and HDL particles thus lose cholesterol and receive triglycerides in turn. These triglycerides are then removed by the action of hepatic lipase, rendering both LDL and HDL smaller and denser. Smaller HDL particles are more rapidly removed from the blood by the kidney, which explains the low HDL cholesterol of individuals with T2DM; small, dense LDL (sdLDL) particles are particularly atherogenic and explain why persons with diabetes already at moderate LDL cholesterol levels are at a high risk of cardiovascular events.

In summary, lipid metabolism in people with diabetes is characterized by hypertriglyceridemia, low HDL cholesterol and sdLDL particles. The level of LDL cholesterol per se typically is not very high in persons with T2DM; as we have shown, rather it is lower in these individuals than in those without diabetes [44]. Nevertheless, the most successful lipid approach to reduce cardiovascular risk, i.e. lowering LDL cholesterol, is also efficacious in people with diabetes. A large meta-analysis enrolling over 18,600 people with diabetes from 14 randomized trials of statins showed that per 1 mmol LDL cholesterol reduction, the MI risk could be reduced by 22% in persons with diabetes, which was not significantly different from the 19% event reduction achieved with the same amount of LDL reduction in individuals without diabetes [45].

The more LDL cholesterol is reduced, the more cardiovascular risk is reduced [46], and this important fact holds true for almost any population and in particular also for individuals with diabetes. Recently, the IMProved Reduction of Outcomes: Vytorin Efficacy International Trial (IMPROVE-IT) [47] showed that not only statins but also ezetimibe are effective in lowering both LDL cholesterol and the risk of atherosclerotic disease in persons with diabetes. In IMPROVE-IT, 18,144 people with acute coronary syndrome were randomized to receive either simvastatin alone or simvastatin plus ezetimibe; in the placebo arm, a mean LDL cholesterol of 70 mg/dL was achieved, whereas in participants allocated to ezetimibe treatment, the mean LDL cholesterol was 54 mg/dL. Compared with placebo, cardiovascular events were significantly reduced by 6% in those receiving ezetimibe during 7 years of follow-up; the amount of risk reduction was the same as would have been expected if the LDL reduction had been achieved with a statin.

Subgroup analysis suggested that in the IMPROVE-IT trial, people with diabetes benefited particularly from LDL cholesterol lowering with ezetimibe. Lowering of LDL cholesterol with a statin or with additional ezetimibe treatment thus has proven efficacy in reducing cardiovascular events in particular in those with diabetes.

Highly potent LDL cholesterol-lowering drugs, proprotein convertase subtilisin kexin type 9 (PCSK9) inhibitors, are now available that are effective in strongly lowering LDL beyond what can be achieved with potent statins [48]. Whether these drugs also reduce cardiovascular events in people with diabetes is under investigation in ongoing clinical outcome trials; preliminary data already suggest a dramatic cardiovascular risk reduction with these innovative drugs.

Given the clear impact of LDL cholesterol reduction on cardiovascular risk reduction in persons with diabetes, the European Society of Cardiology (ESC) recommends an LDL cholesterol level of <70 mg/dL for individuals with T2DM and also for those with T1DM who already have end organ damage, as it does for other populations at very high cardiovascular risk [4]. Importantly, the safety of lowering LDL cholesterol either with statins or with statins plus ezetimibe has been clearly shown in large populations [45, 47].

As mentioned above, the typical lipid abnormality in persons with diabetes is not elevated LDL cholesterol but rather a combination of high triglycerides, low HDL cholesterol and small LDL particle size. Indeed, this lipid triad is a stronger predictor of cardiovascular events than elevated LDL cholesterol in high-risk persons with diabetes [49, 50]. The most important drugs for lowering triglycerides or raising HDL cholesterol are fibrates and nicotinic acid.

Two large trials, Atherothrombosis Intervention in Metabolic Syndrome with Low HDL/High Triglycerides: Impact on Global Health Outcomes (AIM-HIGH) [51] and The Heart Protection Study 2—Treatment of HDL to Reduce the Incidence of Vascular Events (HPS2-THRIVE) [52] investigated the power of nicotinic acid to reduce cardiovascular events over and above background treatment with statins. Both trials were neutral with regard to the major cardiovascular event outcome; nicotinic acid did not lead to a further reduction of cardiovascular events in statin-treated participants. Also the ACCORD lipid arm [53], which tested fenofibrate versus placebo in statin-treated participants with T2DM who were treated with simvastatin, did not show a significant reduction in cardiovascular events. Only the subgroup of participants with both triglycerides ≥204 mg/dL and HDL cholesterol ≤34 mg/dL showed a better cardiovascular outcome with fenofibrate than with placebo. Similar subgroup results were also observed in other trials investigating the power of fibrates to reduce cardiovascular events, for example, in the Helsinki Heart Study, in the Veterans Affairs High-Density Lipoprotein Intervention Trial (VA-HIT), in the Bezafibrat Intervention Project, and in the Fenofibrate Intervention and Event Lowering in Diabetes (FIELD) trial [54]. Therefore, in the subset of individuals with both high triglycerides and low HDL cholesterol, therapy with fibrates on top of statin therapy may reduce cardiovascular risk. Because of interaction and tolerability issues, fenofibrate should be used when a fibrate is combined with a statin.

Blood pressure management

The most recent Joint National Committee (JNC)-8 Guidelines recommend a general blood pressure target of ≤140/90 mmHg for the majority of individuals, in particular also for those with diabetes (see Chapter 42) [55]. Current ADA guidelines [13] recommend a blood pressure target of 130/80 mmHg as an optional target if this can be achieved with good tolerability, especially in younger individuals. Previously, a blood pressure target of <130/80 mmHg had been suggested for the majority of people with diabetes [56]. However, subsequent trial results became available that did not demonstrate a clear benefit of aggressive blood pressure lowering in persons with diabetes.

For example, in the blood pressure arm of the ACCORD trial, 4700 individuals with T2DM were randomized to a systolic blood pressure target <120 mmHg or standard therapy with a systolic BP target of <140 mmHg [57]. Mortality and IHD could not be reduced by more aggressive blood pressure lowering, but stroke events was reduced dramatically by 47%. More intense therapy, however, was associated with more arrhythmic events, hypokalemia, and hypotension, so this aggressive treatment target could not be generally recommended. Another study found that in persons with diabetes and established IHD, overly intense blood pressure lowering led to an increased mortality risk: in people with systolic blood pressure below 110 mmHg mortality was significantly increased compared with those with systolic BP between 125 and 130 mmHg [58]. Also in the VADT [59], a significant increase in cardiovascular event risk was observed when diastolic blood pressure was lowered to <70 mmHg. For persons with diabetes at high risk of cardiovascular events, in particular for those with established CAD, extremely low blood pressure targets therefore do not appear warranted.

Recently, the Systolic Blood Pressure Intervention Trial (SPRINT) was published, showing a significant reduction in cardiovascular events with aggressive blood pressure lowering to <120 versus <140 mmHg systolic blood pressure. However, persons with diabetes were excluded in SPRINT, so that definitive recommendations with regard to aggressive blood pressure lowering in diabetes will need further data [60].

Aspirin treatment

Whereas aspirin therapy in individuals with diabetes and established CAD is clearly indicated, the use of aspirin in the primary prevention of cardiovascular events is less clear, in persons both without and with diabetes. A potential reduction in cardiovascular event risk needs to be balanced against an increase in bleeding risk. Current ADA recommendations suggest aspirin use when the 10-year risk of atherosclerotic CVD is >10%, which usually is the case in men or women aged over 50 years who have at least one additional risk factor. No aspirin is recommended

when the 10-year cardiovascular risk of atherosclerotic cardiovascular disease is below 5%, which usually is the case in men or women below 50 years of age who do not have additional risk factors [13].

Screening for coronary heart disease in diabetes

An interesting issue is whether screening for CAD is useful in asymptomatic individuals with diabetes to guide treatment decisions. Current guidelines recommend against screening for CAD in persons with diabetes. Indeed, in this high-risk population, maximum risk factor control is indicated anyway, and randomized trials did not show a benefit regarding cardiovascular outcome with screening for CAD in individuals with diabetes [13].

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45 Congestive Heart Failure

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Key points

- There is a link between heart failure and not only diabetes but also impaired glucose tolerance.
- Glucose perturbations increase cardiovascular mortality in people with heart failure especially if due to ischemic heart disease.
- Evidence-based heart failure therapy has a proportionately similar efficacy in people with and without glucose perturbations.
- Certain glucose-lowering agents may be harmful (e.g. glitazones).
- Further studies are needed before glucose normalization can be recommended as a possibility for improving the prognosis.

Introduction

The concept that there may be a direct relation between diabetes and heart failure dates back to 1954 when the Danish Professor K. Lundbæk published an article on clinically important complications in people with diabetes underlining that heart disease was common; he was the first to suggest the presence of a diabetes specific cardiomyopathy [1]. Almost 20 years later, Rubler et al. [2] published supporting data, concluding that myocardial disease seemed to be a complication of diabetes in itself and was not caused merely by coronary artery disease (CAD). Shortly thereafter, the Framingham study presented epidemiological evidence for a strong relation between heart failure and diabetes. This study indicated that the relation between these conditions was not only due to traditional risk factors for CAD but also involved other mechanisms [3].

The prevalence of heart failure is increasing in Western societies owing to aging populations, but also because of increased survival in ischemic heart disease (IHD), especially myocardial infarction (MI) [4, 5]. There are many known causes of heart failure, including hypertension, CAD, valvular dysfunction, arrhythmias, anemia, renal failure, and thyroid dysfunction [4, 6–9]. Risk factors for and causes of the development of heart failure are presented in Figure 45.1. They include increasing age, hypertension, IHD (in particular previous MI), electrocardiographic signs of left ventricular hypertrophy, valvular dysfunction and cardiomegaly detected by chest X-ray, increased heart rate, and decreased pulmonary vital capacity. To these, diabetes is added as a strong risk factor. The Framingham study used several of these risk factors to construct a multivariate risk formula to identify high-risk candidates for heart failure [10]. Currently, however, IHD is the leading cause of heart failure in industrialized societies, with diabetes as a rapidly emerging risk factor [9]. Diabetes is one of the important risk factors in IHD [11, 12]. Considering the rapidly growing prevalence of diabetes [13], this means that the combination of diabetes and heart failure will be increasingly common in the future. Poor glucose control contributes to the development of heart failure, as reflected by the relation between an increase in glycated hemoglobin A_{1c} (HbA_{1c}) and the risk for developing heart failure [14, 15]. Based on data from the Swedish National Diabetes Registry, development of future heart failure was related to worse glucose control (>7%, 53 mmol/mol]) in persons with type 2 diabetes mellitus (T2DM) and with a 30% higher risk of heart failure for each 1% increase in HbA_{1c} in those with type 1 diabetes mellitus (T1DM) [14, 15]. Among individuals with heart failure, ~25% have previously known diabetes [16]. Interestingly, there are several reports describing that heart failure severity predicts the appearance of diabetes and increases the development of future glucose disturbances [17, 18]. Long-standing hyperglycemia may, even in the absence of other risk factors such as CAD, valvular heart disease, or hypertension, affect the myocardial tissue in individuals with diabetes, increasing the risk of myocardial dysfunction, and, as already indicated, there have been earlier reports on the existence of a specific diabetes cardiomyopathy [1]. This concept is still debated, however, because the frequent coexistence of diabetes,

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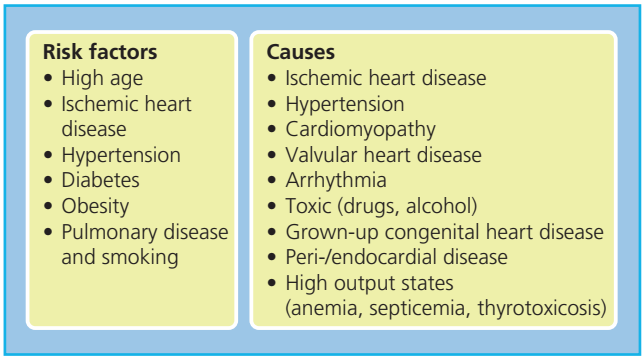


Figure 45.1 Risk factors and causes for heart failure. Source: ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure 2012. *European Heart Journal* 2012; **33**:1787–1847. Reproduced with permission of Oxford University Press.

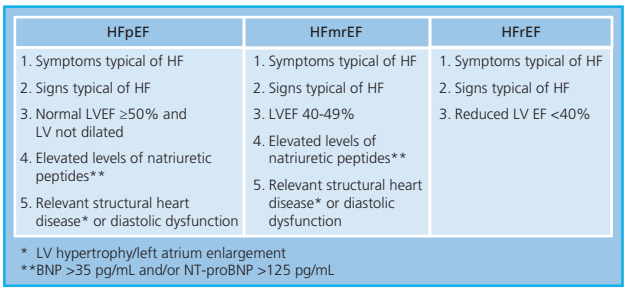
hypertension, and CAD, makes it difficult to decipher whether the myocardial dysfunction is triggered by the glucometabolic disorder itself, or rather is caused by synergistic action of these factors.

In summary, there is a strong link between the existence of heart failure and diabetes and both conditions are becoming increasingly common. The links between these disorders are complex and have not yet been fully explored.

Symptoms and diagnosis

The diagnosis and definition of heart failure

The diagnosis of heart failure is based on a combination of clinical symptoms and characteristic signs of myocardial dysfunction [4], as presented in Figure 45.2. In clinical practice, heart failure is commonly divided into two types based on left ventricular function usually investigated by echocardiography: heart failure with reduced ejection fraction (HF-REF) and with preserved ejection fraction (HF-PEF), also referred to as systolic and diastolic heart failure. The main differences are that in HF-REF systolic



HFpEF	HFmrEF	HFrEF
1. Symptoms typical of HF	1. Symptoms typical of HF	1. Symptoms typical of HF
2. Signs typical of HF	2. Signs typical of HF	2. Signs typical of HF
3. Normal LVEF ≥50% and LV not dilated	3. LVEF 40-49%	3. Reduced LV EF <40%
4. Elevated levels of natriuretic peptides**	4. Elevated levels of natriuretic peptides**	
5. Relevant structural heart disease* or diastolic dysfunction	5. Relevant structural heart disease* or diastolic dysfunction	

* LV hypertrophy/left atrium enlargement
**BNP >35 pg/mL and/or NT-proBNP >125 pg/mL

Figure 45.2 Types of heart failure according to European guidelines in 2016. HF, heart failure; HFpEF, heart failure with preserved ejection fraction; HFmrEF, heart failure with midrange ejection fraction; HFrEF, heart failure with reduced ejection fraction; LVEF, left ventricular ejection fraction. Based on Ponikowski et al. 2016 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure: The Task Force for the diagnosis and treatment of acute and chronic heart failure of the European Society of Cardiology (ESC). Developed with the special contribution of the Heart Failure Association (HFA) of the ESC. *Eur J Heart Fail* 2016 May 20. doi: 10.1002/ejhf.592. [Epub ahead of print]

Table 45.1 Classification of heart failure according to the New York Heart Association (NYHA).

NYHA Class I	No limitation of physical activities Patients without symptoms during ordinary activities
NYHA Class II	Slight to mild limitation of physical activity Patients comfortable at rest and mild exertion
NYHA Class III	Marked limitation of activity Patients comfortable only at rest
NYHA Class IV	Confined to complete rest in a bed or a chair

dysfunction is reduced, impairing the ejection of blood from the left ventricle. In HF-PEF, myocardial relaxation is compromised, which impairs ventricular filling. The diagnosis of HF-PEF is mainly performed by excluding causes other than cardiac for existing symptoms, making it a more difficult diagnosis than HF-REF. Echocardiography is the preferred and most commonly used method for documentation of left ventricular ejection fraction and function. Echocardiographic signs and criteria of diastolic dysfunction, which are influenced by age, heart rate, and body size, are developing and changing and it is important to appreciate that no single echocardiographic variable is sufficient. Judgment of diastolic function should include several variables from the echocardiogram, combining functional abnormalities, addressed by Doppler measurements (mitral inflow with E/A ratio, pulmonary vein velocity, and velocities on tissue Doppler imaging, E′), and structural abnormalities (e.g. left ventricular hypertrophy or dilation of the left atrium) [4, 19]. Further details can be found in published guidelines on heart failure [20, 21].

Plasma concentrations of natriuretic peptides and their precursors (N-terminal pro-brain-type natriuretic peptide [NT-proBNP]; BNP) are also helpful when diagnosing heart failure, particularly when the availability of echocardiography is limited. These peptides are secreted in increased amounts when the load of the atria or ventricles is increased. They are also useful in individuals with diabetes [4, 22]. Cut-off points differ for NT-proBNP and BNP. In individuals presenting with acute onset or worsening of symptoms, the optimal exclusion cut-off point is 300 ng/L for NT-proBNP and 100 ng/L for BNP [4].

The main clinical classification of the severity of heart failure is that presented by the New York Heart Association (Table 45.1). This classification is used for all people with heart failure irrespective of whether seen in a hospital or an outpatient setting and irrespective of etiology.

The diagnosis and definition of glucose abnormalities

Diabetes and its prestates are a group of metabolic disorders characterized by hyperglycemia due to defects in insulin secretion, insulin action, or both. Diabetes is associated with damage, dysfunction, and failure of various organs [23, 24]. The metabolic syndrome is an entity that has been defined in various ways [23], combining different cardiovascular risk factors including abnormalities in the glucose homeostasis. Further details on the classification and diagnosis of diabetes and other glucose abnormalities can be found in Chapter 2.

Epidemiology

Risk factors for heart failure and diabetes

The most important risk factors for cardiovascular disease (CVD) and MI are family history, smoking, abnormal blood lipids, hypertension, diabetes, obesity, and socioeconomic factors [11]. The morbidity is known to increase progressively with the number of existing risk factors [25]. Many of the risk factors for heart failure are by necessity similar to those of CVD, with IHD and hypertension as leading causes. Other common factors influencing the occurrence of heart failure are male gender, smoking, overweight, physical inactivity, valvular heart disease, and atrial fibrillation [4]. T1DM and T2DM and also poor glucose control observed as high fasting plasma glucose and elevated HbA_{1c} are also of considerable importance. In T1DM, glucose control and duration of diabetes are strong risk factors [14, 15, 26–31].

Risk factors for T2DM are family history, age, overweight or increased waist/hip ratio, and a sedentary life-style [32, 33], i.e. similar risk factors to those for heart failure and CAD. Particular risk factors for CAD in T2DM are lipid perturbations, including small, dense, easily oxidized low-density lipoprotein (LDL) particles, low high-density lipoprotein (HDL) cholesterol, and increased triglycerides. Moreover, poor glycemic control observed as high fasting plasma glucose and elevated HbA_{1c} also contribute [34]. Hypertension and signs of renal damage (proteinuria) are other important risk factors for cardiovascular complications and heart failure in persons with diabetes [35]. The Reykjavík Study showed a strong relation between fasting and post-load glucose levels and subsequent risk for hypertension, even after adjustment for age, body mass index, and weight gain, which is interesting since hypertension is one of the main risk factors for heart failure [28, 29]. Individuals with diabetes and heart failure have more IHD and hypertension and a higher HbA_{1c} than those without diabetes [16, 30]. In a registry report from Sweden, including 36,274 individuals hospitalized for heart failure during 2003–2011, 25% had diabetes and as many as 60% had a previous history of IHD [16]. In summary, there are many mutual risk factors for heart failure and glucose abnormalities.

Prevalence of heart failure and glucose abnormalities

Prevalence of heart failure

In the general population, the prevalence of heart failure varies in different studies, partly due to differences in the definition of this disease [4]. The demand that a diagnosis of heart failure should be supported by evidence of dysfunction on echocardiography may be difficult to fulfill in epidemiological studies. Modern echocardiographic techniques did not exist when several of the studies that still serve as important sources of information were conducted [36, 37]. The prevalence of heart failure has been estimated to be 0.6–6.2% in Swedish men with an increase with age [38]. This is similar to the overall prevalence of heart failure in both sexes in the Rotterdam population and in the Reykjavík Study [39, 40]. The prevalence of heart failure was 1–10% in a British outpatient population [20]. It increases considerably when considering elderly populations, as exemplified by the Italian Campania study, in which the prevalence was 9.5%, once again underlining the impact of age [17]. In summary, the prevalence of heart failure is about 1–2%, increasing to >10% at ages above 70 years [41].

Prevalence of diabetes

Diabetes is often an undiagnosed condition and the International Diabetes Federation (IDF) estimates that about 50% of all individuals with this disease are undiagnosed [42]. Diabetes prevalence depends highly on age, type of population investigated, and screening methods. When screening a Belgian outpatient population with one known cardiovascular risk factor, diabetes was detected in 11% and an additional 3% had impaired glucose tolerance (IGT) [43]. The prevalence of diabetes was 7.8% in Swedish men and 5.1% in women aged 35–79 years, with similar proportions reported from a Finnish middle-aged population [44, 45]. The prevalence of diabetes may be considerably higher in selected high-risk populations, especially those with CAD. In the GAMI study, as many as 25% of patients with MI had previously unknown diabetes when investigated with an oral glucose tolerance test (OGTT) 3 months thereafter, and 40% had IGT [46]. In the Euro Heart Survey Diabetes and the Heart, individuals admitted to hospital because of acute and stable CAD were investigated for the presence of diabetes and IGT. Only 29% of the 4961 participants had a normal glucose metabolism and 31% had known and 12% previously unknown diabetes; the remaining 28% had IGT [47]. Similar proportions were detected in populations with cerebral and peripheral vascular disease [48]. Thus the combination of CAD and glucose perturbations is very common and in many previous studies underestimated owing to lack of diagnostic accuracy in combination with a thorough investigation of the glucometabolic state.

There is increasing evidence that the prevalence of the combination of diabetes and heart failure is undiagnosed and common in the general population. In the Reykjavik population study, the prevalence of diabetes and heart failure was investigated with OGTT and X-ray examination, respectively. The prevalence of combined heart failure and diabetes was 0.5% in men and 0.4% in women, increasing with age [40]. Diabetes was found in 12% of those with heart failure compared with only 3% of those without heart failure. Hence there was a strong association between diabetes and heart failure.

Based on Framingham data, Rutter et al. [49] noted that the heart is prone to changes in the form of increased left ventricular mass and wall thickness with worsening glucose tolerance. Kannel et al. [3] and Gustafsson et al. [50] reported on the role of diabetes in heart failure from a general and a hospitalized population, respectively. Their findings indicated a strong association between heart failure and diabetes. Iribarren et al. [51], Bertoni et al. [52], and Nichols et al. [30], focusing on the role of heart failure in people with diabetes, noted that the prevalence of heart failure varied between 1.9 and 22.3%. Finally, Amato et al. found a strong association between diabetes and heart failure in a population of elderly people [17].

Table 45.2 Comparison of the prevalence, incidence, and prediction of heart failure and diabetes in general and patient populations.

		Heart failure in people with diabetes			People with diabetes and heart failure	
Study name	**Campania**	**Medicare sample**	**Kaiser Permanente**	**Kaiser Permanente**	**DIAMOND**	**Framingham**
Authors [ref.]	Amato et al., [17]	Bertoni et al., [52]	Iribarren et al., [51]	Nichols et al., [30]	Gustafsson et al., [50]	Kannel et al., [3]
Participants (no.)	1339	151,738	48,858	9591	5491	5209
Follow-up (years)	3	5	2.2	2.5	5–8	18
Period	<1997	1994–1999	1995–1997	< 1997	1993–2003	1949–
Age (years)	74 (mean) (all >65)	73–76 (all >65)	58 (mean)		52–86, (mean 73)	30–62
HF prevalence	9.5%	22.3%	1.9%	11.8% in people with DM, 4.5% in controls	–	–
Diabetes prevalence	14.7%	–	–	–	14.7% (T2DM)	–
Diabetes and HF association	OR 2.0 95% CI (1.6–2.5)	–	–	–	–	RR men 2.4 women 5.1
Diabetes incidence	9.6%/year in HF patients 6.1%/year in controls	–	–	–	–	
HF incidence	–	12.6/100 PY	–	3.3/100 PY in people with DM, 1.5/100 PY in controls	–	17.5/1000 PY among men, 18.5/1000 PY among women In people with DM 9/1000 PY in men, 14/1000 PY in women
Diabetes predictive factors	HF OR 1.4 (1.1–1.8)	–	–	–	–	–
HF predictive factors	BMI, Waist: hip ratio	Men, white Europeans, IHD, hypertension, stroke, PVD, nephropathy, retinopathy, neuropathy	–	Age, female, diabetes duration, insulin, IHD, creatinine, glucose	–	Diabetes, men
Diabetes mortality	–	–		–	RR 1.5 in people with diabetes	–
Other endpoint	–	–	1% (11 mmol/mol) increase in HbA_{1c} => increased risk of HF by 8%	–	–	–

BMI, body mass index; CI, confidence interval; DM, diabetes mellitus; IHD, ischemic heart disease; HF, heart failure; OR, odds ratio; PVD, peripheral vascular disease; PY, person-years; RR, relative rate.

Information on the incidence, prevalence, and prediction of heart failure is summarized in Table 45.2.

Incidence of heart failure and glucose abnormalities

Incidence of heart failure

Results from the Framingham study indicate that the incidence of heart failure has declined during the last six decades [53]. These data are, however, not supported in other studies [54]. On the contrary, it seems that hospital admissions for heart failure are increasing, resulting in higher healthcare expenditure for people with this diagnosis [55]. Among British outpatients, the incidence of heart failure has been reported to be 4.4/1000 person-years in men and 3.9/1000 person-years in women, rising with age in both genders [56]. The incidence in Finland is similar

among men, 4.0/1000 person-years, but lower in women, 1.0/1000 person-years [57]. In the United States, the incidence of heart failure has remained stable over recent decades, with a level as high as >80 per 1000 individuals above 85 years of age [5, 58].

Incidence of diabetes

The age-standardized annual incidence of diabetes, reported to be 2.2 and 2.3/1000 person-years in Dutch men and women, respectively, is fairly uniform in several European countries [59]. When considering an elderly population, as in the Italian Campania study, the incidence was considerably higher, 6.1% per year. This is different from observations in The Netherlands, where the incidence decreased in the oldest age group [17, 59]. In a study of the local community Laxå in Sweden, the incidence of diabetes was found to have been stable for 30 years at 3.03 cases per 1000 inhabitants [60].

Considerably less is known about the incidence of the combination of diabetes and heart failure. In the Reykjavík population, the age- and gender-standardized incidence of abnormal glucose regulation was 12.6/1000/year, of diabetes 4.6/1000/year, and of heart failure 5.3/1000/year (Figure 45.3) [40]. In addition, there was a strong association between the incidence of glucose abnormalities and heart failure [61].

In the Framingham study, the incidence of heart failure among men and women with diabetes during 18 years of follow-up was two and five times higher, respectively, than among those free from diabetes. The excessive risk of heart failure remained high even after the exclusion of individuals with prior CAD [3].

Pathophysiology

Myocardial structural and biochemical alterations can be identified in the failing heart and many of them seems to be independent of the etiology of myocardial dysfunction. They include changes in myocardial energy production, altered expression of contractile proteins, a desynchronized excitation–contraction coupling, β-adrenergic receptor stimulation, myocyte depletion, and increased activity of a number of cytokines. Many of these aberrations are found in the diabetic heart. Bugger and Abel [62] presented an extensive review of possible pathways and mechanisms to diabetes cardiomyopathy, as summarized in (Figure 45.4). New imaging techniques, e.g. cardiac magnetic resonance imaging (MRI), suggests that there is more fibrotic tissue in the myocardium of people with diabetes and an increased extracellular volume [63], possibly a consequence of hyperglycemia and

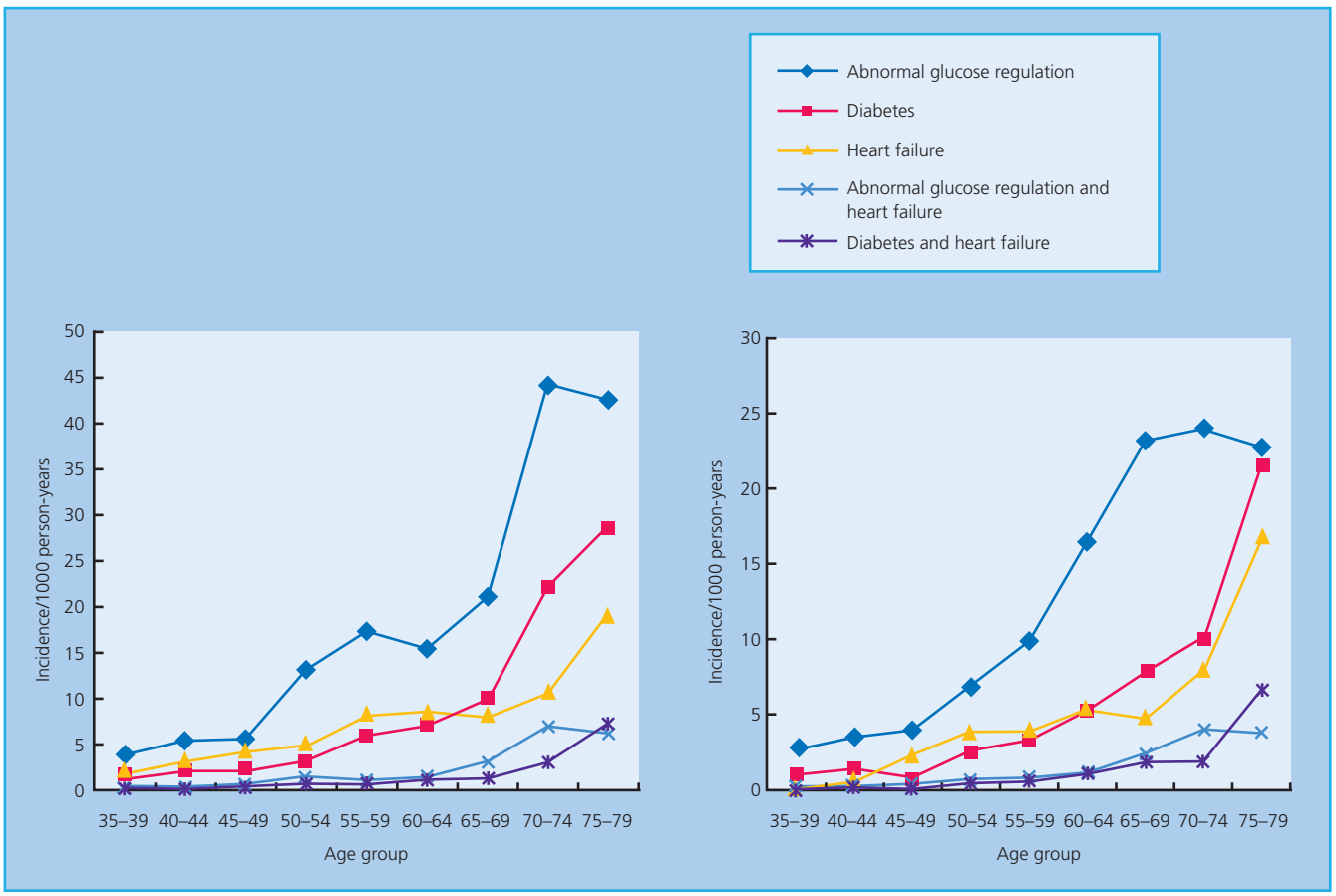


Figure 45.3 Incidence of abnormal glucose regulation, diabetes, heart failure, abnormal glucose regulation and heart failure, and diabetes and heart failure expressed as number of incident cases/1000 person-years among men (left) and women (right) by age. Source: Published previously in Thrainsdottir et al. 2005 [40]. Copyright 2005 by the American Diabetes Association.

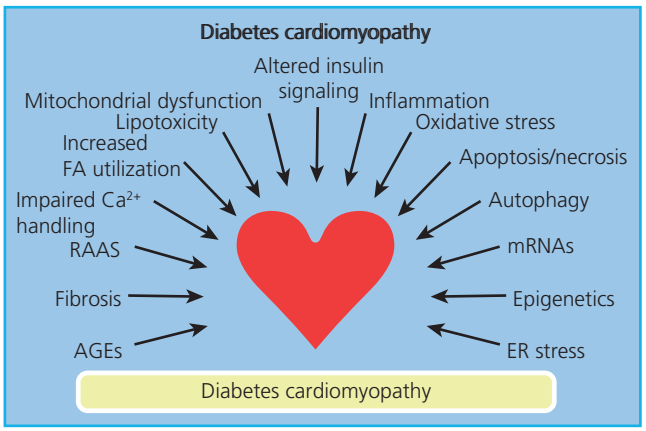


Figure 45.4 Possible mechanisms for diabetes cardiomyopathy. AGEs, advanced glycation end products; RAAS, renin angiotensin aldosterone system; FA, fatty acid. Source: Adapted from Bugger and Abel 2014 [62]. Reproduced with permission of Springer.

the formation of advanced glycated proteins. In this section, some general features of the pathophysiology are presented, followed by a discussion of more diabetes-specific factors.

Heart failure

Heart failure is a clinical syndrome originally induced by myocardial damage but subsequently aggravated by the induction of unfavorable neurohormonal responses. Thus norepinephrine, angiotensin II, endothelin, and aldosterone are all linked to the vicious cycle of myocardial remodeling (Figure 45.5), which if left unopposed will cause successive deterioration of myocardial performance [64].

Metabolic conditions play a significant role in cardiac adaptation and remodeling. This leads to an increase of myosin heavy chain beta, altered troponin-T molecules, diminished storage of creatinine phosphatases, and decreased sarcoplasmatic ATPase activity, which may result in myocyte hypertrophy associated with impaired contractile function and less effective energy supply [65, 66].

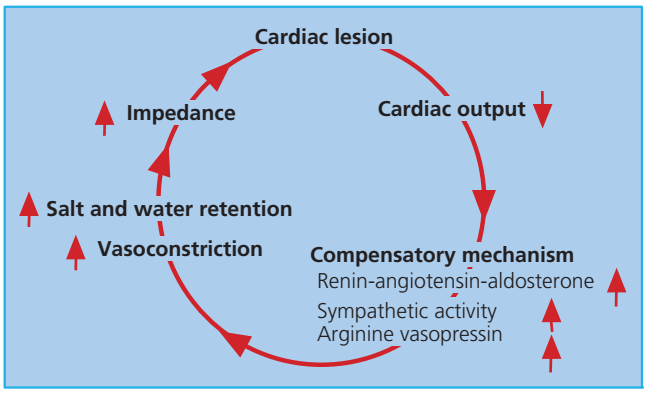


Figure 45.5 Neurohormonal activation caused by depressed myocardial function leads to a vicious circle further compromising the already compromised myocardial function [64].

The myocardium has a high energy turnover with adenosine triphosphate (ATP) as the important source of energy. The two pathways for energy supply are via the breakdown of free fatty acids (FFAs) and of carbohydrates (Figure 45.6). The lipolytic pathway transfers FFAs via β-oxidation to acetyl coenzyme A, which enters the citric acid or Krebs cycle. The carbohydrate pathway produces pyruvate via glycolysis, glycogenolysis, and lactate oxidation. Pyruvate is decarboxylated via pyruvate dehydrogenase to acetyl coenzyme A, which enters the Krebs cycle. The dominant pathway for myocardial energy production is β-oxidation of FFAs, but the myocardium is also dependent on glucose oxidation [67].

When the heart is subjected to ischemic stress or exposed to sustained enhancement of intraventricular pressure, it tends to change towards a more dominant glucose oxidation [67]. This may be counteracted by a reduction of the glucose transporter 4 (GLUT-4), which becomes reduced in heart failure, hampering glucose transport over the cell membrane. At the same time, the heart is subjected to increased FFA concentrations, released via stress influenced by an increased sympathetic tone [68]. It is assumed that prolonged intracellular accumulation of FFA and its metabolites may cause myocardial dysfunction [69].

In addition to these mechanisms, alterations in gene expression and inflammatory activity have been suggested to cause metabolic and mechanical disturbances in heart failure [70–73]. All nucleated cells, including the cardiomyocyte, can produce proinflammatory cytokines as a response to injury such as MI or myocarditis or when the heart fails. Both tumor necrosis factor α (TNF-α) and interleukin 6 (IL-6) levels increase in proportion to the severity and duration of heart failure [70, 71]. This cytokine release may trigger a cascade of events that lead to myocardial structural alterations, with further deterioration of the clinical expression of heart failure.

Heart failure and diabetes

Normally, myocardial energy production is based on β-oxidation of FFAs (70%) with a smaller contribution from glucose oxidation (30%) and lactate. FFAs are produced by lipolysis of endogenous cardiac or exogenous stores of triglycerides. Oxidation of FFAs is an effective supplier of energy in the form of ATP if oxygen supply is sufficient. In conditions with limited oxygen availability, glucose oxidation will provide more energy per mole of oxygen and support more work than FFAs [74]. In persons with diabetes, glucose utilization for energy production is substantially lower, about 10% (Figure 45.6). The shift to an even more pronounced β-oxidation of FFAs causes higher oxygen utilization than under normal circumstances [75]. The major restriction to glucose utilization in the diabetic heart is the slow rate of glucose transport across the sarcolemmal membrane in the myocardium [76, 77]. The impaired glucose oxidation in the diabetic heart can also result from a decreased rate of phosphorylation of glucose, which subsequently limits the entry of glucose into the cell. The depressed phosphorylation is triggered by the increased metabolism of FFAs [75]. Insulin deficiency enhances lipolysis, thereby increasing circulating FFAs [78].

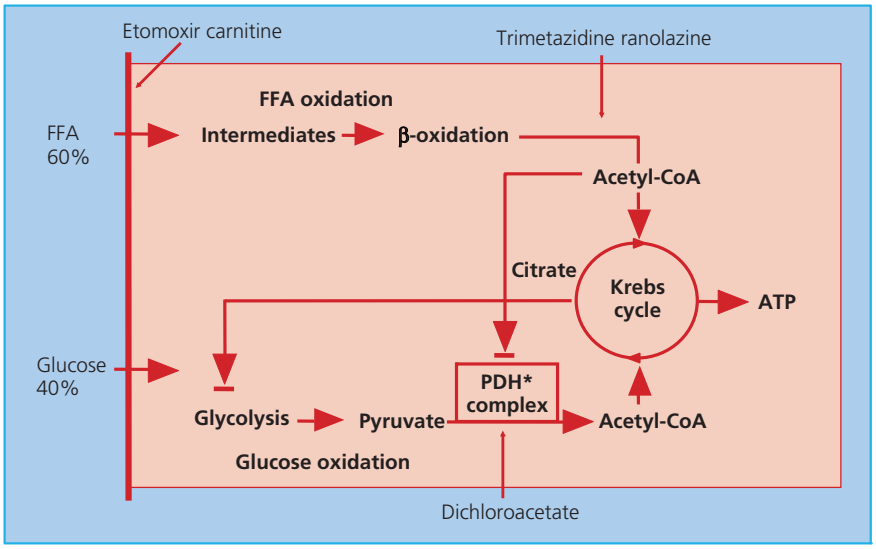


Figure 45.6 Schematic illustration of myocardial energy production of relevance for those with heart failure, with and without diabetes. The site of action for metabolic modulators are indicated. See text for further information [67]. CoA, coenzyme A; FFA, free fatty acid; PDH, pyruvate dehydrogenase.

Myocardial contractility may also be impaired by insulin resistance via reduced Ca^{2+} influx through L-type Ca^{2+} channels and by reverse-mode Na^{+}/Ca^{2+} exchange. Furthermore, chronic hyperinsulinemia is involved in impairment of the phosphatidylinositol 3-kinase (PI3K)/Akt pathway [79].

Individuals with diabetes are also known to have increased risk for other disturbances such as reduced myocardial blood flow and blunted hyperkinetic response to myocardial ischemia, resulting in diminished myocardial function [80–83]. Heart failure is an insulin-resistant state with an increased release of nonesterified fatty acids, which are taken up in muscular tissue and downregulate glucose uptake and utilization [84]. For more extensive information on recent postulated mechanisms for heart failure in diabetes, a review by Seferovic and Paulus [85] is highly recommended.

Another consequence of hyperglycemia is oxidative stress and activation of reactive oxygen species-driven pathways and of processes triggered by increased levels of diacylglycerol and protein kinase C (PKC) as depicted in Figure 45.7.

Prognosis

Heart failure in general

During the past 30 years, mortality from CAD has declined markedly among individuals free from diabetes. In those with diabetes, this decline has been substantially lower in men and not seen at all in women [86]. In the presence of heart failure, the prognosis becomes poor [87]. Survival after heart failure has improved, but the absolute mortality rate following the development of heart failure is still 50% within 5 years of diagnosis [88]. A 50-year follow-up of Framingham data indicated that heart failure survival has improved to some extent [53]. This observation is supported by a report based on the Swedish hospital discharge registry [89]. The mortality in an elderly population with heart failure recruited in Rotterdam was 47% during 6 years of follow-up, which is twice that of persons without heart failure [87]. In a comparable Italian study, the mortality rate was 21.3% after 3 years [17]. Hence heart failure is a malignant disease irrespective of the underlying reason for myocardial dysfunction.

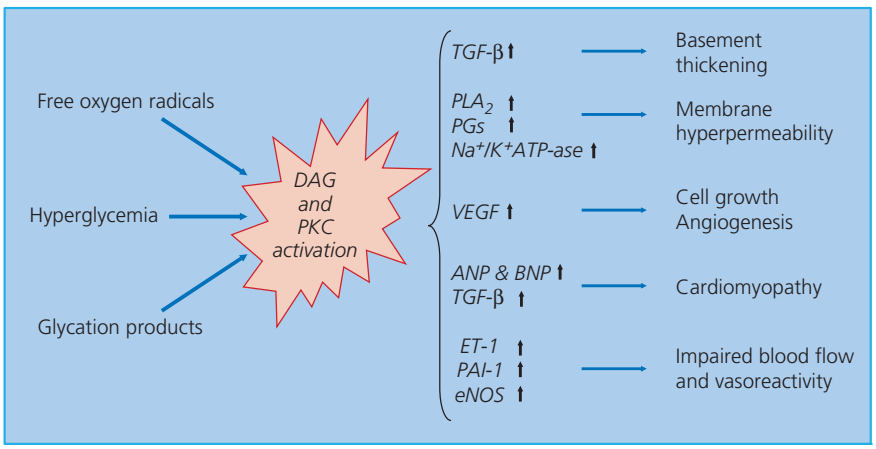


Figure 45.7 Metabolic effects of hyperglycemia-induced activation of protein kinase C (PKC) and diacylglycerol (DAG). See text for further explanation. ANP and BNP, atrial and brain natriuretic peptide; e-NOS, endothelial nitrous oxide synthase; ET-1, endothelin-1; PAI-1, plasminogen activating inhibitor-1; PGs, prostaglandins; PLA_2, phospholipase A_2; TGF-β, transforming growth factor β; VEGF, vascular endothelial growth factor.

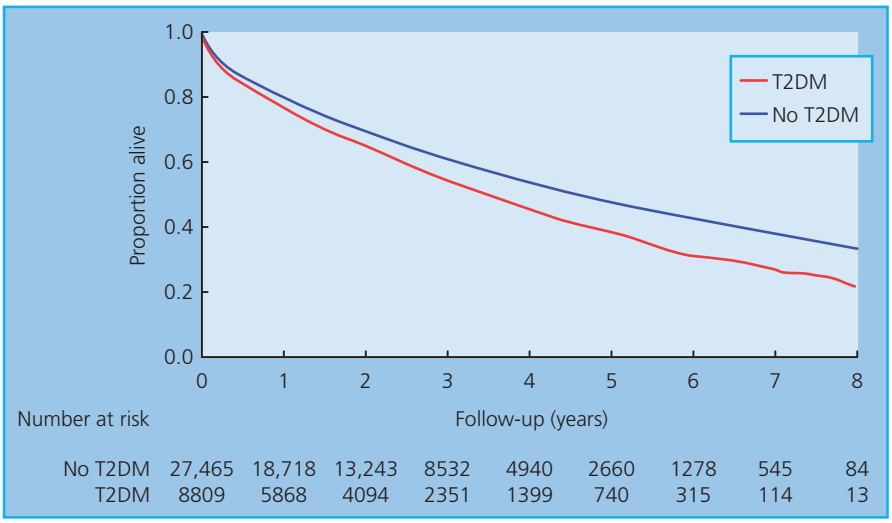


Figure 45.8 Survival after heart failure in persons with and without diabetes in Sweden in the period 2003–2011. Source: Johansson et al. 2014 [16]. Reproduced with permission of John Wiley & Sons.

Diabetes and heart failure

CVD is the most prevalent and vitally important complication of diabetes. In a very large population study in England of 1,921,260 individuals recruited during 1998–2012, heart failure and peripheral arterial disease were the most common initial manifestations of CVD in T2DM [12].

Diabetes increases the risk of death from CAD and, although mortality after MI has improved, the prognosis is still more severe in such individuals [90]. The prognosis for people with diabetes becomes even worse in the presence of heart failure [91–94]. In the first DIGAMI study, performed in people with diabetes and acute MI, heart failure was the most common reason for morbidity and mortality, accounting for 66% of the total mortality during the first year of follow-up [95]. In a recent nationwide registry study including 36,274 people hospitalized for heart failure during 2003–2011 and provided with modern heart failure therapies, survival was indeed significantly shorter in those with T2DM, who had a median survival period of 3.5 years compared with 4.6 years ($p < 0.0001$) (Figure 45.8). The presence of diabetes increased the risk of mortality by 60% (adjusted odds ratio 1.60; 95% confidence interval [CI]: 1.50–1.71) [16].

Treatment

General aspects

Evidence-based treatment of heart failure relies on a combination of angiotensin-converting enzyme (ACE) inhibitors and/or angiotensin receptor blockers (ARBs), β-blockers, diuretics, and aldosterone antagonists [4]. ACE inhibitors, ARBs, and β-blockers reduce mortality and improve symptoms in individuals with moderate to severe heart failure with and without diabetes [96–99]. Diuretics are mandatory for symptomatic treatment owing to fluid overload but should not be used in excess since they induce neurohormonal activation [100]. The addition of aldosterone antagonists is indicated in severe forms of heart failure and may then improve longevity [101]. However, although symptomatically improved, many patients are left with an unfavorable vital prognosis despite the best available pharmacological treatment. In 2014, the PARADIGM-HF study was presented, and showed significantly improved survival and a decreased need for hospitalizations for heart failure with the angiotensin–neprilysin inhibitor LCZ696 versus enalapril and standard treatment (hazard ratio 0.84; 95% CI: 0.76–0.93; $p < 0.001$). In the present context, it is of interest that the mortality benefit was particularly apparent in persons with diabetes [102, 103].

Metabolic modulations with compounds that influence the disturbed metabolic pathways in heart failure have been an area of research of particular importance in persons with diabetes. Attention has been paid to compounds that shift energy production from β-oxidation of FFAs towards the energetically more efficient glucose oxidation under conditions such as in myocardial ischemia and heart failure. Examples of such drugs are trimetazidine, ranolazine, etomoxir, and dichloroacetate [104, 105].

Not only pharmaceutical therapies are important in the treatment of heart failure. Modern heart failure treatment also includes physical activity programs. In severe heart failure with intraventricular conduction defects, cardiac resynchronization therapy (CRT) may be indicated.

Guidelines that deal specifically with diabetes and CVD including heart failure were not available until 2007, when the first European guidelines on the management of diabetes, prediabetes, and CVD were published; they were updated in 2013 [106]. As outlined in the latter, there have been few trials that specifically address the treatment of patients with a combination of glucose abnormalities and heart failure, and so there is a lack of firm evidence regarding the management of such patients. Current data are mostly based on analyses of subgroups of people with diabetes in large HF trials. This results in potential shortcomings related to a poor definition of diabetes and hidden diabetes, and actual glucose-lowering therapy, and also a risk for selection biases with an overrepresentation of less severe diabetes. With

these limitations in mind, available data favor a proportionately similar efficacy of pharmacological and device-oriented therapy in people with and without diabetes. Since the absolute prognosis is considerably worse in individuals with diabetes, the impact expressed as number needed to treat to avoid an event (e.g. hospitalization for heart failure or death) is considerably less in this group of individuals.

Pharmacological therapy of heart failure

Angiotensin-converting enzyme inhibition

ACE inhibitors are recommended in both asymptomatic myocardial dysfunction and overt heart failure. As shown in Table 45.3, they reduce mortality and improve symptoms in individuals with moderate to severe heart failure with and without diabetes [97, 99, 107–109]. Persons with diabetes represented fairly large subgroups in several trials. In SOLVD, the effect of enalapril on compromised left ventricular function was similar in participants with and without diabetes [110]. In ATLAS, comparing high- and a low-dose lisinopril treatment strategies, mortality reduction was at least as good in participants with diabetes as in those without [111]. The GISSI-3 and the SAVE trials reported beneficial effects on morbidity and mortality of ACE inhibitor treatment post-MI in people with diabetes [112–114].

Since hypoglycemic episodes may be provoked by ACE inhibitor therapy in individuals on glucose-lowering therapy, it is recommended that plasma glucose is monitored in the early phase of the introduction of an ACE inhibitor in those on glucose-lowering treatment [115, 116].

Angiotensin-receptor blockers

The use of angiotensin receptor blockers is an alternative to ACE inhibition and may be used, although not recommended in combination with ACE inhibition. They improve morbidity and mortality in people with heart failure with and without diabetes [117, 118].

Table 45.3 Effect of inhibition of the renin–angiotensin system in heart failure trials which included participants with diabetes.

Study [ref]	Participants (no.)	Diabetes (%)	Outcome
CONSENSUS [97]	253	18	31% reduction of 1-year mortality
SAVE [113]	2231	22	19% all-cause mortality risk reduction 21% risk reduction of cardiovascular morbidity
ATLAS [111]	3164	19	14% mortality risk reduction with high-dose ACE inhibitor treatment
GISSI 3 [114]	18131	15	30% reduction in mortality after 6 weeks

ACE, angiotensin-converting enzyme.

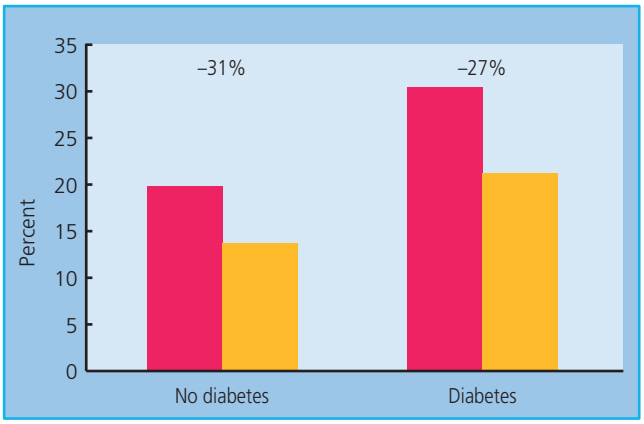


Figure 45.9 Impact of the β-blocker metoprolol on the combined endpoint mortality or hospitalization in individuals with heart failure with and without diabetes participating in the MERIT-HF trial [121]. Note that the relative risk reduction (given in % above the bars) is independent of diabetes state but that the absolute mortality even with metoprolol treatment is considerably higher in the diabetes subgroup [121]. Placebo, red bars; metoprolol, yellow bars.

β-Blockers

Beta blockade decreases myocardial FFA exposure and thereby such treatment has the capacity to favorably influence the metabolic pathway in persons with T2DM and heart failure [119, 120]. Subgroup analyses of participants with diabetes and moderate to severe heart failure in large trials revealed that β-blockers reduce mortality and improve symptoms, hence they are indicated as first-line treatment in such individuals [96, 98, 121–123]. An example of the impact of a β-blocker (metoprolol) added to treatment with ACE inhibitors and diuretics in people with heart failure with and without diabetes is given in Figure 45.9. The relative risk reduction following metoprolol treatment is similar in the two groups. The remaining event rate is still substantially higher in the diabetes cohort than among those without diabetes. Evidence indicates that the use of β-blockers in diabetes alters counter-regulatory responses to hypoglycemia with decreased tremor and palpitations but increased sweating. It seems that this is more common if a non-cardioselective β-blocker (e.g. propranolol) is used and less common with β_1-selective agents or carvedilol. However, the marked clinical benefits of β-blockers in people with diabetes and heart failure outweigh the risks of hypoglycemia [106].

Diuretics and mineralocorticoid receptor antagonists (MRAs)

Diuretics are mandatory for symptomatic relief owing to fluid overload. As already underlined, they should not be used in excess since they induce neurohormonal activation [100]. Loop diuretics are recommended rather than diuretics, which may further impair glucose metabolism. A low-dose MRA is indicated in those with persisting symptoms and a left ventricular ejection fraction ≤35%,

despite treatment with ACE inhibitors and a β-blocker and will reduce the risk of hospitalization and premature death. The mortality benefit with the use of either spironolactone or eplerenone is similar in people with and without diabetes [124–126]. Careful control of kidney function and potassium is essential, because of the increased risk of nephropathy in persons with diabetes.

Ivabradine

Ivabradine may be of use in persons with heart failure in sinus rhythm and a heart rate of ≥70 beats per minute. In the SHIFT trial, it reduced cardiovascular deaths and hospital admissions for worsening heart failure. The benefit was similar in a prespecified subgroup analysis of individuals with and without diabetes [127].

Statins

It has been debated whether statin treatment may impact morbidity and longevity in individuals with heart failure. Two clinical trials, CORONA and GISSI-HF, were both negative in this respect [128, 129]. Statin therapy therefore has no role in the management of heart failure per se. Since IHD with previous MI is frequent in persons with diabetes and heart failure [16], statins may still be indicated to lower LDL-cholesterol.

Cardiac resynchronization therapy

Cardiac resynchronization therapy will improve survival if added to optimal medical treatment in people with sinus rhythm if their left ventricular ejection fraction is low (≤30%), the QRS duration prolonged (≥150 ms) and the ECG shows left bundle branch morphology [130, 131]. There are no specific data on diabetes related to this treatment.

Glucose-lowering treatment

General aspects

In accordance with the pathophysiological aspects on heart failure in persons with diabetes, it has been postulated that meticulous metabolic control may have beneficial effects on progress and prognosis. Chapter 41 deals with some of these aspects. The European guidelines for the management of diabetes recommend an HbA_{1c} (DCCT standard) <7.0% or <53 mmol/mol [106] even in those with heart failure, although glucose control should be individualized. The scientific evidence for very tight glucose control is sparse although more solid for T1DM than T2DM [132]. The negative outcomes of some trials on aggressive glucose lowering have further underlined the uncertainty in this respect [133, 134]. These trials did not, however, consider specifically individuals with heart failure. Considering that both the 20-year follow-up of the first DIGAMI study and the 27-year follow-up of the DCCT study showed long-lasting effects of glucose control on mortality, glucose control should not be completely neglected [135, 136].

There are several already completed or ongoing trials addressing cardiovascular safety with new glucose-lowering agents, including GLP-1 receptor agonists or DPP-4 inhibitors. The increased hospitalization for heart failure observed with the DPP-4 inhibitor saxagliptin in the SAVOR-TIMI 53 trial [137] was not confirmed for sitagliptin in the TECOS trial [138], alogliptin in the EXAMINE trial [139], or the GLP-1 receptor agonist lixisenatide in the ELIXA trial [140]. Regarding cardiovascular benefits of glucose-lowering drugs, a paradigm shift was recently observed when the EMPA-REG OUTCOME study [141] showed a decrease in cardiovascular events, essentially driven by a 38% reduction in cardiovascular mortality and a 35% reduction in hospitalizations for heart failure, in people with T2DM with established CVD randomized to the sodium–glucose co-transporter 2 (SGLT-2) empagliflozin compared with placebo. The impact on heart failure hospitalizations and cardiovascular mortality was clear within the first few months on the drug. The exact mechanisms behind these beneficial effects have to be further elucidated in mechanistic studies. They cannot reasonably be explained by the modest glucose and blood pressure lowering or the weight-reducing effects of empagliflozin. A more plausible explanation, although still speculative, is that a decrease in volume load related to osmotic diuresis and increased sodium excretion, possibly in combination with reduced arterial stiffness, may have had a favorable impact on the development of heart failure, which is prognostically a very serious condition in individuals with IHD [16].

Choice of Glucose-lowering agents

Regarding specific-glucose lowering agents, there is some information available that is of importance for the choice of treatment in people with or at risk for heart failure. The insulin sensitizers thiazolidinediones can provoke or worsen heart failure because of their propensity to induce fluid retention because of sodium retention and plasma volume expansion. Several of these drugs have been withdrawn from the market and those that are still available should be used with great caution in persons with heart failure and are contraindicated in those in NYHA class III–IV [38, 142–144].

Metformin has long been regarded as contraindicated in persons with heart failure because of concerns regarding lactic acidosis, but recent reports have not confirmed this risk and the drug may be used, but not in people with severely compromised kidney function [145].

Insulin treatment in persons with diabetes and heart failure is under debate. The main effect of insulin is to decrease blood glucose, but it may also increase myocardial blood flow, decrease heart rate, and cause a modest increase in cardiac output [146, 147]. Beneficial effects on myocardial function have been reported, but it was also found that insulin may be associated with increased morbidity [148] and mortality [149, 150]. Further studies are needed to establish the specific role of insulin beyond its role as a glucose-lowering agent in persons with diabetes and heart failure.

In general, it can be summarized that there is little information of importance available for the choice of agents for glycemic control in individuals with diabetes and heart failure. Until such information is available, generally accepted management rules should apply [151].

HF-PEF

In general, no randomized clinical trial have shown beneficial treatment effects on prognosis and mortality in individuals with HF-PEF (4,6]. It is recommended that other risk factors are controlled, including hypertension, IHD, and rate control in atrial fibrillation. Impaired myocardial diastolic function and endothelial dysfunction are present in HF-PEF as early expressions of diabetes-related cardiovascular involvement causing decreased myocardial blood flow reserve. It has been suggested that hyperglycemia-related early myocardial and microcirculatory disturbances are dynamic and that they may be reversed by improved metabolic control [152]. One observational study [153] of individuals undergoing intensified glucose control in clinical routine gave support to the assumption that particularly insulin-based glycemic control may be useful. Unfortunately, these observations were not verified in a subsequent prospective study (DADD study), in which people with T2DM, free from previous cardiovascular events and signs of heart failure or CAD, with early signs of diastolic dysfunction were randomized to insulin- or oral-based glucose normalization [154]. It should be underlined that it still is too early to abandon the hypothesis of a favorable relation between glycemic control and myocardial diastolic dysfunction. It may be that the individuals in the DADD trial were too healthy to react to normalization of glucose control. Hence it would be of value to study new agents, such as incretins and SGLT-2 inhibitors, in future trials and to recruit persons at a more advanced disease stage than those selected for the DADD trial. The problem is then the obvious risk for biases caused by hypertensive and CAD and other complications to diabetes. Accordingly, such protocols must include detailed examinations of the participants with this in mind.

Metabolic modulators

Drugs, such as trimetazidine, etomoxir, and dichloroacetate, aimed at shifting myocardial metabolism from oxidation of FFAs towards glycolysis have been tested in people with myocardial dysfunction and diabetes. They act on different parts of the metabolic pathways, as indicated in Figure 45.6. The usefulness must be further explored in clinical trials of appropriate design until their therapeutic role can be considered established, despite some recent promising results [155–157].

Importance of revascularization

In persons with signs of coronary artery ischemia, in stable or unstable situations, revascularization of the coronary arteries with either percutaneous coronary intervention (PCI) or coronary artery bypass grafting (CABG) is recommended if prognosis can be improved and if symptoms are not relieved by medical treatment. The benefits should exceed the risks and should preferably be judged by a multidisciplinary decision-making heart team [158]. Several risk scores are available for judging such benefits and risks, for instance, the SYNTAX score. The most recent guidelines [106, 158] recommend that CABG is preferred in people with diabetes with multivessel coronary artery disease (three-vessel disease), mainly based on the results from the FREEDOM trial [159], but PCI with the use of drug-eluting stents can be considered if the SYNTAX score (based on the coronary angiography findings) is low (≤22). However, it must be borne in mind that it is not always possible to follow the guidelines in everyday practice. It is typical that people with diabetes have a more diffuse atherosclerosis of the coronary arteries and it is not always possible to perform CABG while PCI may be challenging owing to the configuration of the coronary artery stenosis (long and thin stenosis).

In a recent Swedish registry report, based on 36,274 patients hospitalized for heart failure, 60% of the people with diabetes had a reported history of IHD [16]. In those with already developed poor systolic left ventricular function, revascularization might be of use if there are signs of viable myocardium on non-invasive imaging [158]. Nuclear imaging techniques can be used for the detection of coronary ischemia and presence of viability, and MRI can be used for the detection of the transmural extent of myocardial scar tissue, but MRI is not better than nuclear imaging for detection of viability. The STICH trial, including individuals both with and without diabetes, addressed the prognostic importance of CABG in a randomized control trial of patients with left ventricular function ejection fraction <35% and with two- and three-vessel disease. In the intention-to-treat analyses, the STICH investigators reported improved cardiovascular and total mortality in the CABG group [160]. However, in the viability substudy of the STICH trial, there was no correlation of myocardial viability with benefits from CABG, and the recent European Society of Cardiology guidelines state that assessment of viability should not be the sole factor when deciding on the best strategy for people with severe left ventricular function and evident CAD [158].

Gender aspects

Diabetes attenuates the otherwise protective effect for CVD seen in women compared with men, resulting in a first MI at about the same age in women and men with diabetes [11, 161, 162]. The Framingham study was one of the first to report on the high prevalence of heart failure and poor prognosis in women with diabetes [3]. The reason for this equality in cardiovascular risk in men and women with diabetes is not completely understood [162], but women with diabetes more often have multivessel CAD compared with those without diabetes [163]. There is a lack of information on heart failure in women with diabetes, since often both women and those with diabetes were excluded in controlled trials. In registry reports, such as the meta-analysis MAGGIC [164, 165], it is often found that women with diabetes and heart failure are at a greater age and more often have preserved ejection fraction (HF-PEF) than men. Survival after a diagnosis of heart failure was as poor in women as in men with heart failure and much worse than in women without diabetes in several registry analyses addressing gender aspects [164, 165]. Future trials are needed to explore

further the mechanisms behind these findings, for instance, evaluating if CAD, diabetes-related complications affecting myocardial metabolism, and fibrosis are more common among these women.

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46 Cerebrovascular Disease

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Key points

- Diabetes is a strong and independent risk factor for ischemic cerebrovascular disease with a relative risk of ~2.
- Ischemic stroke in persons with diabetes has worse outcomes, including a higher rate of mortality, than in persons without diabetes.
- Although transient ischemic attacks (TIAs) appear to occur less frequently in individuals with diabetes, those who experience a TIA are more likely to go on to have a completed stroke in the immediate period following.
- Individuals with diabetes are predisposed to vascular events, including stroke, for a number of reasons, such as premature atherosclerosis, reduced response to nitric oxide, and a general state of hypercoagulability.
- Prevention of stroke in persons with diabetes is best accomplished through aggressive management of coexisting hypertension and hyperlipidemia, in addition to lifestyle modifications.
- Reduction of glyclated hemoglobin as a proxy for good glycemic control is likely associated with a reduction in macrovascular events.
- Aggressive management of hyperglycemia in the acute stroke period may improve outcomes.

Epidemiology of stroke in general

Cerebrovascular disease is a leading cause of morbidity and mortality. It is a highly prevalent disease, with ~795,000 strokes occurring each year in the United States. Of these, 610,000 are first-time events and 185,000 are recurrent [1]. It is the fourth leading cause of death in the USA, following heart disease, all forms of cancer, and chronic lower respiratory disease. Thus, a woman is nearly twice as likely to die from a stroke as she is from breast cancer, and 10% more likely than to die from lung cancer [2]. Furthermore, it is the number one reason listed for discharge diagnosis for patients discharged from hospitals to chronic care facilities. In total, the cost of stroke to the healthcare system in the USA was $36.5 billion in 2010 [1].

Statistics in other countries are similar to those seen in the USA. The Oxford Vascular Study, which compiled stroke statistics for every person in the county of Oxfordshire in the United Kingdom, demonstrated an overall incidence of 1.62 strokes per 1000 per year [3]. The WHO MONICA study looked at 21 populations in 11 countries (10 in Europe plus China), and found an incidence of 125–361 per 100,000 men, and 61–194 per 100,000 women [4].

Diabetes as a risk factor for stroke

There is strong evidence that diabetes mellitus, whether type 1 (T1DM) or type 2 (T2DM), is a strong risk factor for ischemic cerebrovascular disease (Table 46.1). Observational studies have demonstrated associations between the two diseases. A model created from data from the Framingham Heart Study showed that diabetes confers an increased relative risk (RR) of 1.4 in men and 1.72 in women [5]. The Honolulu Heart Study showed that diabetes increases the risk of thromboembolic stroke 2–3-fold over individuals without the disease in Japanese men living in Hawaii [6].

The effect of diabetes is stronger in ethnic minorities in the USA. The Greater Cincinnati and Northern Kentucky Stroke Study found that as a sole risk factor, diabetes increased the odds ratio (OR) for having an ischemic stroke by 2.1 in people of white European ancestry; however, in African Americans, that OR was increased by 2.7. These results held true across all age cohorts [7].

Similarly, the Northern Manhattan Study found that diabetes was a stronger risk factor for ischemic stroke among African Americans and Caribbean Hispanics than among white Europeans. In these ethnicities, diabetes increased stroke risk by

Textbook of Diabetes, Fifth Edition. Edited by R. Holt, C. Cockram, A. Flyvbjerg and B. Goldstein.

Table 46.1 Risk factors for stroke.

- Hypertension
- Diabetes
- Tobacco use
- Hyperlipidemia
- Atrial fibrillation
- Carotid artery disease

1.8 and 2.1, respectively, partly due to increased prevalence of the disease. The fraction of strokes that could be directly attributable to diabetes as a risk factor was 14% among African Americans and 10% among Caribbean Hispanics [8].

The Copenhagen City Heart Study found a difference in the effect of diabetes among men and women. Thus, while diabetes increased the RR of first stroke, incident stroke, and hospital admission for stroke among men by 1.5–2, among women the same RRs were increased by 2.0–6.5 [9].

In addition to its effects as a sole risk factor, diabetes also exacerbates the effects of other risk factors. Thus, in people with isolated systolic hypertension, diabetes confers additional risk of ischemic stroke or transient ischemic attack (TIA).

Stroke in people with diabetes

In epidemiological studies, ischemic stroke occurs at a younger age in individuals who have diabetes. They are also more likely to be African American. Among other risk factors, persons with diabetes who have ischemic stroke are more likely to have hypertension and hyperlipidemia, and to have experienced a myocardial infarction in the past [7].

Furthermore, diabetes increases the risk of death from stroke. In a prospective study in a Finnish cohort, men had an increased RR of 6 for mortality from ischemic stroke, whereas women had an RR of 8.2. These RRs were higher than those for systolic blood pressure, smoking, or total serum cholesterol. In this cohort, the fractions of stroke deaths directly attributable to diabetes were 16% in men and 33.3% in women [10].

In terms of stroke subtype, diabetes is most commonly associated with lacunar infarcts, that is, a small, deep infarct in the region of a single penetrating arterial branch. Conversely, the highest prevalence of diabetes is found in people with demonstrated microvascular disease. Similarly, lacunar disease is more likely to be associated with diabetes than hemorrhages in the same location [11–14] (Figure 46.1).

Diabetes is also associated with both extracranial and intracranial stenosis. In a study of 510 people referred for asymptomatic carotid bruits, only 200 had extracranial stenosis by Doppler examination. A total of 66 had asymptomatic intracranial stenosis, of whom 37 had concurrent extracranial stenosis. Nineteen of the people with intracranial stenosis had diabetes [15] (Figure 46.2). Interestingly, a recent analysis of the SPS3 study demonstrated that people with diabetes and lacunar strokes had higher rates of intracranial stenosis, although whether this causally related to the infarct is not clear [16].

TIA is less common in persons with diabetes than in those without. This may indicate that diabetics are more likely to present with completed infarct rather than reversible ischemia [17]. However, individuals with diabetes who do present with TIA are more likely to go on to full-blown ischemic stroke in the following 2 days as predicted by the ABCD2 score, representing the predictive factors of age >60 years, blood pressure >140/90 mmHg, clinical features of motor or speech involvement, duration >60 min, and diabetes [18].

Diabetes is a risk factor for coronary artery disease, and therefore for myocardial infarction (MI) and subsequent development of atrial fibrillation. In one large retrospective study of the relation between diabetes and atrial fibrillation or atrial flutter, diabetes was found after logistic regression to be a strong independent predictor for atrial arrhythmias in a review of over 850,000 charts over a 10-year period. The OR found for diabetes was 2.13, 95% confidence interval (CI) 2.10–2.16 [19]. In turn, atrial fibrillation has been repeatedly demonstrated to be a strong risk factor for cardioembolic stroke, with an estimated 75,000 strokes per year attributable to the arrhythmia [20].

Furthermore, diabetes increases the risk of cardiac embolization. The CHADS2 score is a validated method of stratifying risk of cardioembolic stroke in people with atrial fibrillation. It assigns one point each for the presence of congestive heart failure, hypertension, age >75 years, and diabetes, and two points for previous stroke or transient ischemic attack. Each point increase was associated with a 1.5-fold increased risk of stroke. Diabetes alone, then, would increase the risk of stroke in a person with atrial fibrillation from 1.9 to 2.8 [21]. Although the CHADS2 score is not perfect, and attempts have been made to improve its precision [22], it has the benefit of being very easy to use, thus guiding the non-stroke practitioner towards using anticoagulation in the appropriate section of the population.

From large observational studies, there does not appear to be an association between diabetes and hemorrhagic strokes. However, in the Hemorrhagic Stroke Project, a case–control study of young people with intracerebral hemorrhage, diabetes conferred an adjusted OR of 2.4. The risk factor with the most impact was, as predicted, hypertension, which outweighed the contribution from diabetes by more than twofold [23].

Prediabetes and other risk factors

Whereas it is well established that diabetes is a strong risk factor for ischemic stroke, forms of prediabetes are not so clearly indicated as risk factors. Selvin et al. looked at individuals with and without diabetes in the Atherosclerosis Risk In Communities (ARIC) trial and compared HbA_{1c} levels drawn at a specified visit, not necessarily related to time of incident stroke [24]. With increasing tertiles of glycation across the normal

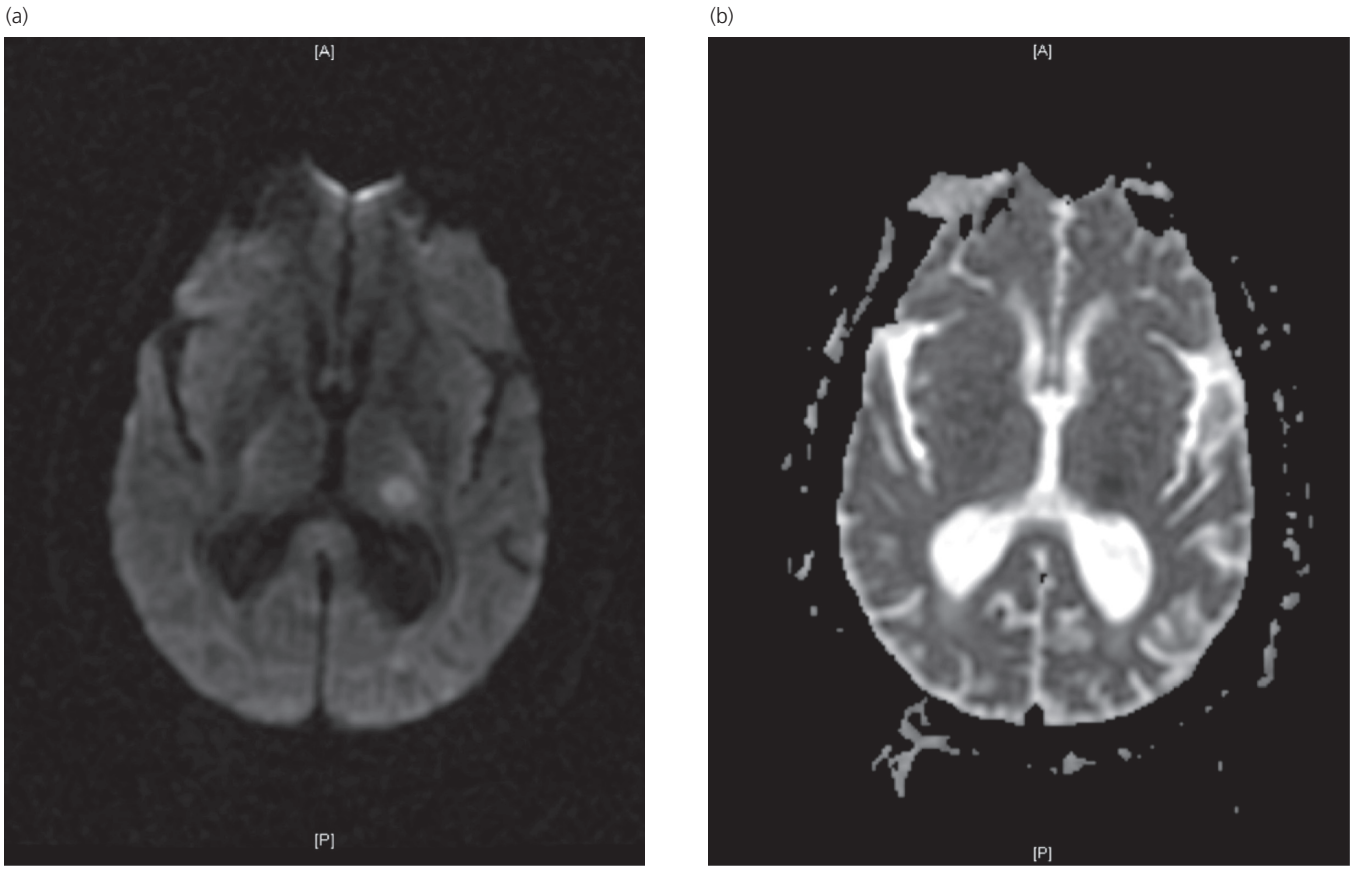

Figure 46.1 Lacunar infarct in the left posterior thalamus. (a) Diffusion-weighted imaging, showing hyperintensity in the area of restricted diffusion, corresponding to acute ischemia. (b) Apparent diffusion coefficient image corresponding to the slice seen in (a), demonstrating hypointensity in the same distribution, confirming the presence of acute ischemia.

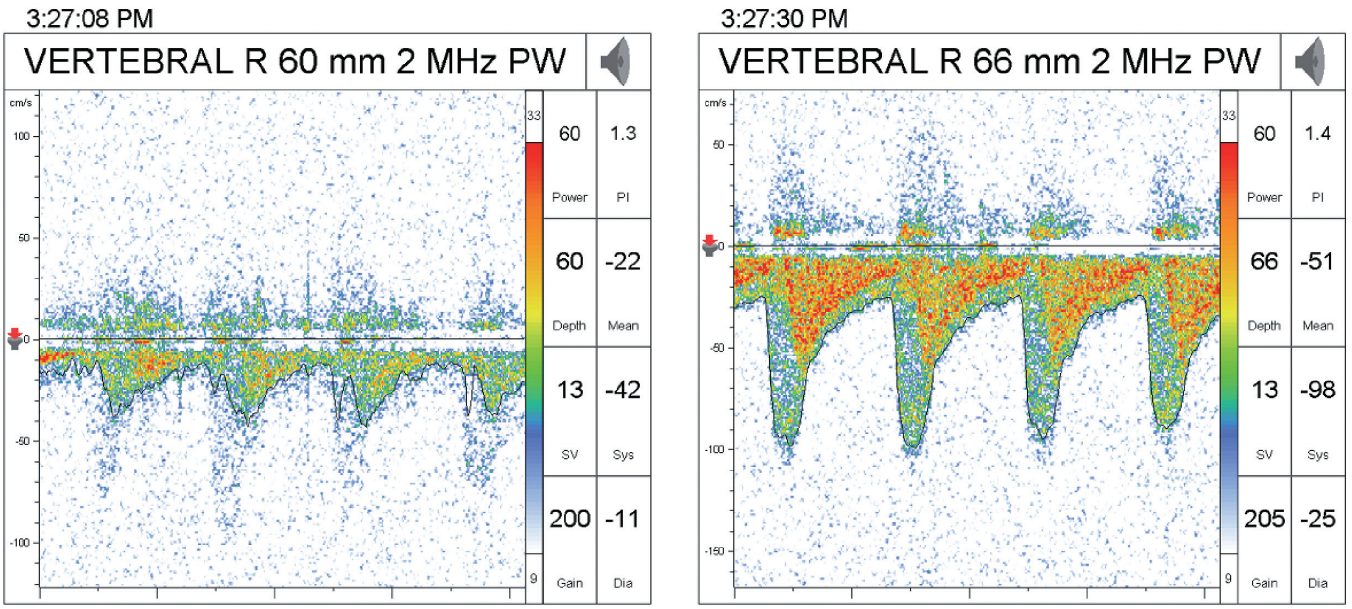

Figure 46.2 Intracranial vertebral artery stenosis as seen by transcranial Doppler ultrasound. The image on the left shows normal flow pre-stenosis and the image on the right shows increased velocity of flow post-stenosis.

distribution within each group, the risk of stroke increased in both cohorts, although it was only in those with diabetes that the difference achieved statistical significance.

In contrast, Myint et al. abstracted data from the European Prospective Investigation into Cancer (EPIC) on glycated hemoglobin levels in persons without known diabetes and correlated these data with stroke risk [25]. In this population, it was only after levels were higher than 7.0% that an increased risk of stroke was demonstrated, compared with those with HbA_{1c} <5.0% 31 mmol/mol. Given that these individuals most likely actually had undiagnosed diabetes, this finding may not implicate chronic hyperglycemia alone as the primary risk factor for stroke.

Insulin resistance, another forme fruste of diabetes, likewise has demonstrated conflicting evidence for association with stroke. The ARIC study investigated hyperinsulinemia in persons without diabetes and found a mild increase in risk of stroke of 1.19 with each increase of 50 pmol/L of fasting insulin. After adjustment for other risk factors such as age, systolic blood presire, and smoking, the increase in risk was not as well defined [26].

Obesity, a proxy for insulin resistance and prediabetes, has also been linked to stroke, through a number of epidemiological studies. For example, the Copenhagen City Heart Study found that body mass index (BMI) was independently associated with increased risk of stroke [27]. Similarly, the Nurses' Health Study found, as expected, an increasing risk of stroke with increasing BMI, with an RR of stroke of 2.37 (95% CI 1.60–3.50) seen in people with BMI >32 Kg/m^2 [28]. However, the ARIC study was unable to demonstrate any relationship between BMI and stroke, or between waist/hip ratio, a better measurement of abdominal obesity, and stroke [26]. In addition, when adjustment for cardiovascular risks is performed, the relative risk of BMI for stroke is once again attenuated.

Although these individual forms of prediabetes have not conclusively been shown to predispose people to stroke, the constellation of diseases together called the metabolic syndrome has been. The combination of hypertension, hyperlipidemia, insulin resistance, and abdominal obesity creates an environment that is highly susceptible to vascular damage and ischemic sequelae.

In a Finnish cohort, the metabolic syndrome in the absence of diabetes or cardiovascular disease (CVD) was associated with stroke with an RR of ~2, after adjustment for multiple other risk factors [29]. Similarly, a cohort from the ARIC study who likewise were free of diabetes, coronary heart disease (CHD), or stroke had an increased RR of 1.5–2 for ischemic stroke. In addition, on separating out each risk factor, there appeared to be a synergistic effect from the combination over the RRs inherent in each component [30].

Pathophysiology of ischemic stroke in diabetes

Diabetes predisposes individuals to vascular thrombo-occlusive events in a number of ways. There is accelerated atherosclerosis in both large- and medium-sized vessels. There is disordered endothelial response, and the blood is hypercoagulable [31].

Carotid intima-media thickness (IMT) is a useful proxy for early atherosclerosis, as it is easily measured by Doppler examination. Furthermore, IMT is associated with primary stroke, with an increased RR per standard deviation (0.163 mm) of 1.57 in individuals who had not had a previous stroke [32]. It also predicts recurrent stroke, with each 0.1 mm increase in IMT associated with an increased risk of 18% [33].

Diabetes is associated with increased IMT. The Insulin Resistance Atherosclerosis Study demonstrated an increase in common carotid IMT in people with long-standing diabetes, but not in those with newly diagnosed diabetes. Nor was there an association with internal carotid artery IMT [34].

Conversely, persons with diabetes with stroke have been found to have greater IMT. In A study of 438 Japanese people with T2DM, common carotid IMT was significantly higher in those who had stroke, even after adjustment for age, BMI, and smoking status [35]. Similarly, in a Czech cohort, IMT was increased in people with stroke and diabetes [36].

Atherosclerosis also affects the ability of endothelium to release nitric oxide (NO), a potent vasodilator. In diabetes, blood vessels have either reduced NO production or altered NO metabolism. In addition to its vasodilating effects, NO protects against platelet aggregation and enables the blood vessel to withstand ischemic conditions. With decreased NO activity, the vessel will tend more towards vasoconstriction, with predictably poor response to ischemia.

People who have suffered a stroke have decreased NO in circulating blood, along with increased peroxynitrite ($ONOO^-$), a reactive oxygen species. These results were particularly evident in larger strokes. Since the measurements were performed for acute stroke, these levels are likely to represent the outcome of ischemia rather than the cause. However, the correlation supports a role for decreased NO in the effects of stroke [37].

The cerebral vasculature has a diminished response to inhibition of NO synthase (NOS). In a small study of men with diabetes treated with a synthetic NOS inhibitor, N^G-monomethyl-L-arginine, the blood flow through the internal carotid artery was significantly lower than in men without diabetes treated likewise [38].

As further indirect evidence of the role of NO in stroke, 3-hydroxy-3-methylglutaryl-coenzyme A (HMG-CoA) reductase inhibitors (statins) have multiple beneficial effects beyond their most common one, that of lowering plasma cholesterol. Among these effects are increasing the expression of endothelial NOS and also decreasing the activity of Rho-kinase, a proconstrictor enzyme [39]. Statins have been demonstrated to lower the risk of recurrent stroke in several large studies [40–42]. Whether the beneficial effect of statins in stroke is due to their cholesterol-lowering effect, their ability to stabilize atherosclerotic plaques, their effects on vascular function, or more likely a combination of all of these, is very difficult to ascertain.

In addition to the above predisposing factors, the blood of a person with diabetes is hypercoagulable. Studies have demonstrated increased thrombin generation [43], increased prothrombin fragments, and increased thrombin–antithrombin III complexes [44]. Furthermore, the elevated prothrombotic levels were significantly associated with macroangiopathic complications.

Thrombus formation is further promoted by platelet hyperreactivity in the blood of individuals with diabetes. In persons with metabolic syndrome, platelets have been shown to have increased activity both through closure time as measured by the platelet function analyzer (PFA-100), increased fibrinogen binding after exposure to adenosine diphosphate, implying activation of the GPIIa/IIIb receptors, and by expression of activated ligands on the platelet surface [45]. In diabetes, platelets were hyperreactive as measured by light transmittance aggregometry and expression of surface ligands [46].

Hence, taken together, the person with diabetes has a vascular environment that is highly susceptible to thrombo-occlusive complications. With early atherosclerosis and disordered endothelial response, the person with diabetes is predisposed to thrombophilia. The blood, in its hypercoagulable state combined with platelets that are highly active in themselves, is far more likely to form clots.

Lacunar strokes are caused by damage to smaller parenchymal vessels. The most common cause is microatheroma, as demonstrated in pathological case series published by Fisher [47–49], the neurologist responsible for naming the lacunar syndromes. Lipohyalinosis and fibrinoid necrosis also cause microangiopathies, and both are most commonly found in the setting of chronic hypertension of severe acute blood pressure elevations, as seen in hypertensive encephalopathy [50, 51].

Primary prevention of stroke in persons with diabetes

Primary prevention of stroke is of paramount importance, as the disability from stroke and healthcare costs associated with the acute and chronic care of stroke are so extensive. The approach to prevention in the person with diabetes is of necessity multifactorial.

Medical therapy aimed at achieving normoglycemia is the foundation. The Diabetes Control and Complications Trial (DCCT) investigated intensive insulin regimens including subcutaneous insulin injections and external insulin pumps in T1DM. The goal for treatment was HbA_{1c} levels of <6.0% (42 mmol/mol). The comparison group had no such goals apart from prevention of hyperglycemia or hypoglycemia [52]. The intensive treatment group achieved a reduction of 57% in the combined endpoints of non-fatal MI or stroke, cardiac death, or revascularization procedure. The majority of this improvement was associated with the decrease in HbA1c [52].

Among oral antidiabetes agents, metformin has been shown to decrease diabetes-related endpoints including stroke by 32% and diabetes-related mortality including from stroke by 42% compared with conventional therapy. Furthermore, it was more effective in reducing these outcomes compared with other intensive therapies such as sulfonylureas (e.g. chlorpropamide or glibenclamide) or insulin. However, it should be noted that the HbA1c was similar among the groups, and so the benefits obtained were not explicable on the basis of improved glycemic control [53].

Rosiglitazone, a thiazolidinedione, on the other hand, has been linked with increased risk of MI and death from cardiovascular causes. Stroke was not assessed separately in the meta-analysis reporting these findings [54]. An interim report from an ongoing trial directly assessing the effect of rosiglitazone on cardiovascular outcomes has not upheld these findings [55]. Pioglitazone, another medication in the same class, was not associated with worse cardiovascular outcomes including stroke, and in fact reduced a secondary outcome of all-cause mortality, non-fatal MI and non-fatal stroke, by 16% [56].

The United Kingdom Prospective Diabetes Study (UKPDS) failed to show any reduction in macrovascular complications of T2DM despite a 0.9% reduction in HbA_{1c} in an intensive treatment group. Microvascular complications such as retinopathy and neuropathy were significantly reduced [57]. A 10-year follow-up study of the same cohort after attempts to maintain treatment differences had desisted showed that the original treatment cohort had persistent decrease in microvascular complications and also in MIs and deaths from any cause [58]. Hence glycemic control, at least in T2DM, has not been linked to a reduction in risk for stroke.

Given how susceptible persons with diabetes are to the effects of other vascular risk factors such as hypertension and hyperlipidemia, the therapeutic regimen must also address these states. In treating hypertension in persons with diabetes, the classes of medications with effects on the angiotensin–renin system appear to have the greatest benefit (see Chapter 42).

The HOPE trial examined people either with vascular disease (including coronary artery disease or stroke) or diabetes plus one other cardiovascular risk factor, such as hypertension, tobacco use, or elevated low-density lipoprotein cholesterol (LDL-C) levels. In this high-risk population, ramipril, an angiotensin converting-enzyme (ACE) inhibitor, decreased the risk of death from cardiovascular causes with an RR of 0.74, and reduced the risk of stroke with an RR of 0.68. As the mean reduction in blood pressure was only 3/2, the benefits were not attributable to the blood pressure-lowering effect of the medication. The effect was similar whether or not the participants had had a stroke prior to enrolment [59].

The LIFE trial examined people with diabetes, hypertension, and left ventricular hypertrophy. Participants were treated with either losartan, an angiotensin-2 receptor antagonist, or atenolol. Although, again, both medications achieved the same reduction in blood pressure, the primary endpoint of cardiovascular mortality, MI, or non-fatal stroke was reduced with an RR of 0.76. Notably in this trial, only 40% of participants achieved a systolic blood pressure of <140 mmHg, implying that further benefits would likely accrue with more intensive management [60].

A recent trial of intensive multifactorial medical management in individuals with diabetes with microalbuminuria showed a reduction in all-cause mortality, cardiovascular mortality, and cardiovascular events. The regimen was designed to achieve the following goals: HbA_{1c} levels of <6.5% (48 mmol/mol), fasting total serum cholesterol levels of <175 mg/dL, systolic blood pressure of <130 mmHg, and diastolic blood pressure of <80 mmHg. Stroke was not a prespecified endpoint in this study; however, there were six strokes in six participants in the intensive medical group, compared with 30 strokes in 18 participants in the control group [61].

Although antiplatelet treatment has been recommended for the primary prevention of coronary disease, the Antithrombotic Trialists' Collaboration meta-analysis failed to demonstrate a significant improvement in the primary prevention of ischemic stroke in persons with diabetes. Overall, nearly 5000 people were treated with aspirin, with only a 7% reduction in serious vascular events. The 95% CI was wide enough to include a possible 25% risk reduction, a value that is consistent with the prevention of secondary stroke in this population. It may be that in this population at high risk, the potential benefits of prophylactic aspirin outweigh the hemorrhagic complications [62].

Most of the early trials of antithrombotic medications were performed only on men. In the Women's Health Study, a study performed among female health professionals with no history of coronary or cerebrovascular disease, low-dose aspirin (100 mg every other day) was associated with a 17% risk reduction in stroke, a result of a 24% risk reduction in ischemic stroke and a non-significant increase in hemorrhagic stroke. These findings were especially pronounced in women older than 65 years of age at the time of enrolment, and also in the subgroup with diabetes [63].

Treatment of acute stroke in persons with diabetes

Treatment of acute stroke is limited by the vulnerability of the neuron to ischemic insult. With decreasing cerebral blood flow, the parenchyma becomes less likely to recover from even short durations of ischemia. With cerebral blood flow <20 mL per 100 g of tissue, neurological dysfunction begins to appear. However, it is not until the cerebral blood flow falls below 10 mL per 100 g of tissue that irreversible ischemia occurs, in a matter of minutes [64].

Thrombolysis has been demonstrated to be effective in the treatment of acute stroke provided that the medication is given within the first 3 h after symptom onset, as defined by the last time the individual was seen at their neurological functional baseline (Table 46.2). The NINDS trial of intravenous tissue plasminogen activator (t-PA) demonstrated a 30–50% increased likelihood of minimal or no disability 3 months after treatment. The thrombolysis was associated with a 6.4% chance of symptomatic intracranial hemorrhage, but the mortality data at 3 months were not statistically different between the treatment and the placebo groups [65].

Based on this trial, treatment with intravenous t-PA became standard of care in this early time period. Although more recent data from the ECASS-III trial [66] suggested that it is not only safe but also clinically effective to a lesser extent in a select group of patients to give intravenous t-PA in the window between 3 and 4.5 h after the onset of symptoms, this has not yet become standard practice. In addition, individuals with diabetes who had had a previous stroke by history or on imaging were excluded from the trial.

Table 46.2 Management of acute ischemic stroke.

- 0–3 h Intravenous tissue-plasminogen activator (t-PA)
- 0–6 h Intra-arterial t-PA
- 0–8 h Mechanical clot retrieval (MERCI device)
- Permissive hypertension for the first 3–5 days
- Aspiration precautions
- DVT prophylaxis

Intravenous t-PA is the only acute intervention approved by the US FDA. Both intra-arterial t-PA and mechanical clot retrieval remain experimental, although widely used. Intravenous t-PA should remain the standard of care when it is not contraindicated, with the other interventions to be used as auxiliary therapy

Thrombolysis in the person with diabetes with acute stroke is not as successful as in the general population. In a series of 27 individuals treated with intravenous t-PA, none of those with diabetes achieved recanalization of the occluded artery as measured by transcranial Doppler ultrasound [67]. The series was not large enough to demonstrate a significant difference. In another study examining which factors might predict major neurological improvement in people treated with intravenous t-PA, there was a trend towards people with diabetes being less likely to achieve that improvement [68].

Beyond intravenous thrombolysis, intra-arterial thrombolysis has been examined in patients up to 6 h after the onset of stroke symptoms. The PROACT II trial found that participants treated with intra-arterial urokinase had a 58% RR reduction to achieve minimal or no functional disability at 90 days after treatment. Mortality rates were comparable, and recanalization rates were greatly improved with the medication [69]. Current guidelines support the use of intra-arterial thrombolysis in the period between 3 and 6 h after the onset of symptoms. However, the medication has not been approved by the US Food and Drug Administration (FDA) for this indication [70].

In a case series of 100 people treated with intra-arterial thrombolysis with urokinase, diabetes was associated with poor functional outcome at 3 months. It was not associated with symptomatic intracranial hemorrhage [71]. However, since diabetes is independently associated with worse outcomes following acute ischemic stroke, it is not clear whether these data have any meaning for clinical practice.

Other interventional techniques include clot retrieval. Three devices have been tested: the MERCI device, a corkscrew type device; the PENUMBRA device, a direct clot aspirator; and the Solitaire stent retrieval system. The last device is the one most commonly used clinically today: compared with the MERCI

device, it had improved chances of restoring partial or complete restoration of blood flow with an OR of 4.87 [72]. However, a note of caution about interventional therapy has been raised with the publication of the IMS-III trial, which failed to show any benefit of endovascular therapy after treatment with intravenous t-PA, although there was no increased risk of these therapies either [73]. At the same time, these sorts of trials are very difficult to carry out, and analysis of IMS-III shows that a sizable proportion of participants randomized to receive endovascular therapy did not have any procedure attempted owing to lack of an appropriate target thrombus [74]. In support of the use of interventional therapy, the MR CLEAN trial enrolled 500 people in The Netherlands and randomized them to endovascular intervention plus usual care (which could include intravenous t-PA) versus usual care alone. The majority of interventional treatments used stent retrieval. The interventional group had an absolute risk reduction of achieving a good functional outcome of 13.5%, with a number needed to treat of 7.4 [75].

Hyperglycemia at the time of stroke treatment is associated with worsened outcomes. In a series of 73 people treated with intravenous t-PA, age, diabetes, admission glucose >140 mg/dL, and early reocclusion on transcranial Doppler ultrasound were significantly associated with worsened functional outcome as defined by a score of >3 on the modified Rankin scale. However, after logistic regression, only the hyperglycemia remained as an independent predictor of poor outcome. In particular, it was associated with larger infarct size, lesser degree of neurological improvement, and worse clinical outcome if recanalization was achieved [76].

Similarly, baseline hyperglycemia is associated with a greater likelihood of going on to symptomatic intracranial hemorrhage after intravenous thrombolysis. There appears to be a dose–response relationship between levels of serum glucose and likelihood of hemorrhage. This was especially true when levels were above 11.1 mmol/L (200 mg/dL), where 25% of patients suffered symptomatic intracranial hemorrhage. In a repeat analysis substituting the presence of diabetes for glucose levels, diabetes was associated with an OR of 3.61 for all hemorrhages, and 7.46 for symptomatic hemorrhage [77].

Furthermore, both those individuals who acutely worsened and those who showed lack of improvement at 24 h were more likely to have elevated blood glucose at baseline. Hyperacute worsening in patients treated with either intravenous or intra-arterial thrombolysis, or both, was not surprisingly associated with intracerebral hemorrhage and lack of recanalization. However, it was also associated with higher serum glucose. With every increase of 50 mg/dL of glucose, the OR for worsened outcome was 1.50 and the OR for mortality was 1.38. Even in those individuals who achieved recanalization, higher blood glucose predicted worse outcomes [78]. Similarly, serum glucose >144 mg/dL and also cortical involvement and time to treatment were independent predictors of lack of improvement at 24 h after treatment with intravenous thrombolysis. The OR for hyperglycemia was 2.89. Furthermore, lack of improvement at 24 h predicted poor functional outcome at 3 months [79].

Although these data are understandably disheartening, they should by no means be taken to imply that people with diabetes and acute stroke should not receive thrombolysis, or that these individuals do not benefit from the treatment. Furthermore, it is not clear whether the hyperglycemia seen in people with acute stroke and diabetes is secondary to the ischemic insult as a stress response or instead part of the chronic diabetic state and thus purely a complicating factor.

Interestingly, one study examined how persistent hyperglycemia differed from transient hyperglycemia in functional outcomes in addition to mortality. When hyperglycemia was present at baseline and when measured 24 h after admission, it was inversely associated with neurological improvement in the first 7 days, 30-day functional outcome, and 90-day negligible dependence. At the same time, persistent hyperglycemia was positively associated with increased mortality at 90 days and parenchymal hemorrhage. When hyperglycemia was absent at baseline but present at 24 h after admission, it was likewise inversely associated with 90-day negligible dependence and positively associated with death and parenchymal hemorrhage. In this study, baseline hyperglycemia alone (without persistence at 24 h) was not associated with poor outcomes. These data suggest that it may not be the stress response hyperglycemia that causes damage in the acute stroke setting [80].

However, intensive treatment of hyperglycemia may be associated with improved outcomes, as has been demonstrated for MIs [81]. A small pilot study found that hyperglycemic patients could be treated with insulin infusions safely, but the numbers were too small to compare functional outcomes at 1 month [82]. The use of insulin drips in another study to maintain glucose levels between 5.0 and 7.2 mmol/L (90–130 mg/dL) in people with acute ischemic stroke, started no later than 12 h after the onset of symptoms, was associated with a trend towards better functional outcomes and minimal or no neurological symptoms as measured by the NIH stroke scale. There were hypoglycemic episodes in the group treated with continuous infusion, but the majority of these were asymptomatic [83]. Clearly, further study is required on this subject.

Hyperglycemia as defined by serum glucose >400 mg/dL was a contraindication for inclusion in the NINDS trial for some of the reasons above, and also because extreme hyperglycemia can cause focal neurological deficits that mimic stroke [65]. Current guidelines recommend starting aggressive glycemic control if serum glucose is >200 mg/dL, while acknowledging that levels above 140–185 mg/dL may still be harmful [70]. Although it may be reasonable to attempt to bring down the glucose level and see if any focal symptoms improve or resolve, and then treat with thrombolysis if no improvement is seen, this approach has yet to be tested.

In terms of oral antidiabetes agents in the acute stroke setting, one study looked at the role of sulfonylureas taken pre-stroke and during the acute hospitalization. Sulfonylureas have an effect on $NC_{Ca\text{-}ATP}$ channels that are regulated by the SUR1 receptor, like pancreatic β cells, and which are open only during ischemic episodes, causing cell death. Theoretically, then,

treatment with sulfonylureas should be neuroprotective during ischemia. Although the numbers were small, and people with more severe strokes (NIH stroke scale >9) were excluded, people on the medication were more likely to have a decrease of 4 points on the NIH stroke scale or a score of 0, and were more likely to achieve an excellent functional recovery at discharge. The effect was particularly noticeable in non-lacunar strokes [84].

Further care for the person with acute stroke is best handled in a certified stroke unit, with multidisciplinary care from a team consisting of vascular neurologists, stroke-trained registered nurses, physical therapists, occupational therapists, and speech and swallow specialists. This care results in a reduction in mortality of ~25% [85].

Blood pressure control in acute ischemic stroke is a subject of ongoing debate. Current thinking still supports the concept of permissive hypertension in the peri-stroke period. Most vascular neurologists would allow the blood pressure to remain untreated until the systolic blood pressure rises above 220 mmHg or the diastolic blood pressure above 120 mmHg. The period when permissive hypertension should be allowed is also controversial. Typically, the blood pressure is left untreated for the first 3–5 days after stroke [70].

The majority of medical complications after stroke relate to the disability associated with neurological deficits. However, deep venous thrombosis (DVT) and aspiration pneumonitis are the two preventable complications. Prevention of DVT is accomplished through subcutaneous anticoagulation with either heparin or low molecular weight heparin with or without external compressive devices [70]. Initiation of treatment is typically immediately on admission, regardless of the size of infarct. One unblinded study studied heparin versus enoxaparin and found a reduction in thrombosis with the low molecular weight heparin [86].

Prevention of aspiration is more complicated. Protection of the airway is often compromised in the acute period after stroke. Frequent suctioning and positioning help to prevent aspiration. Swallow evaluations should be undertaken before oral nutrition is started in any one in whom dysphagia is suspected. Placement of nasogastric tubes (NGTs) is often required for nutrition, and frequently patients will require a percutaneous endoscopic gastrostomy (PEG) tube for long-term provision of nutrition. Hydration is necessary, either intravenously before enteral access is established, or via NGT or PEG tubes to prevent dehydration and electrolyte abnormalities. Antibiotics should be started in any patient suspected of infection, and fever should prompt an aggressive search for a source. Hyperthermia itself causes neurological deterioration, so antipyretics should be administered [70].

Secondary Prevention of Stroke in Diabetes

The management of the person with diabetes after stroke is similar to that for primary prevention as outlined above. The eighth report of the Joint National Committee on Prevention and Treatment of Hypertension recommends that persons with diabetes should be maintained at a blood pressure of <140/90 mmHg, and that it may take multiple antihypertensive medications to achieve this goal [87]. As suggested by the studies described above, ACE inhibitors and angiotensin receptor blockers provide greater protection against cardiovascular events including stroke.

Table 46.3 Prevention of ischemic stroke in the person with diabetes.

- Tight glycemic control
- Antihypertensives with ACE inhibitors or angiotensin receptor blockers
- Anticholesterol treatment, especially with HMG-CoA reductase inhibitors (statins)
- Lifestyle modifications (tobacco cessation, weight loss, etc.)
- Antiplatelet therapy (either aspirin, clopidogrel, or dipyridamole) *or*
- Anticoagulation in people with atrial fibrillation

Similarly, the American Heart Association and the American College of Cardiology have published guidelines on the management of cholesterol in individuals with diabetes [88]. All people who have clinical atherosclerotic cardiovascular disease, including stroke or TIA, should be offered treatment with a statin medication, at high intensity if there are no known safety concerns. In the situation where such an event has not occurred, people with diabetes and an LDL-C >70 mg/dL should also be treated with a statin. The guidelines suggest a goal of lowering the LDL-C by 50% when high-intensity statin treatment is used. Guidelines from the Endocrine Society likewise endorse aggressive lowering of LDL-C without specific goal thresholds for treatment [89].

Antiplatelet therapy should be started in all people who have had a non-cardioembolic ischemic stroke (Table 46.3). Although the Antithrombotic Trialists' Collaboration meta-analysis failed to show benefit in people with diabetes, post hoc analysis of data from the CAPRIE study found that such individuals treated with clopidogrel had a decreased rate of stroke, MI, or death of 15.6% compared with a 17.7% risk in those treated with aspirin [90]. Similarly, in a post hoc subgroup analysis of a study of cilostazol, people with diabetes had a decreased rate of recurrent stroke on the medication compared with placebo, with an RR reduction of 41.7%. This finding was especially evident in those with lacunar stroke [91]. These findings need to be verified with further trials. The use of a combination of dipyridamole and aspirin was demonstrated to be non-inferior to clopidogrel in the prevention of recurrent stroke in the PRoFESS trial. The prevalence of diabetes in this study was 28% in each group, and subgroup analysis within diabetes likewise did not demonstrate any difference between the two treatments [92].

In individuals who have had ischemic stroke secondary to extracranial carotid stenosis, carotid endarterectomy remains the preferred treatment of choice for carotid artery stenosis >70% (Figure 46.3). For degrees of stenosis between 50 and 70%, the benefits of surgery are much smaller, and decisions to treat will depend on the complication rate at local institutions [29]. However, the recent CREST trial suggests that carotid artery stenting is equivalent to surgical revascularization with respect to rates of

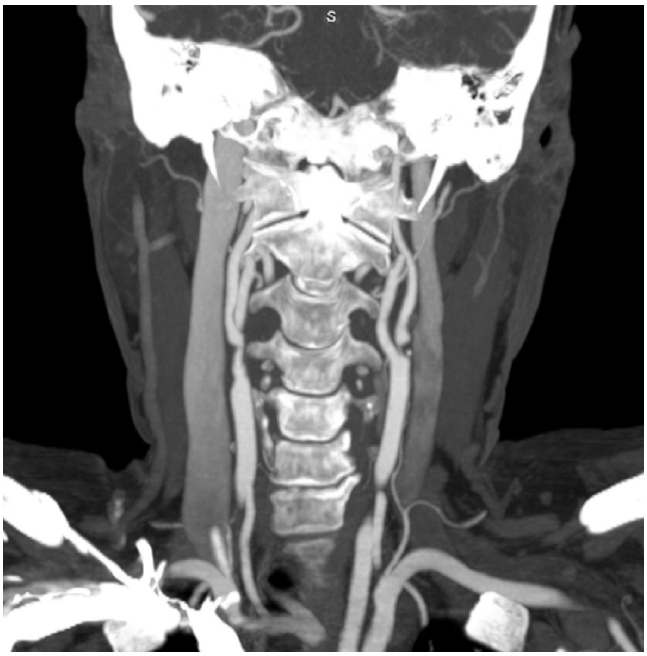

Figure 46.3 Computed tomography angiography with iodinated contrast of the neck. There is mild stenosis seen at the origin of the right internal carotid artery. There is critical stenosis ("string sign") at the origin of the left internal carotid artery, corresponding to severe atherosclerotic plaque.

periprocedural stroke, MI, or death, or rate of recurrent stroke. However, periprocedural stroke was more likely in the stenting group, whereas MI was more likely in the endarterectomy group. People younger than 70 years of age fared better when stented, whereas those over 70 years of age had better outcomes when they received endarterectomy. This dichotomization likely represents the risk of undergoing an endovascular procedure with an increasing atherosclerotic burden [93].

Persons with diabetes with atrial fibrillation, paroxysmal or otherwise, should be anticoagulated with warfarin to a goal of an International Normalized Ratio (INR) of 2.0–3.0. The risk reduction associated with treatment with anticoagulation is 68%, with an absolute risk reduction in the annual stroke rate from 4.5 to 1.4% [94]. This reduction in risk is so strong that one study estimated that a person would have to fall 295 times in one year for the risk of subdural hematoma secondary to trauma to outweigh the benefits gained from anticoagulation [95]. There is no reason to assume that this is any different for persons with diabetes.

Recently, several novel oral anticoagulants have been developed for the prevention of stroke in people with atrial fibrillation. Dabigatran [96], a direct thrombin inhibitor, and rivaroxaban [97] and apixaban [98], both direct Factor Xa inhibitors, have been demonstrated to be at least equivalent to warfarin in reducing the risk of recurrent ischemic stroke, with fewer hemorrhagic complications. These medications have a significant advantage over warfarin in convenience for both practitioner and patient, in that they do not require monitoring of levels, nor do they interact significantly with other medications, or require dietary adjustment. However, at present, there is no reliable method of reversing their anticoagulant effect in the setting of a hemorrhagic complication or need for emergency surgery. Prothrombin complex concentrate has normalized prothrombin times in animal models, and a dedicated reversal agent is being developed for the direct Factor Xa inhibitors (andexanet alfa) [99]. At present, we prefer the use of warfarin for prevention of stroke in people with atrial fibrillation unless they are unable to tolerate it or if their INR is too difficult to maintain in the therapeutic range.

Conclusions

Diabetes is a strong risk factor for ischemic stroke, and stroke in diabetes is both more severe in presentation and outcome and more recalcitrant to acute treatment. Although many etiologies of stroke are made more common by diabetes, the most common type of stroke found in persons with diabetes is lacunar microvascular infarction. Prevention of stroke in the person with diabetes is best served through aggressive management of concurrent hypertension and hyperlipidemia. Careful glycemic control also likely reduces the risk of stroke, but the risk reduction is not nearly as robust. Antiplatelet therapy also plays important role; a single antithrombotic agent is sufficient for the prevention of ischemic stroke. Hyperglycemia in the acute phase after ischemic stroke is associated with poor outcomes, and aggressive management likely improves functional recovery.

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47 Peripheral Vascular Disease

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Key points

- Peripheral arterial disease is very common, affecting up to 30% of all people with diabetes.
- Amputations are much more common in people with diabetes and occur 5–8 times more often than in those without the disease.
- Atherosclerosis is common in people with diabetes, and measurement of ankle blood pressure may identify both people with peripheral arterial disease at an early asymptomatic stage.
- People with diabetes have atherosclerotic lesions located more peripherally than people without diabetes and therefore are more commonly inoperable for technical reasons.
- People with diabetes have more complications in surgery, both locally (infections) and systemically (e.g. cardiac, pulmonary) than people without diabetes.
- Treatment of atherosclerosis in people with diabetes is basically the same as in those without diabetes.

Introduction

Peripheral vascular disease includes diseases to arteries and veins outside the thoracic region. Because of space limitations, this chapter mainly covers the three most common arterial diseases: peripheral arterial disease, carotid artery disease, and aortic aneurysmatic disease. Other, rarer, manifestations of atherosclerotic disease (e.g. renovascular hypertension, abdominal angina, and ischemia of the upper extremities) are mentioned briefly. Special considerations in individuals with diabetes are dealt with in relevant sections, e.g. infection in an ischemic foot in a person with diabetes is described in the section that includes critical limb ischemia.

Atherosclerosis is the main cause of peripheral arterial disease, and the overall pathogenesis is covered in Chapter 41. It is important to appreciate that the pathogenetic mechanisms of clinical atherosclerosis are dual: chronic obstructive and thrombotic. Whereas the chronic obstructive mechanism is the main cause of lower limb ischemia, including in persons with diabetes, it is often preceded by a thrombotic event; a person with mild claudication suddenly experiences significantly shortening of walking distance or sudden onset of rest pain. Alternatively, the seemingly healthy person suddenly develops claudication. Of course, a heart attack or stroke in a person with chronic obstructive disease and claudication is also a thrombotic event.

In general, individuals with diabetes more often develop symptoms of atherosclerotic complications, they do so at a younger age, they are more difficult to treat, and they have more complications with treatment (especially with invasive treatment).

Peripheral arterial disease

Peripheral arterial disease is a chronic condition that, like atherosclerosis in other vascular beds, develops over decades. The World Health Organization (WHO) definition includes exercise-related pain and/or ankle brachial index (ABI) <0.9. On average, symptoms from the lower limbs develop 5–10 years later than from the coronary circulation. Acute ischemia may develop because of:

1 thrombosis in a vessel with pre-existing atherosclerotic plaques and/or stenosis;
2 embolism (e.g. from mural thrombus in the heart);
3 an arterial lesion upstream; or
4 as a result of trauma.

Diabetes is a major contributor to peripheral arterial disease.

Peripheral arterial disease is traditionally divided into four stages (Fontaine):

1 asymptomatic (ABI <0.9);
2 functional pain (claudication);
3 rest pain; and
4 non-healing ulcers or gangrene.

Textbook of Diabetes, Fifth Edition. Edited by R. Holt, C. Cockram, A. Flyvbjerg and B. Goldstein.

Incidence

In population-based studies in Western Europe, the incidence of symptomatic peripheral arterial disease is 3–4% among 60–65-year-olds, increasing to 15–20% in persons aged 85–90 years [1–3]. Similar findings have been reported in the United States. Looking at asymptomatic cases where the ABI is <0.9, the incidence is much higher, in ~20% of all persons above 65 years of age, ranging from 10% in those 60–65 years of age to almost 50% in those aged 85–90 years [1–3]. Critical limb ischemia, defined as ABI <0.4 or rest pain and/or non-healing ulcers, occurs in 1% of persons aged 65 years or older.

Prevalence of peripheral arterial disease in people with diabetes

The prevalence of peripheral arterial disease in people with diabetes depends on the usual atherosclerosis risk factors and duration of diabetes. There have been only a few demographic studies of the general population. Using ABI <0.9 as the selection criterion, Lange et al. [4] found a prevalence of 26.3% in people with diabetes compared with 15.3% in people without diabetes on screening 6880 Germans above 65 years of age, of whom 1743 had diabetes. Similar findings have been reported by others: 20–30% of those with diabetes have peripheral arterial disease [5, 6]. Claudication is twice as common in those with diabetes as those who do not have diabetes.

Pathophysiology

It is outside the scope of this chapter to describe the pathophysiology of peripheral arterial disease in detail (see Chapter 41); however, in brief, the pathophysiology in people with diabetes is similar to that in people without diabetes. The abnormal metabolic state that accompanies diabetes directly contributes to the development of atherosclerosis. Proatherogenic changes include increases in vascular inflammation and alterations in multiple cell types. Both mechanisms of atherosclerotic complications are of importance in peripheral arterial disease (gradual narrowing resulting in stenosis and acute thrombosis in existing atherosclerotic lesions). Obviously, the long-term accumulation of lipids in the vessel wall is important and sudden local thrombosis can occur at any time, although in most cases this happens after symptoms (claudication) have developed.

To reach the stage of critical limb-threatening ischemia, advanced atherosclerosis has developed. Often, multiple segments of the arterial tree from the aorta to the foot are affected (stenotic and/or occluded). In people with diabetes, the atherosclerotic lesions are more peripherally located than in people without diabetes. Whereas the iliac and femoral arteries are most commonly stenotic and/or occluded in individuals without diabetes, in those with diabetes it is most often the crural or pedal arteries that are severely affected by atherosclerosis. In fact, in some cases of ischemic ulcers of the toe in a person with diabetes, foot pulses may be present due to very distal occlusive disease. This poses a challenge for revascularization because the results in general are better the more proximal the reconstruction is, and worse with distal disease and poor "run off" (vessels to receive the blood supply due to the revascularization procedure).

In order to develop ischemic non-healing ulcers, perfusion has to be very poor. The most reliable method for assessment of peripheral perfusion in those with diabetes is measurement of toe pressure. A toe pressure below 20–25 mmHg signals a poor chance of healing of a peripherally located ulcer. The special considerations related to the potentially dramatic course of infection in a diabetic foot are dealt with in Chapter 48.

Asymptomatic stage

The asymptomatic stage of peripheral arterial disease is especially interesting because it is associated with an approximately threefold increased mortality compared with matched controls [7, 8]. This excess mortality is caused by accompanying cardiovascular disease (CVD). Asymptomatic peripheral arterial disease can be identified by a very simple test: measurement of ankle blood pressure. This test takes only a few minutes and is expressed as the ABI, where the ankle pressure is divided by the highest of the two arm blood pressures. In this manner, variations in blood pressure between measurements do not influence the test result. Not only is an ABI <0.9 associated with increased mortality from cardiovascular causes, but also the level of ABI reduction is predictive: the lower the ABI, the worse is the prognosis [7].

Identifying an asymptomatic person with an ABI <0.9 is not a case for evaluation with respect to revascularization of the lower limbs, but a case for serious preventive cardiovascular medicine.

Claudication

Claudication is experienced by the individual as pain in lower limb muscles appearing after walking, most often in the calf, the thigh, and more rarely the buttocks. The walking distance eliciting the pain is very variable, beginning after 10–15 m in severe cases, whereas other may report pain only when walking fast uphill for more than 500 m. It is important for both the patient and the treating physician to understand that claudication, although it may be incapacitating for a few, and troublesome for many, signals severe vascular disease systemically, and that cardiovascular morbidity and mortality are high (elevated 3–4-fold compared with matched controls).

Rest pain

Rest pain typically begins at night when the individual is in the horizontal position. The positive effect of gravity on lower limb perfusion is then abolished. The person typically complains about pain in the toes or feet during the night, and most have experienced that standing or sitting up relieves the pain. Many people will sleep sitting in a chair.

In individuals with diabetes, symptomatology may differ because of coincidal peripheral neuropathy. Just as myocardial ischemia can be masked, symptoms from the lower extremity may be lacking even though peripheral ischemia exists. This is especially important when a person with diabetes presents with a small ulcer or wound on the lower limb, even if they think that there is a good explanation for developing the ulcer, such

as a relevant trauma. The lack of symptoms to signal peripheral ischemia combined with the risk of escalating infection in a diabetic foot has prompted many diabetologists to recommend routine assessment of peripheral circulation at regular intervals in all people with diabetes.

Non-healing ulcers

Non-healing ulcers often begin after minor trauma (e.g. hitting a toe against a chair or wearing shoes that are too small). In some cases the ulcers develop without any trauma and those will often progress to gangrene if not treated. Ischemic ulcers develop on toes or on the foot, typically at points where shoes are in firm contact. Hence they are usually easy to discriminate from venous ulcers, which are located at the level of the ankles or lower calf.

Rest pain, non-healing ulcers, and/or gangrene are often referred to as critical ischemia. The "diabetic foot" is dealt with in Chapter 48.

Diagnosis

Most often the history and objective findings will ensure the diagnosis, but measurement of ankle blood pressure (ABP) will quantify the ischemia and can be used to monitor changes in the disease (Figure 47.1). In some people with diabetes, the media of smaller arteries become calcified, making them incompressible. Thus, very high ankle pressures resulting in elevated ABI (>1.3) signal media sclerosis and should be recognized as a falsely elevated measurement. In fact, ABI >1.3 is associated with a marked increased mortality because media sclerosis is found in people with diabetes and those with renal failure.

Because small arteries are rarely affected by media sclerosis, measurement of toe pressure is an alternative for the assessment of peripheral arterial disease. The strain gauge technique is most commonly used (Figure 47.2), although alternative methods for measurement of toe pressure have been developed recently. Toe pressure is also useful for the prediction of healing of ulcers and amputation wounds.

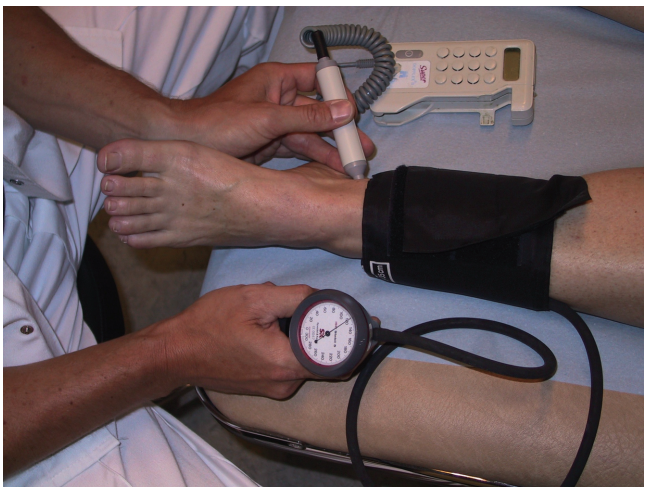

Figure 47.1 Measurement of ankle pressure using the Doppler technique.

Figure 47.2 Measurement of toe pressure using the strain gauge technique.

Prognosis

The risk of amputation is only 1–2% at 5 years. About 25% of people with claudication will experience a worsening of their symptoms from the lower legs; however, 75% will be unchanged or improve without revascularization [9]. In contrast, the "systemic" risk is huge; mortality at 5 years will be 15–25% and many more people will have non-fatal myocardial infarction (MI) or stroke.

The risk for a person with diabetes and peripheral arterial disease is much higher than that of a person with peripheral arterial disease. An individual with diabetes has an eight times greater risk of amputation at the level of the transmetatarsal bones or above than someone without diabetes [10]. In addition to the already severely increased mortality of peripheral arterial disease, people who additionally have diabetes have a further doubling of their risk of death [10–12].

Treatment

Treatment of people with symptoms from the lower limb therefore involves two aspects:

- treatment of symptoms from the lower limb; and
- prevention of cardiovascular complications.

The former includes lifestyle modification, medical therapy, and interventional therapy by either percutaneous transluminal angioplasty (PTA) or open surgery, whereas the latter includes lifestyle modification and preventive medical therapy.

It is beyond the scope of this chapter to detail all aspects of lifestyle modification and preventive medical therapy; however, it is extremely important for the reader to understand that individuals with peripheral arterial disease derive at least as much benefit from lifestyle modification and aggressive preventive medical therapy than any other group of people (see Chapter 42). Most of the lifestyle changes that are beneficial to the person with diabetes will also benefit the peripheral arterial disease, especially smoking cessation, regular exercise, weight loss, and dietary changes.

Medical prevention follows the same guidelines as for other clinical atherosclerotic manifestations such as ischemic heart disease and can be summarized as follows: aggressive statin treatment almost irrespective of cholesterol levels, antiplatelet therapy and blood pressure control. In this chapter, only details of lifestyle modification and medical therapy relevant to PTA and surgery are discussed.

Treatment of symptoms from the lower limb

Most people should be managed without invasive intervention with PTA (and/or surgery). Because the risk of cardiovascular complications (cardiac and cerebral) is much higher than the risk of amputation, the main focus should be on preventive measures in order to halt the atherosclerotic process. The conservative approach with respect to revascularization is especially important for people with diabetes because of the increased risk of surgical complications and poorer results of revascularization. One exception are those with critical limb ischemia. Early revascularization before widespread infection can be limb saving.

Exercise therapy has proven effective for improvement of walking distance, and regular exercise for 3 months can be expected to improve walking distance by 200–250% [13]. Because exercise also reduces cardiovascular morbidity and mortality, it cannot be stressed enough (for both the patient and the physician) that this is extremely important. Because the effect on walking distance is so good, and because it is important for survival, exercise therapy should always be tried before considering interventional treatment. There are only a few exceptions where interventional treatment may be considered early on:

- individuals with a very short walking distance, who are not able to carry out important daily responsibilities such as their work; and
- those at risk of amputation (rest pain and non-healing ulcers).

The dilemma of explaining to patients that the symptoms they are experiencing from the lower limb are signaling high cardiovascular risk rather than lower limb risk is challenging. First, there is (or has been) a general perception that atherosclerosis in the limb is less dangerous than in other locations. The author hopes that the introductory remarks in this chapter have changed this potential misperception for the reader. Medical therapy for claudication includes cilostazol and statins. Both drugs have been shown in placebo-controlled trials to improve walking distance by 30–50% and the latter furthermore reduces the cardiovascular risk. Other drugs have not proven useful in improving walking distance significantly [14].

Interventional treatment

Interventional treatment (endovascular or open surgery) for peripheral arterial disease is indicated when:

- exercise and other lifestyle modification have failed to improve symptoms to an acceptable state;
- claudication is incapacitating; or
- critical limb ischemia is present (rest pain, non-healing ulcers, and/or gangrene).

Again, for the person with diabetes, the indication for revascularization should be considered very carefully in those with only claudication. The choice between PTA and open surgical management depends on the location and extent of disease. In general, endovascular treatment can be expected to perform well in cases of shorter lesions, whereas open surgery is preferred in cases of extensive occlusive disease. Obviously, whenever comparable results can be obtained, PTA is preferred for the simple reason that it is less invasive and associated with fewer complications than open arterial reconstructions. In people with severe comorbidity that might complicate the outcome of open surgery, PTA would be preferred even though theoretically surgery would be the treatment of choice if only patency of the revascularization procedure was considered.

The arterial lesions that cause obstruction of blood supply to the lower limb are most often located in the distal abdominal aorta just proximal to the aorta–iliac bifurcation, in the iliac arteries, and in the common and superficial femoral arteries. The arteries in the calf, the anterior and posterior tibial and the peroneal arteries, are often involved in persons with diabetes with critical ischemia. In general, when individuals with diabetes present with symptoms, they have a more distal involvement with open arteries down to the level of the popliteal artery and then occlusive disease of the calf vessels and sometimes also the arteries in the foot. The results of revascularization for people with diabetes with toe or foot ulcers are worse than those for the general population partly because reconstructions yield better results with respect to patency when the lesions are more centrally located.

Percutaneus transluminal angioplasty

In principle, PTA can be performed anywhere between the heart and the feet. In general, the more centrally located the lesions being treated are, the better the results (especially with PTA). Also, the shorter the stenosis or occlusion, the better the results, and stenting improves patency in most cases. Endovascular-treated common iliac arteries, as an example, remain patent in 60–80% of cases after 5 years, and thereafter they may be redilated. Primary stenting has become the preferred treatment in most cases. Obviously, because serious complications are rare, the tendency to offer PTA for iliac artery obstruction is greater than for occlusive disease that is more peripherally located.

PTA of the superficial femoral artery (Figure 47.3) may relieve symptoms, but the results depend on the extent of disease. In principle, with increasing length of a lesion there is an increasing risk of early reocclusion. Stenting appears to improve patency, at least for longer lesions (Table 47.1) [15]. When the indication for PTA

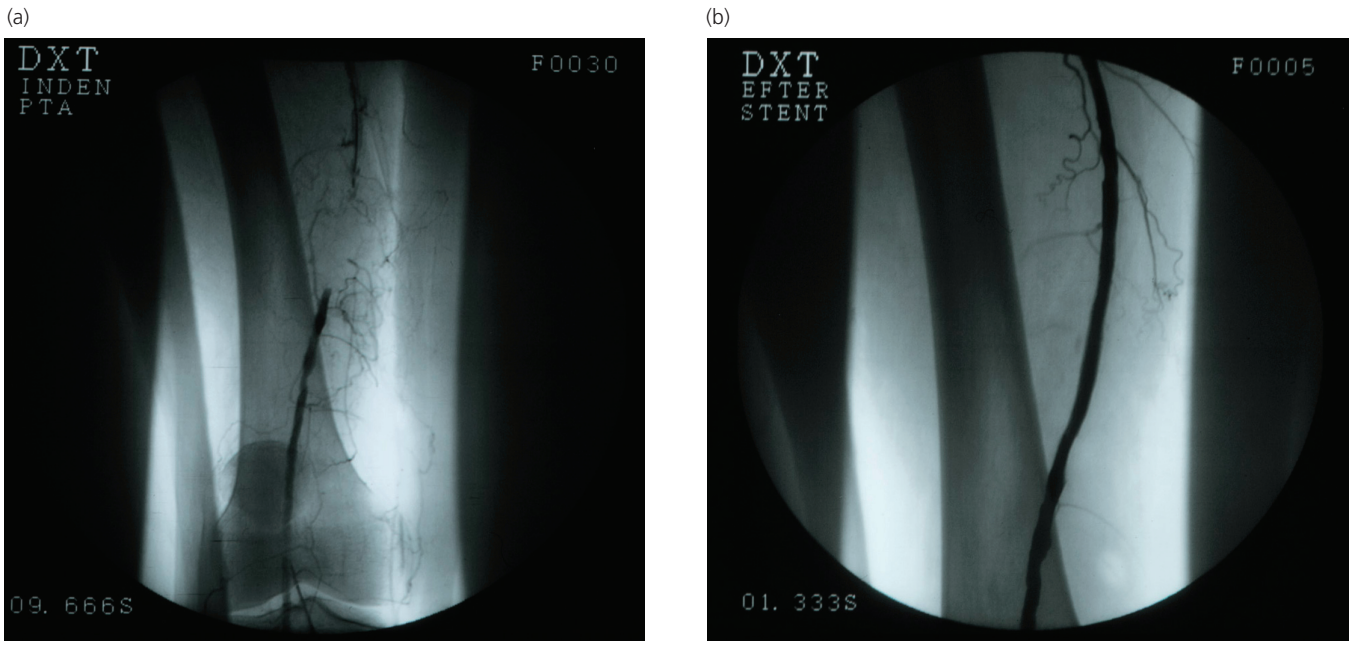

Figure 47.3 Short occlusion of the superficial femoral artery (a) treated with PTA and stenting (b).

is claudication, patency is better than if the indication is critical ischemia. This difference relates to the more extensive nature of the disease in the case of critical limb ischemia (poor run-off vessels). The 3-year patency is 48%, which may be improved to 64% if stenting is added. In cases of critical limb ischemia, the results at 3 years show a patency of 30% without stenting and 63% with stenting (Table 47.1) [15]. PTA of crural vessels is also feasible; however, the long-term results are not good. Data on limb salvage with PTA of crural vessels alone are still scarce despite these procedures having been developed extensively in the last 5 years. Adjunctive medical therapy to improve patency following PTA and stenting, with anticoagulation and/or antiplatelet therapy, has been tested in only a few trials. Antiplatelet drugs improve patency, and the combination of aspirin and clopidogrel may be beneficial [16].

Table 47.1 Pooled patency of vascular reconstructions (TASC[a] II).

	Patency (%)			
Reconstruction	**1 year**	**3 year**	**5 year**	**10 year**
Endovascular				
Iliac artery	86	82	71	
Fem-pop stenosis PTA	77	61	55	
Fem-pop occl. PTA	65	48	42	
Fem-pop stenosis PTA + stent	75	66		
Fem-pop occl. PTA + stent	73	64		
Open surgery				
Aorto-bifemoral bypass			90	80
Fem-fem crossover			75	
Fem-pop vein			80[b]	
Fem-pop PTFE			30–75[b]	

[a]Inter-Society Consensus for the Management of Peripheral Arterial Disease (TASC).
[b]Secondary patency.
Fem, femoral; occl., occlusion; pop, popliteal; PTA, percutaneous transluminal angioplasty; PTFE, polytetrafluoroethylene.

Open surgical revascularization

Open surgical revascularization still dominates as the treatment of choice in cases of critical limb ischemia, because of the extensive nature of the atherosclerotic lesions in these patients. For claudication, open surgical treatment is rarely performed, whereas for extensive disease of the distal aorta and iliac arteries, the aorto-bifemoral bypass remains the procedure with the best long-term outcome. In addition, femoral–femoral crossover bypass may be performed for unilateral iliac artery occlusion. Also, endarterectomy of the femoral artery, as described below, may be an option for treatment of claudication. Only one trial has compared open surgery with endovascular treatment of critical limb ischemia, the Bypass versus Angioplasty in Severe Ischaemia of the Leg (BASIL) trial [17]. The primary efficacy outcome measure was amputation-free survival, but because approximately two-thirds of the endpoints were deaths, only one-third of the endpoints really determined which procedure was best. Within 6 months postoperatively, there was no difference in the primary endpoint, but thereafter bypass patients seemed to do better [17].

In general, two surgical techniques are used: endarterectomy and bypass. Endarterectomy is performed by separating the intima from the media, and in this manner the atherosclerotic lesion can be removed. Endarterectomy can be used in cases with severe

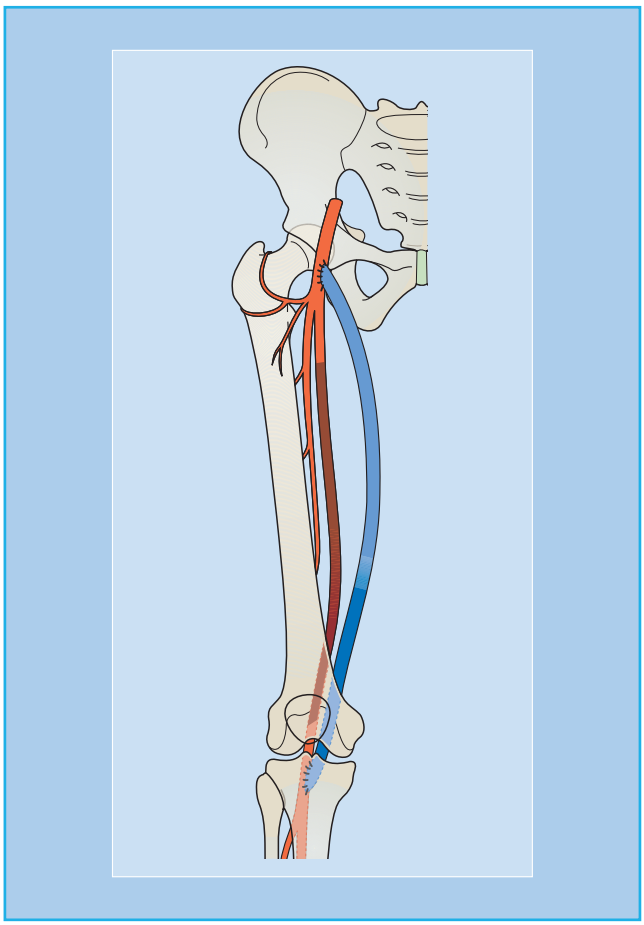

Figure 47.4 Long superficial femoral artery occlusion treated with femoro-popliteal bypass.

occlusive lesions of limited anatomic extension, in the external iliac or in the common femoral artery. The advantage of this technique is that it can often be performed without the use of artificial graft material and patency is excellent. Bypass is preferred when the obstructive and/or occlusive lesions are extensive (e.g. total superficial femoral artery occlusion or multiple serial lesions warranting a femoral–crural bypass) (Figure 47.4). Bypass surgery can be performed with artificial materials or with autologous veins. For bypass of aortic or iliac artery origin, artificial grafts are almost always used. This is because there is no easily removable vein with similar dimensions that can be used in these locations. Also, Dacron or polytetrafluoroethylene (PTFE) grafts perform very well in the aorto-iliac–femoral region. For peripheral bypasses, typically originating from the common femoral artery, autologous vein grafts are preferred for two reasons: they last longer (much better patency) (Table 47.1) and they carry less risk of infection. For longer bypasses, such as from the common femoral to the popliteal artery below the knee, a saphenous bypass is performed, leaving the vein *in situ*. This means that the vein is left in its original anatomical location; however, the proximal and distal ends are anatomized to the arterial system. The venous valves are cut with a knife mounted on a catheter and side branches are occluded. In this manner, the vein retains its nervous innervations and native vascularization.

Complications of endovascular treatment

Complications relate mainly to the site of puncture and the risk of peripheral embolization. "Systemic" cardiovascular complications are rare. Hematoma in the groin access point is common; however, it only rarely requires any action to be taken. Development of an iatrogenic pseudo-aneurysm is seen in 0.5–1% of cases and can easily be treated with ultrasound-guided compression or ultrasound-guided thrombin injection.

Complications of open surgical treatment

These can be divided into local and systemic categories. The former relate to the actual incisions and dissections including wound healing and infections. Whereas complications from accidental damage to other organs and/or structures are very rare, wound healing problems and infections are unfortunately fairly common. In particular, surgery on the lower limb involving the groin and peripheral incisions have wound complications in 10–20% of cases (e.g. hematoma, lymph oozing or necrosis of the wound) [18]. Infections are seen in 3–5% of cases, approximately one-third involving the vascular reconstruction. Infection of the vascular reconstruction is more frequent when using artificial graft material [18].

Systemic complications to open surgical revascularization relate to the surgical trauma and to the stress response. In vascular reconstructions involving the aorta and other central arteries, the cardiopulmonary complication rate is considerable. Implantation of an aorto-bifemoral bypass graft is associated with a 30-day mortality of 2–5% and a rate of "general" complications of 10–15% (e.g. pulmonary, cardiac, renal, prolonged stay in the intensive care unit and stroke) [18]. Systemic complications to peripheral revascularizations occur less frequently; however, they are considerable. When the indication is claudication, the morbidity with respect to general complications is low, 2–4%; however, in cases of critical ischemia and peripheral bypass surgery, the morbidity increases to 10% with a 30-day mortality of 3–5%. This difference in morbidity is a reflection of the more advanced level of generalized atherosclerotic disease in patients with critical ischemia. In people with diabetes, complications are more common especially with open surgery. A doubling of risk should be expected.

Results of endovascular and open surgical reconstructions

These are summarized in Table 47.1. In general, when treating more centrally located arterial obstruction, the long-term results are better. In addition, treating people with claudication results in better long-term outcome than operating on those with limb-threatening ischemia. This difference relates to the generally poorer condition of the peripheral circulation in cases of critical ischemia with better run-off vessels in the person with claudication.

In peripheral reconstructions, vein grafts perform better. It may seem unrewarding to treat people with critical limb ischemia with a peripheral bypass using an artificial graft when there is only a 50% chance of being patent at 1 year; however, if the alternative is amputation and/or very poor quality of life (i.e. severe rest pain), 1 year with a functioning graft may very well be worthwhile for both the patient and surgeon. Limb salvage as a result is almost always better than patency of the reconstruction because in many cases, once the ischemic limbs with tissue loss have healed, the "need" for amputation becomes less. This is because wound healing increases the needed blood supply, but once wounds are healed, resting blood flow needs are less. People with diabetes typically have poorer outcome of vascular reconstructions, with patency rates that are inferior to those in individuals without diabetes. People with diabetes have more complications to treatment; not only infections but also systemic complications are more common.

Acute lower limb ischemia

This condition is most often caused by thrombosis in existing atherosclerosis (i.e. a patient with previous symptoms of chronic peripheral arterial disease). Another common cause is thrombosis of a popliteal aneurysm. Embolism remains a common cause, although not as often as in the past because of better anticoagulant therapy for people with atrial fibrillation. About 80% of emboli are of cardiac origin; however, aneurysms of the aorta or peripheral aneurysms may give rise to peripheral emboli.

Other causes include trauma and iatrogenic lesions (e.g. from arteriography with puncture of the femoral artery). Aortic dissection may cause lower limb ischemia and also acute deep venous thrombosis (phlegmasia cerulea dolens). The incidence in Western Europe is 300–400 per million per year.

Pathophysiology

Thrombosis is caused by plaque rupture and subsequent thrombosis. Distal to the acute occlusion, arterial flow is slow and, when combined with a hypercoagulable condition, it may lead to further thrombosis. The degree of ischemia depends on the location and degree of collateral development. Therefore, thrombosis is often better tolerated than embolism because people with existing atherosclerosis most often have developed collaterals.

Emboli will typically occlude an artery at a bifurcation; in the lower limbs, at the aortic bifurcation (saddle embolus), iliac artery, and femoral artery bifurcation. About 60% of cardiac emboli will end in the lower limbs, 15% in the arms, and the rest in the brain and other organs. Microemboli, typically from aneurysms, affect small peripheral arteries, and are therefore the cause of "blue toe" syndrome.

Symptoms

Acute ischemia is characterized by pallor, pain, pulselessness, paresthesia, and paresis (the "5 Ps"). Symptoms may begin dramatically and in some cases the late signs of ischemia, paresthesia, and paresis occur within a few hours. More often, symptoms begin with pain and paresthesia and later sensory and muscular paresis. Acute ischemia is traditionally divided into three classes: viable, threatened, and irreversible (Table 47.2).

Diagnosis

Diagnosis is often easy, with typical clinical signs. ABI will be low, if measurable at all. Imaging with either duplex ultrasound, magnetic resonance angiography (MRA), computed tomography angiography (CTA), or digital subtraction angiography (DSA) is possible, but may delay treatment. In cases of thrombosis, it is most often desirable to perform arteriography with subsequent thrombolysis in order to visualize the underlying pathology causing the thrombosis.

Prognosis

If revascularization is possible before irreversible ischemia has occurred, the limb can be salvaged and normal function regained. Comorbidity is high in cases of acute ischemia; when acute revascularization is needed, the procedure-related mortality is 10–20% because of release of toxic substances from ischemic tissue combined with existing cardiac disease.

Treatment

Thrombosis in existing atherosclerotic lesions may be treated by endovascular or open surgery. The former is preferred if

Table 47.2 Separation of threatened from viable extremities.

		Findings		Doppler signals	
Category	**Description/prognosis**	**Sensory loss**	**Muscle weakness**	**Arterial**	**Venous**
Viable	Not immediately threatened	None	None	Audible	Audible
Threatened:					
a. Marginal	Salvageable if promptly treated	Minimal (toes) or none	None	(Often) inaudible	Audible
b. Immediate	Salvageable with immediate revascularization	More than toes, associated with rest pain	Mild, moderate	(Usually) inaudible	Audible
Irreversible	Major tissue loss or permanent nerve damage inevitable	Profound, anesthetic	Profound, paralysis (rigor)	Inaudible	Inaudible

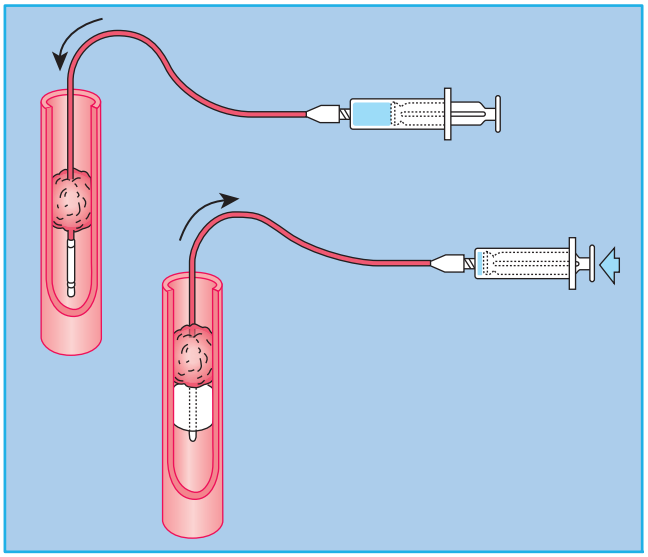

Figure 47.5 Embolectomy performed with a balloon catheter.

revascularization is not imminent. By catheter-directed intra-arterial thrombolysis, the underlying atherosclerotic lesions will be exposed and may in some cases be treated by PTA and/or stenting. In other cases, bypass surgery may be needed. Inoperable cases may be converted into operable cases by thrombolysis because distal thrombosis most often makes surgery (and PTA) useless when there are no run-off vessels. Another advantage of thrombolysis is that emergency surgery is converted into a less urgent intervention. Emboli can be treated by embolectomy by inserting a balloon catheter, in either the femoral or popliteal artery, and retracting the emboli after inflating the balloon (Figure 47.5). Some cases of embolism may also be treated by thrombolysis.

Prevention

Arterial emboli have a high recurrence rate and the underlying case should be treated, if possible, with corrective treatment for atrial fibrillation and resection or exclusion of aneurysms. If the source of embolism cannot be eliminated, anticoagulation must be considered.

Atherosclerosis of renal and mesenteric arteries

Renal artery obstruction

Renal artery obstruction can cause severe hypertension and renal failure but interventional treatment may improve both conditions. Today, open surgical management is only rarely performed because endovascular management is much less invasive and is feasible in the majority of cases. Open surgery, thromboendarterectomy or bypass, is performed when renal artery disease is combined with other pathology such as aortic occlusion or abdominal aortic aneurysms.

However, recently, the CORAL study showed that renal artery revascularization (stenting) of atherosclerotic lesions in order to treat renovascular hypertension is not better than optimal medical therapy [19]. This was surprising and has reduced the use of this intervention, and so it is now mainly used to (and indicated for) treat renal artery stenosis due to fibro-muscular dysplasia. There may be rare cases where revascularization is performed in order to improve renal function; however, this is done on an empirical background.

Mesenteric artery occlusive disease

Mesenteric artery occlusive disease may cause abdominal angina. Just like atherosclerotic lesions in other locations, many cases are asymptomatic and probably do not need intervention with regard to the obstructive disease, but lifestyle changes and medical preventive treatment are indicated. Patients with classic symptoms—postprandial pain occurring 10–20 min after a meal in addition to weight loss—often benefit from revascularization. However, many patients have less obvious symptoms, and the mere occurrence of a lesion on one of the three main vessels supplying blood to the gastrointestinal tract (celiac trunk, superior and inferior mesenteric artery) does not warrant interventional treatment. In general, a single lesion in one of the three arteries mentioned above is seldom thought to cause ischemia. Diagnosis is possible by ultrasound of the suprarenal vessels in most cases, otherwise CTA, MRA, or DSA may be needed. Interventional treatment today is mainly balloon angioplasty and stenting. Long occlusions of the superior mesenteric artery and/or occlusive mesenteric disease combined with other pathology of the aorta may be treated by open surgery (e.g. aorto-mesenteric bypass or transposition).

Ischemia of the arm

Atherosclerosis and ischemia of the arm are much less common than in the lower limb. The most common location for development of atherosclerosis in the arteries supplying the upper extremity is in the brachiocephalic trunk and subclavian arteries central for the origin of the vertebral arteries. Rarely, occlusive lesions are located more peripherally in the subclavian or axillary arteries. Takayasu vasculitis may also cause upper extremity ischemia.

Typical symptoms of chronic arm ischemia

These include "claudication," i.e. pain when using the arm. In typical cases, pain is encountered when performing tasks with the arms elevated, such as hanging laundry, or other physical use of the arm. Critical ischemia with rest pain or gangrene is rare but may occur. Diagnosis is easy, with lack of pulses at palpation. Measurement of bilateral blood pressure and ultrasound may locate and quantitate the stenotic lesion. If blood pressure cannot be measured by auscultation, a Doppler device may be used as for measurement of ankle blood pressure. Additionally, or in case of severe ischemia, finger pressure measurement by the strain gauge technique may be used. Upper arm angiography by CTA, MRA, or DSA may be supplemental.

The prognosis is often good because development of critical ischemia and the necessity for amputation are rare. Patients with finger gangrene should be investigated for vasculitis.

Treatment of upper extremity atherosclerosis is similar to that of atherosclerosis in other vascular distributions: risk factor reduction by lifestyle changes and preventive medications for all, and revascularization in some. In fact, only rarely is interventional treatment indicated, but in cases of incapacitating functional pain and/or critical ischemia, revascularization should be considered. Endovascular treatment dominates because of its less invasive nature for lesions near the origin of the brachiocephalic trunk and subclavian arteries. For lesions that cannot be treated by endovascular techniques, such as long lesions or lesions that cannot be crossed by a guide wire, bypass surgery is indicated (carotid–subclavian bypass). Peripheral bypass of the upper extremity (e.g. at the level of the brachial artery) is rare and patency is poor.

Acute arm ischemia

This is most often caused by embolization, but alternatively can be caused by thrombosis in an existing stenosis such as of the subclavian artery. Whereas the former may be treated easily by embolectomy via a small incision in the cubital fossa, the latter may be more complex to treat, perhaps requiring intra-arterial thrombolysis before vascular reconstruction. Embolism is most often of cardiac origin, from either atrial fibrillation, mural thrombus in the heart, or valve disease. Vascular causes include a subclavian aneurysm or stenosis. Microemboli may occur peripherally and present as gangrene of one or more fingers. Extravascular causes include a cervical rib. Obviously, eradication of the embolic source is crucial, if possible. Treatment of the peripheral ischemia may include thrombolysis, but in most cases collaterals develop and amputation does not become necessary.

Aortic aneurysmal disease (abdominal aortic aneurysm)

This section focuses on abdominal aortic aneurysms because thoracic aortic aneurysms are not considered part of peripheral vascular disease. The main difference between individuals with and without diabetes with respect to treatment of aneurysms is that those with diabetes are more prone to complications after surgery; however, because of the nature of preventive surgery for aneurysms, this only rarely causes changes in management once the risk of surgery has been weighed against non-surgical treatment.

Aneurysm of the aorta is a common condition in the elderly, especially in the infrarenal aorta. An artery by definition becomes aneurysmal when the diameter locally increases by more than 50% compared with the "normal" diameter proximal or distal to this site. In cases of the infrarenal aorta, an aneurysm is present when the diameter exceeds 30 mm.

The prevalence of abdominal aortic aneurysm is ~5% in men over 70 years of age; however, only a minority of them will have a size that mandates surgery (diameter >5–6 cm). In individuals with other atherosclerotic manifestations, such as peripheral arterial disease or carotid disease, the incidence of abdominal aortic aneurysms is 2–3 times greater. There is a 2 : 1 ratio of aortic aneurysms occurring in men : women. Finally, the tendency to develop abdominal aortic aneurysms is partly inherited, as the risk for a man with a father or brother with aortic aneurysm is ~20%. People with diabetes seem to have a slightly lower incidence of abdominal aortic aneurysm, ~80% of those without diabetes [20].

Pathophysiology

Arteries enlarge with age, and the diameter of the infrarenal aorta is normally below 20 mm in a 70-year-old man. If the wall weakens locally, an aneurysm develops. A true aneurysm develops when all three layers in the arterial wall are involved and dilate as in the case of the typical infrarenal aortic aneurysm. False aneurysms or pseudoaneurysms develop after iatrogenic trauma, such as PTA or other transfemoral procedures, and at arterial anastomotic sites. Finally, dissection occurs when a rupture of the intima allows blood to enter between the layers of the artery wall.

Aortic aneurysms may rupture, almost certainly leading to death. It is estimated that 80–90% of patients with ruptured aneurysms die before they get to hospital. Ruptured aneurysms causes an estimated 2–3% of all deaths among men, whereas the proportion for women is 1%.

In most abdominal aortic aneurysms, there is an atherosclerotic degeneration of the vessel wall that dilates; however, it is unclear why atherosclerosis in some people results in occlusive disease and in others in aneurysm development. Accelerated breakdown of elastin has a role in aneurysm development. The simultaneous presence of both occlusive and aneurysmal disease is common in many patients. Inflammatory aneurysms are present in 5–10% of aortic aneurysms where the aortic wall is thickened as part of perianeurysmal or retroperitoneal fibrosis.

Symptoms from abdominal aortic aneurysms

Symptoms are rare and most are asymptomatic. Diagnosis is often made coincidentally, such as when a patient complains of slight upper gastric pain and has an ultrasound of the gallbladder, which discloses the aortic aneurysm. Also, typically, a patient may complain of back pain and have a lumbar X-ray. Whether the patient's pain is really related to the abdominal aortic aneurysm, to gallstones, or to the back is often difficult to ascertain.

Some patients will sense a pulsation in the abdomen, while large aneurysms may cause discomfort or compress surrounding organs, mainly the gastrointestinal tract. The main risk is rupture, which, when intraperitoneal, most often leads to immediate death. If rupture is into the retroperitoneal space, a hematoma may be contained and the patient may survive for hours. Rupture and development of a hematoma lead to pain in the abdomen and/or back. Chronic rupture is rare because almost all cases will be fatal within hours.

Aneurysms may cause peripheral embolization, resulting in a cyanotic or gangrenous toe as the first symptom.

Diagnosis

Diagnosis is easy as ultrasound is very accurate in making the diagnosis and estimating the diameter of the aneurysm (Figure 47.6). In the few cases where ultrasound is inconclusive, a primary computed tomography (CT) scan may be necessary. Otherwise, CT or MR scanning is only performed when the size of the

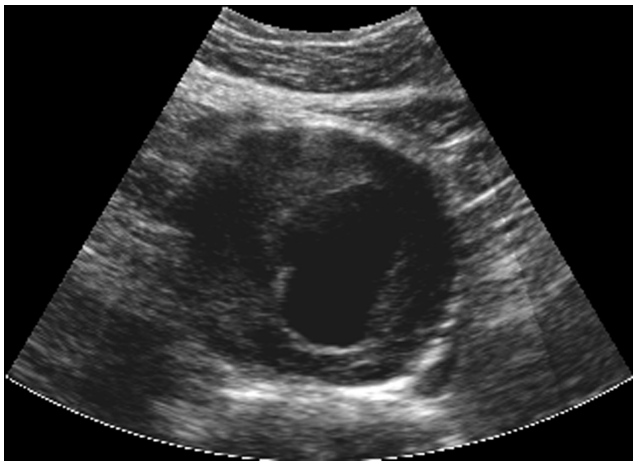

Figure 47.6 Ultrasound image of abdominal aortic aneurysm. Note the presence of a large thrombus inside the aneurysm sac.

aneurysm dictates to an extent that intervention should be considered. Arteriography is rarely performed for abdominal aortic aneurysm; however, in cases of both abdominal aortic aneurysm and symptoms of peripheral arterial disease, an arteriogram may be warranted for planning of the revascularization procedure. A patient with acute abdominal pain in preshock should always be suspected of ruptured abdominal aortic aneurysm.

Prognosis

The risk of rupture is related to the size of the aneurysm. When the diameter exceeds 6 cm, the annual risk of rupture is 10–20%, whereas the risk of rupture in the case of an aortic aneurysm with a diameter of 3–4 cm is <1%. Aneurysms tend to expand; small aneurysms dilate by 1–2 mm/year whereas larger aneurysms may expand 2–3 times faster. Smoking and hypertension seem to increase the rate of growth. Rupture is associated with 90% mortality but the survival for those who reach hospital and have immediate surgery is ~50–60%. Concomitant coronary disease is responsible for a 50–100% increased mortality of patients with aneurysms even when aneurysm mortality is disregarded.

Treatment

Treatment of abdominal aortic aneurysms involves, in addition to surgery for some, the same preventive treatment as is given to other people with atherosclerotic manifestations: lifestyle changes and medical therapy with platelet inhibitors, statins, and blood pressure control.

Treatment of a ruptured aortic aneurysm is always interventional (open surgical or endovascular) unless the patient's overall condition is considered too poor to attempt rescue. In some cases, a fatal aortic aneurysm may be a dignified death, for example, in an elderly person with both end-stage renal failure and heart failure. Symptomatic non-ruptured aneurysms should be treated acutely or subacutely because of the risk of imminent rupture.

Treatment of large asymptomatic abdominal aortic aneurysm reduces mortality [21], and those with an asymptomatic aneurysm should be offered elective interventional treatment if the risk of rupture exceeds the risk of the procedure and if the patient is fit for the procedure and expected to have some good-quality years remaining. Because any procedure for treatment of aortic aneurysm either carries a considerable perioperative risk or involves a very long postoperative period with potential reinterventions, the decision to offer interventional treatment is not always easy, and almost always a decision is made in consultation with the patient and their family.

The choice between treatment modalities is made keeping these facts in mind: open surgery is a well-proven procedure with known risks and long-term results, including an overall 3–5% perioperative mortality, but limited aneurysm morbidity after the procedure. Endovascular aneurysm repair (EVAR) has been shown to have lower perioperative morbidity: 1.5% for EVAR compared with 4.5% for open surgery [22–24]. Because the long-term results of EVAR are unknown (5–10 years), continuous surveillance with annual CT or ultrasound scans is necessary. Until fairly recently, the number of reinterventions because of either migration or failure of the implanted device, both leading to endo-leak (blood re-entering the excluded aneurysm sac, which is thereby again at risk of rupture) were considerable; however, more recent data show improvement and it is 10–15% at 3 years [24].

As an example of choice of treatment modality, a 65-year-old man with a 6-cm aneurysm and no other known comorbidity should be offered treatment, preferentially open surgery, because his perioperative risk will be low (2–3%), whereas the annual risk of rupture is ~10%. At the other end of the spectrum is the 80-year-old man with previous coronary artery bypass graft surgery and with a similar-sized aneurysm of 6 cm. His risk with open surgery includes >10% 30-day mortality in addition to a considerable risk of other complications. Endovascular treatment could be a good alternative for this man if he is expected to live at least 3–5 years.

EVAR has been considered to be a treatment alternative for patients unfit for open surgery. The EVAR-2 trial tested this hypothesis and participants found to be unfit for open repair were randomized to either conservative management or EVAR. Survival was not improved by EVAR and it was poor in both groups: ~50% of participants in both groups were dead at 3 years and only one-quarter of deaths were aneurysm related [25]. Hence being found unfit for surgery in this study indicated a poor prognosis in general that EVAR did not affect.

Open surgical treatment with resection of the aneurysm and replacement of the diseased part of aorta with an artificial graft has been performed for around 50 years (Figure 47.7). Complications of open surgical repair relate to the considerable surgical trauma of this major procedure. Approximately 10–20% of patients will develop general complications such as cardiac, pulmonary, and renal complications in addition to prolonged stay in the intensive care unit and stroke.

Endovascular treatment of aortic aneurysms involves inserting a collapsed prosthesis via the femoral artery, placing it below the renal arteries, and deploying and fixing it (stenting) under X-ray guidance. The technique mostly used today involves inserting

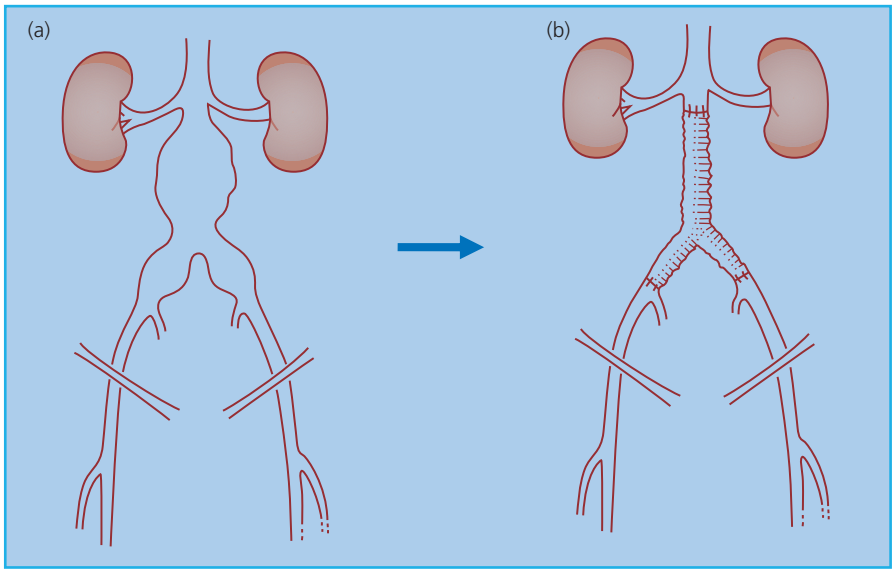

Figure 47.7 Abdominal aortic aneurysm treated by resection and implantation of an aorto-bi-iliac bypass graft.

a bifurcated graft from one femoral artery and then placing the other limb via the contralateral femoral artery (Figure 47.8). There are few complications to EVAR in the perioperative period, but a considerable number of patients will need reinterventions, which in most cases can be performed by endovascular techniques. These include placement of another proximal stent because of endo-leak and embolization of inferior mesenteric or internal iliac arteries.

Screening

The value of population-based screening for abdominal aortic aneurysms is now well documented. A meta-analysis of four randomized controlled trials found aneurysm-related mortality to be reduced by 43% in people being offered screening [26]. Today, it is recommended in many countries that men older than 65 years and previous smokers undergo ultrasound screening. Family members who are direct descendants and siblings of those with aortic aneurysms should also undergo screening.

Peripheral aneurysms

Aneurysms may develop at other locations, popliteal and femoral arteries being the second and third most common locations. More than 50% of patients with peripheral aneurysms also have an aortic aneurysm. Symptoms are different in the sense that rupture is less common; however, symptoms derived from compression (popliteal vein thrombosis, pain, and other symptoms of

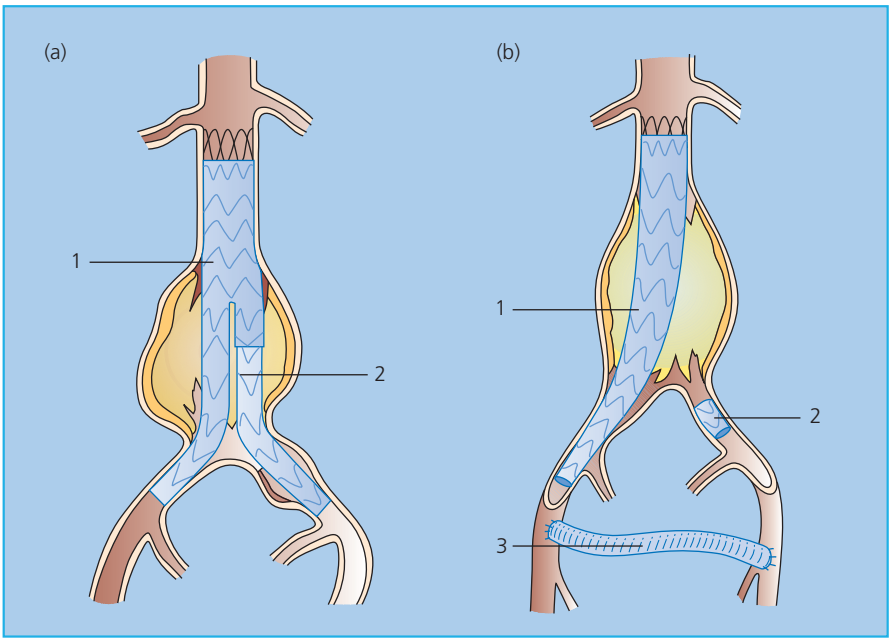

Figure 47.8 Abdominal aortic aneurysm treated by endovascular repair. (a) First the bifurcated graft is inserted via the right femoral artery and fixed by stenting at the proximal and distal end of the graft. The left limb (2) is inserted via the left femoral artery and connected to the main graft. (b) Insertion of an aorto-uni-iliac endograft (1) combined with a femoro-femoral bypass graft (3) is used when one of the iliac arteries (2) cannot be passed.

nerve compression), peripheral embolization, or thrombosis of the aneurysm most often bring the patient to medical attention.

Treatment is the same as for aortic aneurysms: general prevention against atherosclerotic disease and intervention in symptomatic cases. Popliteal aneurysms are generally treated surgically by exclusion and bypass or by resection and replacement by a short graft. Femoral aneurysms are treated by resection and placement of a graft. Endovascular management is possible; however, graft thrombosis and failure of stent graft material have so far made indications unclear. Large asymptomatic peripheral aneurysms should probably be treated by either open or endovascular surgery; however, no documentation is currently available that such treatment is beneficial.

Aneurysms of visceral or renal arteries may occur but are rare. Treatment is interventional when they are large. Endovascular management is under development; however, its indications are unsettled.

Carotid artery disease

This section focuses on stroke and carotid disease because cerebrovascular disease in general is dealt with in Chapter 46. The relationship to atherosclerosis for many people with stroke is well documented, although stroke, unlike other ischemic conditions, has other common pathogenetic mechanisms.

It is very important to discriminate between symptomatic disease and asymptomatic cases. People with recent cerebrovascular symptoms and an ipsilateral stenosis are comparable to those with a recent acute coronary event: the risk for a new thromboembolic event is very high and diagnostic workup and treatment should be started immediately. The pathogenetic mechanism is similar to that of an acute coronary event with plaque rupture and subsequent thrombosis; however, in the case of the carotid, embolization into a cerebral artery is much more common than thrombotic occlusion of the carotid artery itself. Perhaps the larger diameter of the carotid artery explains this difference.

The prevalence of carotid stenosis is high. Among people with acute cerebrovascular symptoms, an ipsilateral stenosis of >50% diameter reduction is found in 15–20% of cases. In people with other clinical atherosclerotic manifestations, a carotid stenosis is found in 20–30%.

Pathophysiology and symptoms

See Chapter 46, dealing with cerebrovascular disease.

Prognosis

The risk of stroke is increased in the presence of carotid stenosis. For asymptomatic people with a carotid stenosis exceeding 60% diameter reduction, the annual risk of ipsilateral stroke is ~1% with optimal medical prevention (antiatherosclerotic treatment). When carotid stenosis is related to recent ipsilateral cerebral ischemic symptoms (symptomatic stenosis), the risk is much higher, especially just after the first event. The 30-day risk of stroke in people with previous cerebrovascular symptoms is as high as 10% when an ipsilateral carotid stenosis is present. Thereafter, the risk gradually declines and after 1 year it is ~2–3% annually, similar to asymptomatic carotid stenosis. The 3-year risk of ipsilateral stroke is 15–30% in symptomatic patients with a stenosis >70% diameter reduction.

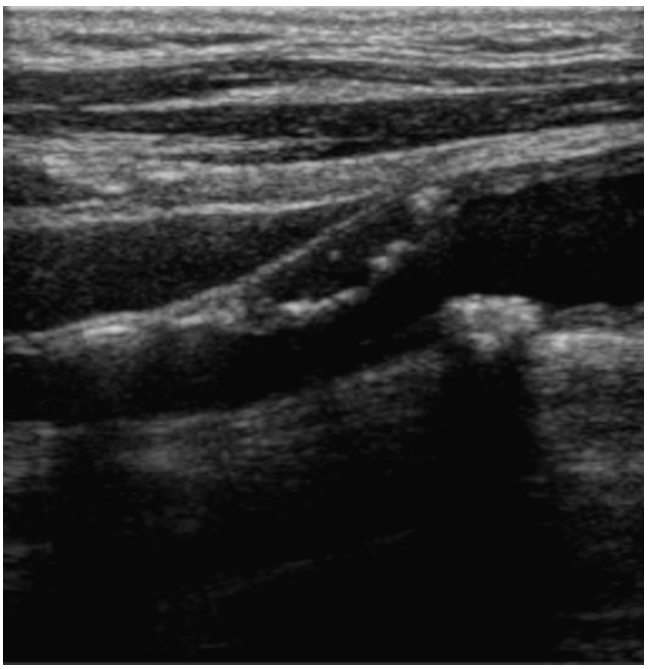

Figure 47.9 B-mode ultrasound image of carotid stenosis. The top part is echolucent, indicating a high content of lipid/necrotic core; the bottom part is echogenic, indicating a fibrous plaque.

Diagnosis

Diagnosis of carotid disease should be carried out by duplex ultrasound scanning (Figure 47.9). The accuracy of the method is well documented both for identification and quantification of degree of stenosis. Many surgeons will perform carotid endarterectomy based only on ultrasound examination.

Treatment

Treatment of people with carotid stenosis is like that of any other condition related to atherosclerosis: treatment of the atherosclerotic disease itself and treatment of local manifestations. Risk factor reduction, including changes in lifestyle, is exactly the same as for patients with other clinical manifestations of atherosclerosis, although there may be regional variation in the choice of antiplatelet agents. Aggressive lipid lowering reduces both the risk of recurrent stroke and the risk of coronary events especially in this patient group [27–29].

It is important to realize that any invasive treatment for carotid stenosis is performed to prevent future "local" events (stroke). Hence the risk of the intervention itself should be weighed against the absolute risk of an event. Furthermore, the most common complication of surgery and stenting is ipsilateral stroke, the event

that the procedure is supposed to prevent. Most important, the overall risk to the patient (including that of other conditions) should be weighed against the absolute risk reduction derived from the procedure.

Symptomatic carotid stenosis

Symptomatic patients with carotid stenosis benefit from endarterectomy when the stenosis is >50–70% diameter reduction and neurological symptoms are within 6 months of surgery [30, 31]. The North American Symptomatic Carotid Endarterectomy Trial (NASCET) and European Carotid Surgery Trialist's Collaborative Group (ECST) trials [30, 31] randomized simultaneously, but independently, symptomatic individuals with carotid stenosis to best medical treatment or best medical treatment plus endarterectomy. Both trials showed significant benefit (50% relative risk reduction) in those with stenosis >70% diameter reduction, whereas in the group with 50–69% stenosis there was only a marginal effect, and in participants with stenoses <50% there was no benefit.

Subsequent reanalysis of the pooled data from these two trials, however, showed that the time interval between onset of neurological symptoms and surgery was the most important predictive factor of benefit for the patient [32]. In general, the earlier an operation is executed, the greater is the benefit. The overall absolute risk reduction of ~15% conveyed by endarterectomy could be doubled when patients received surgery within 2 weeks of symptoms. With the knowledge gained during the last 10–15 years concerning the vulnerable plaque and plaque rupture, this finding does not come as a great surprise; however, when these trials were designed, this pathogenetic mechanism of acute ischemia was unknown.

Sex, age, and degree of stenosis are also factors that influence the benefit of surgery [32]. Male sex, older age, and greater severity of stenosis all increase the risk of future stroke in people with stenosis without any increased risk of the surgical procedure, hence the overall benefit is greater.

Asymptomatic carotid stenosis

Asymptomatic carotid stenosis is more controversial, although two major trials have shown a small but statistically significant benefit of surgery. First, the Asymptomatic Carotid Atherosclerosis Study (ACAS) trial showed a 50% relative risk reduction of ipsilateral stroke, but the absolute risk reduction was marginal, only 1% per year [33]. Later, the Asymptomatic Carotid Surgery Trial (ACST) reproduced these findings [34]. Taking into consideration that the average annual mortality during the trials was 3–4%, in addition to other ischemic events that were unaffected by the procedure, it may be questioned whether the cost–benefit is reasonable both for the patient and for society. The medical treatment offered during these trials was much poorer than that recommended today; hence the outcomes of these trials may not be reflective of the risk in these patients today. If or when better criteria for selection of patients at higher risk become available, selective surgery for high-risk cases of asymptomatic carotid stenosis may yield greater or even much greater benefit.

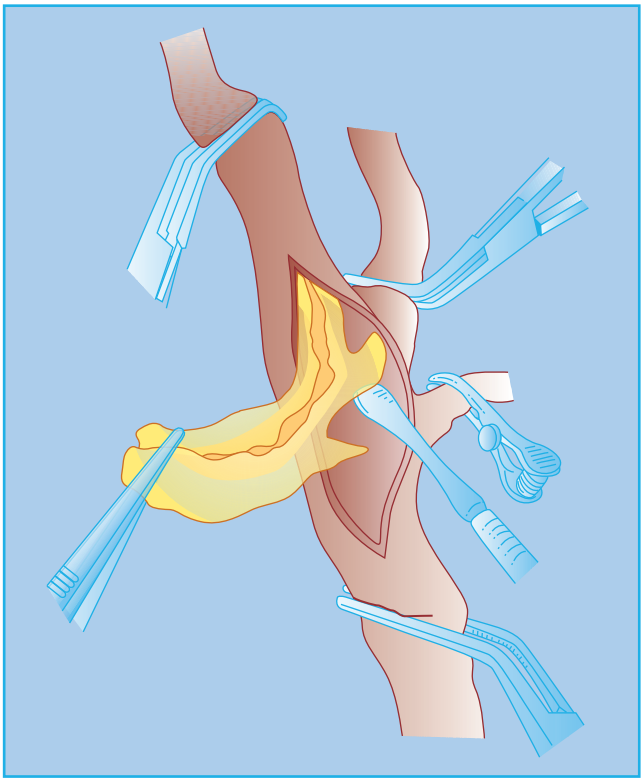

Figure 47.10 Carotid endarterectomy where the intima–media complex is dissected free of the adventitia and removed.

Technical considerations

Technically, carotid endarterectomy may be performed in two ways: classic endarterectomy (Figure 47.10) or eversion endarterectomy. In the latter, the internal carotid artery is divided from the bifurcation, and endarterectomy is performed by everting the vessel wall, thereby removing the carotid lesion. After the stenosis has been removed, the bifurcation is reconstructed by reanastomosing the internal carotid to the bifurcation.

Carotid endarterectomy may be performed under general or local anesthesia. Classically, general anesthesia has been preferred; however, this has carried the challenge of monitoring cerebral circulation during clamping of the carotid artery. A variety of methods have been used, including electroencephalography, stump pressure, distal internal carotid artery pressure, evoked potentials, near-infrared spectroscopy, transcranial Doppler ultrasound, and more. None of these methods has proven ideal, and so some surgeons use a shunt on a selective basis, whenever their method for monitoring indicates risk of cerebral ischemia during clamping, whereas others use a shunt routinely. By contrast, performing endarterectomy under local anesthesia gives the surgeon the opportunity to communicate with the patient during clamping. Having the patient awake and responsive during surgery may represent the best monitoring of cerebral function during clamping. Also, local anesthesia may carry less cardiac and pulmonary risk. Smaller trials and a meta-analysis indicated superiority of local anesthesia [35]; however, the later General Anesthesia versus

Local Anesthesia for carotid surgery (GALA) trial reported its results after randomizing 3529 participants to either universal or local anesthesia for carotid endarterectomy, and there was no difference in the risk of perioperative stroke or death [36].

Carotid stenting

This has not yet been proven in randomized clinical trials to prevent ipsilateral ischemic events. Seven randomized controlled trials comparing stenting with endarterectomy have been published; however, so far they have focused only on comparison of perioperative complications. The two most recent trials, the EVA-3S and the SPACE trials, failed to show an advantage of the less invasive carotid stenting method with respect to perioperative events [37, 38]. In fact, the EVA-3S trial was stopped early because of excess complications in the stenting group [37]. A Cochrane meta-analysis, including all seven randomized controlled trials, favored surgery with respect to the primary outcome of perioperative death and ipsilateral stroke [39]. Most recently, the CREST trial showed equivalence of stenting and endarterectomy, but in a trial with a combined endpoint of death, stroke, and MI. The latter included MI as detected by the increase in enzymes in patients without any other symptoms. So focusing on the risk of death and stroke, stenting was associated with more complications [40]. Nevertheless, it is important to acknowledge that technology does develop rapidly and some of the trials may have used devices and/or technologies that are already outdated. Similarly, there may be differences in trial design, and criticism has been made specifically regarding the training of the investigators in some studies. Interestingly, stenting appears to be associated with higher complication rates when performed early after onset of neurological symptoms and in the elderly—the two strongest indications. Finally, one should keep in mind that stenting should be evaluated in long-term studies, and compared not only with endarterectomy, but also with medical therapy, which has improved dramatically the last 10–20 years.

It may be questioned whether the evidence for carotid endarterectomy is outdated. Three of the four major trials proving endarterectomy to be of value for symptomatic and asymptomatic surgery were performed when the only fairly constant preventive medication given was aspirin. The last trial randomized 8–10 years ago, and only 30% of the participants were taking statins. It was stated in the design of these trials that hypertension and hypercholesterolemia were treated when present; however, in that era, the treatment goals for both hypertension and hypercholesterolemia were much more lax than they are now. Also, new drugs have been introduced and their benefit documented since these trials randomized patients (e.g. statins, newer antiplatelet agents, dual antiplatelet therapy, and newer antihypertensive drugs). It may be speculated that if these drugs were used systematically, the risk in people with carotid stenosis would be much less, not least in those with vulnerable plaques. Therefore, new trials are needed to test how today's medical therapy compares with intervention and if the best medical therapy remains inferior to surgery or stenting. New trials are *not* unethical—it is unethical not to undertake new trials.

Carotid revascularization prior to coronary artery bypass surgery has been practiced in some institutions whereas others have not found it useful. The potential advantage is avoiding cerebral ischemia during the relative hypotension "on pump"; however, the complications of carotid revascularization have outweighed the gains, as evaluated by recent reviews.

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9 Other Complications of Diabetes

48 Foot Problems in People with Diabetes

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Key points

- Diabetic foot problems remain the most common cause of hospital admissions amongst persons with diabetes in Western countries.
- Up to 50% of older individuals with type 2 diabetes have risk factors for foot problems.
- Up to 85% of lower limb amputations are preceded by foot ulcers.
- All persons with diabetes should be screened for risk of foot problems on an annual basis: those with risk factors require regular podiatry, patient education, and instruction in foot self-care.
- Most foot ulcers should heal if pressure is removed from the ulcer site, the arterial circulation is sufficient, and infection is managed and treated aggressively.
- Any individual with a warm unilateral swollen foot without ulceration should be presumed to have an acute Charcot neuroarthropathy until proven otherwise.

Introduction

"Superior doctors prevent the disease. Mediocre doctors treat the disease before evident. Inferior doctors treat the full-blown disease."

[Huang Dee, China, 2600 BC]

This Chinese proverb suggests that inferior doctors treat the full-blown disease and, until recent years, this was sadly the case with diabetic foot disease. Realizing the global importance of diabetic foot disease, the International Diabetes Federation (IDF) focused on the diabetic foot throughout the year 2005, during which there was a worldwide campaign to "put feet first" and highlight the all too common problem of amputation among people with diabetes throughout the world. To coincide with World Diabetes Day in 2005, *The Lancet* launched an issue dedicated almost exclusively to the diabetic foot—this was the first time that any major non-specialist journal had focused on this worldwide problem; however, major challenges remain in getting across important messages relating to the diabetic foot:

1 Foot ulceration is common, affecting up to 25% of people with diabetes during their lifetime [1].

2 Over 85% of lower limb amputations are preceded by foot ulcers, and diabetes remains the most common cause of non-traumatic amputation in Western countries [2].

3 Prevention is the first step towards solving diabetic foot problems. Although it was estimated in 2005 that a leg is lost to diabetes somewhere in the world every 30 s and more recently every 20 s, a more important fact is that up to 85% of all amputations in diabetes should be preventable [2, 3].

4 Reductions in amputations will only be achieved if healthcare professionals from all specialties realize that, as Brand once stated, "pain is God's greatest gift to mankind": it is the loss of pain that permits people with neuropathy to develop ulcers and continue walking on them despite the presence of often overwhelming infection [4]. Moreover, the International Working Group on the Diabetic Foot (IWGDF) has now developed a risk score aimed at assessing the risk of a person with an infected foot ulcer subsequently requiring an amputation [3].

5 Strategies aimed at preventing foot ulcers are cost-effective and can even be cost-saving if increased education and effort are focused on those with recognized risk factors for the development of foot problems [5].

6 Diabetes is now the most common cause of Charcot neuroarthropathy in high-income countries, another condition that should generally be preventable [6].

Much progress in our understanding of the pathogenesis and management of the diabetic foot has been made over the last few decades. This has been matched by an increasing number

Textbook of Diabetes, Fifth Edition. Edited by R. Holt, C. Cockram, A. Flyvbjerg and B. Goldstein.

Table 48.1 Epidemiology of foot ulceration and amputation.

Study	Country	Year	N	Prevalence (%)		Incidence (%)		Risk factors for foot ulcers (%)
				Ulcers	Amputation			
Samann et al. [11]	Germany	2008	4778	0.8[†]	1.6	–	–	>40
Al-Mahroos & Al-Roomi [12]	Bahrain	2007	1477	5.9	–	–	–	45
Abbott et al. [13]	UK	2002	9710	1.7	1.3	2.2	–	>50
Manes et al. [14]	Greece	2002	821	4.8	–	–	–	>50
Müller et al. [15]	Netherlands	2002	665	–	–	2.1	0.6	–
Ramsay et al. [16]	USA	1999	8965			5.8[a]	0.9[a]	–
Vozar et al. [17]	Slovakia	1997	1205	2.5	0.9	0.6	0.6	–
Kumar et al. [18]	UK	1994	821	1.4[b]	–	–	–	42
Moss et al. [19]	USA	1992	2900	–	–	10.1[c]	2.1[c]	–

[a]Incidence figures over 3 years.
[b]Active ulcers: 5.4% past or current ulcer.
[c]Incidence figures over 4 years.

of publications in peer-reviewed journals. Taken as a percentage of all PubMed-listed articles on diabetes, those on the diabetic foot increased from 0.7% in the period 1980–1988 to more than 2.7% in 1998–2004 [4]. Prior to 1980, little progress had been made in the previous 100 years despite the fact that the association between gangrene and diabetes was recognized in the mid-19th century [7]. For the first 100 years following these descriptions, diabetic foot problems were considered to be predominantly vascular and complicated by infection. It was not until during the Second World War, for example, that McKeown performed the first ray excision on a person with diabetes and osteomyelitis but good blood supply; this was performed under the encouragement of Lawrence, who had diabetes himself and was co-founder of the British Diabetic Association, now Diabetes UK [8].

In the last three decades, many major national and international societies were formed, including diabetic foot study groups and the IWGDF was established in 1991. New editions of two leading international textbooks on the diabetic foot have been published in the last decade [9, 10], and a number of collaborative research groups are now tackling many of the outstanding problems regarding the pathogenesis and management of diabetic foot disease.

In this chapter, the global term "diabetic foot" will be used to refer to a variety of pathological conditions that might affect the feet of people with diabetes. First, the epidemiology and economic impact of diabetic foot disease are discussed, followed by the contributory factors that result in diabetic foot ulceration. The potential for prevention of these late sequelae of neuropathy and vascular disease are discussed, followed by a section on the management of foot ulcers. The chapter closes with a brief description of the pathogenesis and management of Charcot neuroarthropathy, an end-stage complication of diabetic neuropathy. Throughout, cross-referencing will be provided to other chapters that also cover aspects of diabetic foot disease, particularly those on diabetic neuropathy (see Chapter 40), peripheral vascular disease (see Chapter 47), bone and rheumatic disorders in diabetes (see Chapter 53), and infection (see Chapter 55).

Epidemiology and economic aspects of diabetic foot disease

As foot ulceration and amputation are closely inter-related in diabetes [2], they will be considered together in this section. A selection of epidemiological data for foot ulceration and amputation, originating from studies from a number of different countries [11–19], is provided in Table 48.1. Globally, diabetic foot complications remain major medical, social, and economic problems that are seen in all types of diabetes and in every country [20]; however, the reported frequencies of amputation and ulceration vary considerably as a consequence of different diagnostic criteria used and also regional differences [21]. Diabetes remains a major cause of non-traumatic amputation across the world, with rates being as much as 15 times higher than in people without diabetes.

Although many of the studies referred to and listed in Table 48.1 were well conducted, methodological issues remain, which make it difficult to perform direct comparisons between studies and/or countries. First, definitions as to what constitutes a foot ulcer vary, and second, surveys invariably include only people with previously diagnosed diabetes, whereas in type 2 diabetes, foot problems may be the presenting feature. In one study in the UK, for example, 15% of people undergoing amputation were first diagnosed with diabetes on that hospital admission [22]. Third, reported foot ulcers are not always confirmed by direct examination by the investigators involved in the study. Finally, as can be seen from the table, in those studies that assessed the percentage of the population that had risk factors for foot ulceration, 40–70% of people fell into that category. Such observations clearly indicate the need for all diabetes services to have a regular screening program to identify such high-risk individuals.

Health economics of diabetic foot disease

In addition to causing substantial morbidity and even mortality, foot lesions in individuals with diabetes additionally have substantial economic consequences.

Diabetic foot ulceration and amputations were estimated to cost United States healthcare payers $10.9 billion in 2001 [23, 24]. Corresponding estimates from England based upon national datasets and economic modeling suggested that the total annual costs of diabetes-related foot complications in 2010–2011 was £580 million, or 0.6% of the National Health Service expenditure [25]; however, similar problems to those noted with epidemiology exist when comparing data on the costs of diabetic foot lesions, related not only to methodology but also to whether direct and indirect costs were included. Moreover, few studies have estimated costs of the long-term follow-up of people with foot ulcers or amputations [2].

Data from the USA suggest that in 2007 $18.9 billion was spent on the care of diabetic foot ulcers and $11.7 billion on lower extremity amputations [26]. Having estimated the total cost of diabetic foot disease to be $30.6 billion in 2007, the authors went on to estimate the potential savings based upon realistic reductions in ulceration and amputation to be as high as $21.8 billion. Such strong economic arguments may help to drive improvements in preventive foot care that could potentially lead to significant savings for healthcare systems. A recent and worrying study from Arizona, USA, demonstrates the false economics of attempting to reduce costs in diabetic foot screening. In their attempt to reduce costs, the legislature removed payment to podiatrists for screening and treating Medicaid patients: although this resulted in an annual saving of $351,000, the increased hospitalizations in this population for diabetic foot disease cost $16.7 million per year [27]!

Etiopathogenesis of diabetic foot lesions

"Coming events cast their shadow before."

[Thomas Campbell]

If we are to be successful in reducing the high incidence of foot ulcers and ultimately amputation, a thorough understanding of the pathways that result in the development of an ulcer is increasingly important. The above words of the Scottish poet Thomas Campbell can usefully be applied to the breakdown of the diabetic foot. Ulceration does not occur spontaneously: rather, it is the combination of causative factors that result in the development of a lesion. There are many warning signs or "shadows" that can identify those at risk before the occurrence of an ulcer. It is not an inevitable consequence of having diabetes that ulcers occur: ulcers invariably result from an interaction between specific pathologies in the lower limb and environmental hazards. The breakdown of the diabetic foot traditionally has been considered to result from an interaction of peripheral vascular disease, peripheral neuropathy, and some form of trauma. Other causes are also briefly described.

Peripheral vascular disease

Although described in detail in Chapter 47, brief mention of the role of peripheral vascular disease in the genesis of foot ulcers must be made here. Peripheral vascular disease tends to occur at a younger age in people with diabetes and is more likely to involve distal vessels. Reports confirm that peripheral vascular disease is a major contributory factor in the pathogenesis of foot ulceration and subsequent major amputations [28, 29]. In the pathogenesis of ulceration, peripheral vascular disease itself in isolation rarely causes ulceration: as will be discussed for neuropathy, it is the combination of risk factors with minor trauma that inevitably leads to ulceration (Figure 48.1). Thus, minor injury and subsequent infection increase the demand for blood supply beyond the circulatory capacity and ischemic ulceration and the risk of amputation ensue. In recent years, neuroischemic ulcers in which the combination of neuropathy and PVD exists in the same person, together with some form of trauma, are becoming increasingly common in diabetic foot clinics.

Diabetic neuropathy

As discussed in Chapter 40, the diabetic neuropathies represent the most common form of the long-term complications of diabetes, affect different parts of the nervous system and may present with diverse clinical manifestations [30]. Most common amongst the neuropathies are chronic sensorimotor distal symmetrical polyneuropathy and the autonomic neuropathies. It is the common sensorimotor neuropathy together with peripheral autonomic sympathetic neuropathy that together have an important role in the pathogenesis of ulceration.

Sensorimotor neuropathy

As noted in Chapter 40, this type of neuropathy is very common and it has been estimated that up to 50% of older persons with type 2 diabetes have evidence of sensory loss on clinical examination and therefore must be considered at risk of insensitive foot injury [30]. This type of neuropathy commonly results in a sensory loss, confirmed on examination by a deficit in the stocking distribution to all sensory modalities; evidence of motor dysfunction in the form of small muscle wasting is also often present. While some individuals may give a history (past or present) of typical neuropathic symptoms such as burning pain, stabbing pain, and paresthesia with nocturnal exacerbation, others may develop sensory loss with no history of any symptoms. Other individuals may have the "painful-painless" leg with spontaneous discomfort secondary to neuropathic symptoms but who on examination have both small- and large-fiber sensory deficits; such people are at great risk of painless injury to their feet.

From the above, it should be clear that a spectrum of symptomatic severity may be present, with some individuals experiencing severe pain and, at the other end of the spectrum, those who have no spontaneous symptoms, but both groups may have significant sensory loss. The most challenging individuals are those who develop sensory loss with no symptoms because it is often difficult to convince them that they are at risk of foot ulceration as they feel

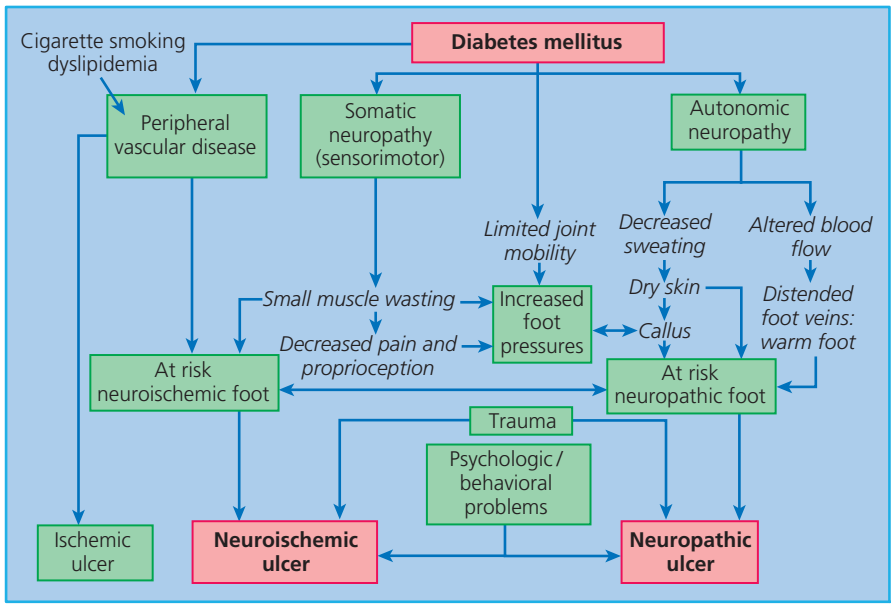

Figure 48.1 Pathways to foot ulceration in diabetes. Source: Boulton et al. 2006 [9]. Reproduced with permission of John Wiley & Sons.

no discomfort, and motivation to perform regular foot self-care is difficult. The important message is that neuropathic symptoms correlate poorly with sensory loss, and their absence must *never* be equated with lack of foot ulcer risk. Thus, assessment of foot ulcer risk must *always* include a careful foot examination after removal of shoes and socks, whatever the neuropathic history [30].

The person with sensory loss

A reduction in neuropathic foot problems will only be achieved if we remember that those with insensitive feet have lost their warning signal—pain—that ordinarily brings patients to their doctors. Hence the care of a someone with sensory loss is a new challenge for which we have no training. It is difficult for us to understand, for example, that an intelligent person would buy and wear a pair of shoes three sizes too small and come to the clinic with extensive shoe-induced ulceration. The explanation is simple: with reduced sensation, a very tight fit stimulates the remaining pressure nerve endings and is thus interpreted as a normal fit—hence the common complaint when we provide patients with custom-designed shoes that "these shoes are too loose." We can learn much about the management of such patients from the treatment of people with leprosy [31]. Although the cause of sensory loss is very different from that in diabetes, the end result is the same, hence work in leprosy has been very relevant to our understanding of the pathogenesis of diabetic foot lesions. It was Brand (1914–2003), who worked as a surgeon and a missionary in South India, who described pain as "God's greatest gift to mankind" [32]. He emphasized the power of clinical observation to his students and one remark of his that was very relevant to diabetic foot ulceration was that any person with a plantar ulcer who walks into the clinic without a limp must have neuropathy. Brand also taught us that if we are to succeed, we must realize that with loss of pain there is also diminished motivation in the healing of, and prevention of, injury.

Peripheral sympathetic autonomic neuropathy

Sympathetic autonomic dysfunction of the lower limbs leads to reduced sweating and results in both dry skin that is prone to crack and fissure and to increased blood flow (in the absence of large-vessel obstructive peripheral vascular disease) with arteriovenous shunting leading to the warm foot. The complex interactions of the neuropathies and other contributory factors in the causation of foot ulcers are summarized in Figure 48.1.

Other risk factors

Of all the other risk factors for ulceration (Table 48.2), one of the most important is a past history of similar problems. In many series this has been associated with an annual risk of reulceration of up to 50%.

Table 48.2 Factors increasing risk of diabetic foot ulceration. More common contributory factors are shown in bold.

Peripheral neuropathy
• **Somatic**
• **Autonomic**
Peripheral vascular disease
Past history of foot ulcers
Other long-term complication
• **End-stage renal disease**
• Visual loss
Plantar callus
Foot deformity
Edema
Ethnic background
Poor social background

Other long-term complications

Persons with other late complications, particularly nephropathy, have been reported to have an increased foot ulcer risk. Those most at risk are people with end-stage renal disease who are on dialysis [33, 34]. It must also be remembered that those with renal transplants and more recently combined pancreas–renal transplants are usually at high risk of ulceration even if normoglycemic as a result of the pancreas transplant.

Plantar callus

Callus forms under weight-bearing areas as a consequence of dry skin (autonomic dysfunction), insensitivity, and repetitive moderate stress from high foot pressure. It acts as a foreign body and causes ulceration [35]. The presence of callus in an insensate foot should alert the physician that this individual is at high risk of ulceration, and callus should be removed by the podiatrist or other trained healthcare professional.

Elevated foot pressures

Numerous studies have confirmed the contributory role that abnormal plantar pressures play in the pathogenesis of foot ulcers [4, 36].

Foot deformity

A combination of motor neuropathy, cheiroarthropathy, and altered gait patterns is thought to result in the "high-risk" neuropathic foot with clawing of the toes, prominent metatarsal heads, high arch, and small-muscle wasting (Figure 48.2).

Ethnicity and sex

Men have a 1.6-fold increase in ulcers [13]. With respect to ethnic origin, data from cross-sectional studies in Europe suggest that foot ulceration is more common in white Europeans than other racial groups; for example, the North-West Diabetes Foot Care Study in the United Kingdom showed that the age-adjusted prevalence of diabetic foot ulcers (past or present) for Europeans, South Asians, and African Caribbeans was 5.5, 1.8, and 2.7, respectively [37]. Reasons for these ethnic differences certainly warrant further investigation. In contrast, in the southern USA, ulceration was much more common in Latino Americans and Native Americans than in white people of Northern European ancestry [38]; however, more recent data confirmed this increased risk in Latinos, despite the foot pressures being actually lower in this group [39].

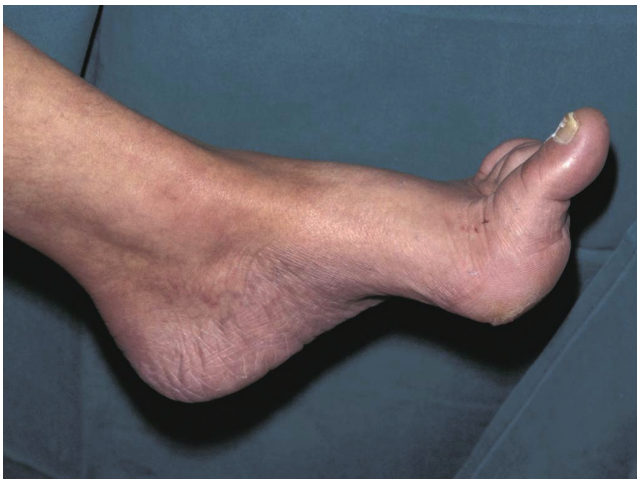

Figure 48.2 The high-risk neuropathic diabetic foot demonstrating high arch, prominent metatarsal heads, clawing of toes, and callus under first metatarsal head.

Pathway to ulceration

It is the combination of two or more risk factors that ultimately results in diabetic foot ulceration (Figure 48.1). Reiber et al. [40] took the Rothman model for causation and applied it to amputation and foot ulceration in diabetes. This model is based on the concept that a component cause (e.g. neuropathy) is not sufficient in itself to lead to ulceration, but when the component causes act together, they result in a sufficient cause that will inevitably result in ulceration. Applying this model to foot ulceration, a small number of causal pathways were identified; the most common triad of component causes, present in nearly two out of three incident foot ulcer cases, was neuropathy, deformity, and trauma. Edema and ischemia were also common component causes. Other simple examples of two-component causeways to ulceration are loss of sensation and mechanical trauma such as standing on a nail, wearing shoes that are too small; or neuropathy and thermal trauma (e.g. walking on hot surfaces or burning the feet in the bath); finally, neuropathy and chemical trauma may result in ulceration from the inappropriate use of, for example, chemical "corn cures." Similarly, this model can be applied to neuroischemic ulcers where the three-component causes comprising ischemia, trauma, and neuropathy are often seen [41].

Prevention of diabetic foot ulcers

Screening

It has been estimated that most foot ulcers are potentially preventable, and the first step in prevention is the identification of the "at-risk" population. Many countries have now adopted the principle of the "annual review" for persons with diabetes, whereby every person is screened at least annually for evidence of diabetic complications. Such a review can be carried out either in the primary care center or in a hospital clinic.

A taskforce of the American Diabetes Association addressed the question of what should be included for the annual review in the "comprehensive diabetic foot examination (CDFE)" [42]. The taskforce addressed and concisely summarized the recent literature in this area and recommended, where possible using evidence-based medicine, what should be included in the CDFE for adults with diabetes. Whereas a brief history was regarded as important, a careful examination of the foot, including assessing its neurological and vascular status, was regarded as essential. There is a strong evidence base to support the use of simple

Table 48.3 Key components of the diabetic foot examination.

Inspection
Evidence of past/present ulcers?
Foot shape?

- Prominent metatarsal heads/claw toes
- Hallux valgus
- Muscle wasting
- Charcot deformity

Dermatological?

- Callus
- Erythema
- Sweating

Neurological
10-g monofilament at four sites on each foot plus one of the following:

- Vibration using 128-Hz tuning fork
- Pinprick sensation
- Ankle reflexes
- Vibration perception threshold

Vascular
Foot pulses
Ankle brachial index, if indicated

clinical tests as predictors of risk of foot ulcers [13, 42]. A summary of the key components of the CDFE is provided in Table 48.3. Whereas each potential simple neurological clinical test has advantages and disadvantages, it was felt that the 10-g monofilament had much evidence to support its use, hence the recommendation that assessment of neuropathy should comprise the use of a 10-g monofilament plus one other test. In addition to the simple tests listed in Table 48.3, a possible test for neuropathy was assessment of the vibration perception threshold. Although this is a semiquantitative test of sensation, it was included as many centers in both Europe and North America have such equipment. As can be seen from Table 48.3, this is not regarded as essential, but strong evidence does support the use of vibration perception threshold as an excellent predictor of foot ulceration [43, 44]. More recently, a "3-minute foot examination" has been proposed, mainly for use in primary care; this comprises 1 min each for history, physical examination, and what to teach [45].

With respect to the vasculature, the ankle brachial index was recommended, although it was realized that many centers in primary care may not be able to perform this in day-to-day clinical practice.

Intervention for high-risk individuals

Any abnormality found in the above screening test would put the person into a group at higher risk of foot ulceration. Potential interventions are discussed under a number of headings, the most important of which is education.

Education

Previous studies have suggested that persons with foot ulcer risk lack knowledge and skills and consequently are unable to provide appropriate foot self-care [46]. People need to be informed of the risk of having insensate feet and the need for regular self-inspection, foot hygiene, and chiropody/podiatry treatment as required, and they must be told what action to take in the event of an injury or the discovery of a foot ulcer. Studies summarized by Vileikyte et al. [47, 48] suggest that people with diabetes often have distorted beliefs about neuropathy, thinking that this is a circulatory problem and link neuropathy directly to amputation. Thus, an education program that focuses on reducing foot ulcers will be doomed to failure if patients do not believe that foot ulcers precede amputations. It is clear that much work is required in this area if appropriate education is to succeed in reducing foot ulcers and subsequently amputations. The potential for education and self-care at various points on the pathway to neuropathic ulceration is shown in Figure 48.3.

There have been a small number of reports that assessed educational interventions, but they were mostly small, single-center studies. In the most recently published study, even though the foot care education program was followed by improved foot care behavior, there was no evidence that such targeted education was associated with a reduced incidence of recurrent foot ulcers [49]. It has been suggested that people with diabetes find the concept of neuropathy difficult to understand: they are reassured because they have no discomfort or pain in their feet. It may be that using visual aids (which can also be used for the diagnosis of the at risk foot) may help people with diabetes to understand that there is something different about their feet compared with their partner's, for example. This might include the use of the administered indicator plaster (Neuropad): when applied to the foot this changes color from blue to pink if there is normal sweating [50]. The absence of sweating, such as in a high-risk foot, results in no color change, enabling patients to see that there is something different about their feet. A similar visual aid is the PressureStat (Podotrack) (Figure 48.4) [51]. This is a simple, inexpensive semiquantitative footprint mat that is able to identify high plantar pressures. The higher the pressure, the darker is the color of the footprint. Similarly, this can be used as an educational aid and might help the person with diabetes realize that specific areas under their feet are at particular risk of ulceration.

In summary, foot care education is believed to be crucial in the prevention of ulceration, although there is little support for this from randomized controlled trials. Further studies in this area are therefore urgently required.

Podiatry/chiropody

Although not available in every country, regular nail and skin care from a podiatrist/chiropodist is essential in the high-risk neuropathic foot. Attempted self-care has been reported in several cases to cause ulceration, and similarly self-care of calluses should be discouraged. Chiropodists and podiatrists should be attached to

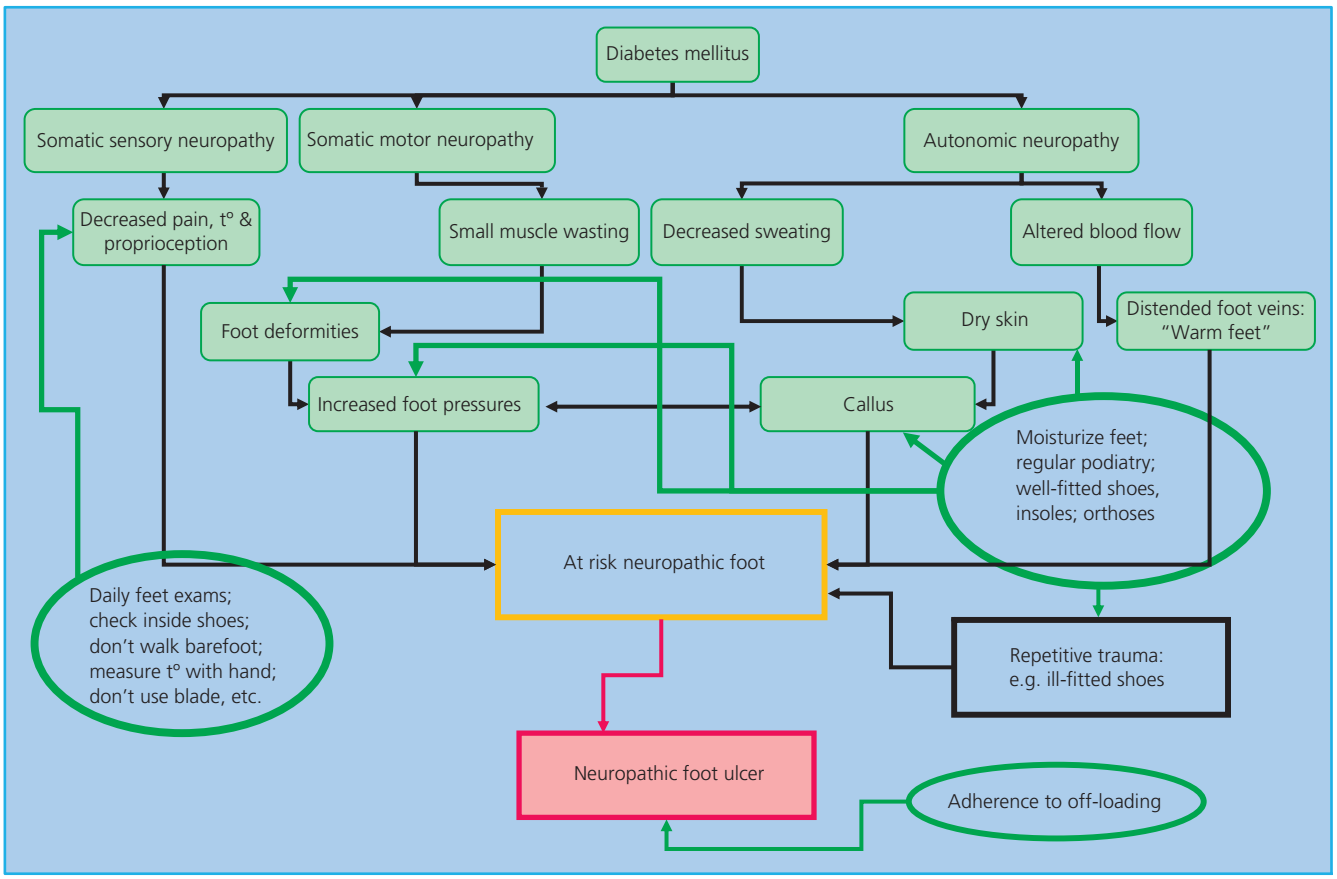

Figure 48.3 The potential for education and self-care in prevention of neuropathic foot ulcers. t°, temperature. Source: Courtesy of L. Vileikyte MD, PhD.

the foot care team if available and can also educate the person with diabetes while treating the feet.

Footwear/othoses/hosiery

Inappropriate footwear is a common cause of foot ulceration in insensitive feet, whereas good footwear can reduce ulcer occurrence [46]. This statement is supported by randomized controlled trials [52]. There is evidence from the literature also to support the use of specialist hosiery that might reduce foot pressures and give all-round protection to high-risk neuropathic feet [53, 54].

Self-monitoring of skin temperature

It has been known for some time that prior to skin breakdown and ulceration, the involved area of the foot tends to warm up as a consequence of local inflammation. In an appropriately designed, randomized controlled trial, Lavery et al. [55] randomized people with a history of neuropathic foot ulceration to one of three groups, the main intervention being self-monitoring of skin temperature of both feet; those who received this skin temperature thermometer were advised to rest or contact their foot clinic should there be a maintained difference in temperature between the two feet. This study clearly showed that those who monitored their skin temperatures and followed the advice had a markedly reduced incidence of recurrent ulceration (8% vs. 30%). Hence infrared temperature home monitoring might help to identify the "preulcerative" foot and permit intervention prior to actual skin breakdown. Another study provided further support for this notion [56].

Injected liquid silicone

Injected liquid silicone under high-pressure areas of the diabetic foot has been used for some years in the USA and is supported by a randomized controlled trial [57] that confirmed that people receiving active agent had reduced foot pressures and increased subcutaneous tissue under the high-pressure areas of the forefoot. This therapy is now available in certain European countries, and a follow-up study [58] confirmed that the effect of this "injectable orthosis" lasts for up to 2 years, although booster injections may be required from time to time.

Foot ulcers: diagnosis and management

Foot ulcer classification

Despite increasing efforts in the early identification and preventive foot care education of high-risk patients, foot ulcers continue to be a major issue in diabetes management and may indeed be

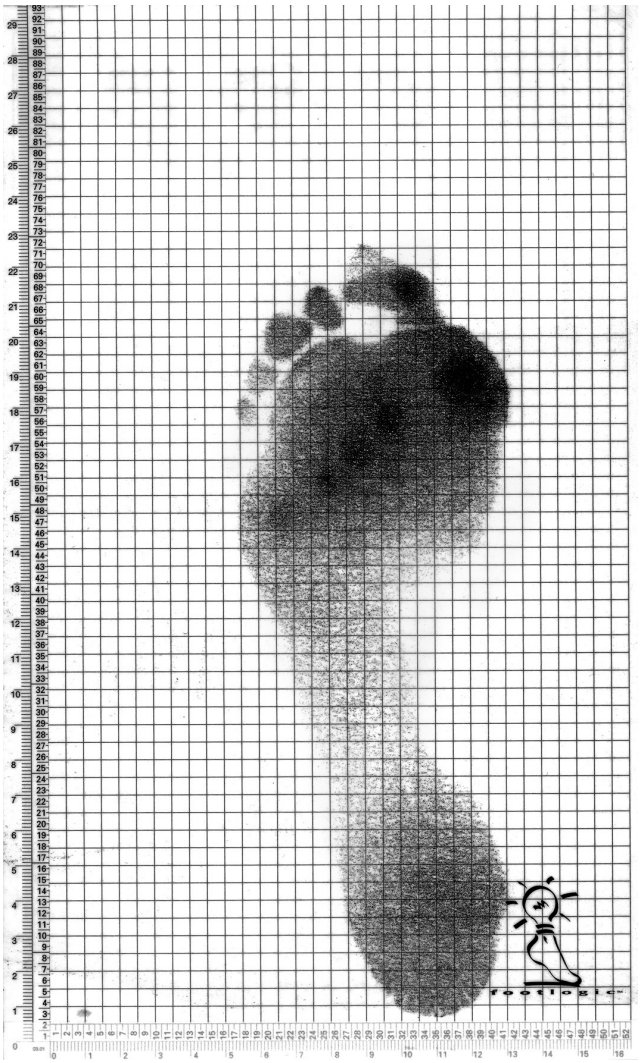

Figure 48.4 A black-and-white pressure distribution of one footstep using PressureStat: the darkest areas represent highest pressures, in this case under metatarsal heads 1 and 3 and the hallux.

the presenting feature of type 2 diabetes. The principles of management depend on a careful assessment of the causative factors, the presence or absence of infection, the degree of neuropathy, and/or ischemia in the foot. Before discussing the management of specific types of ulcers, it is important to consider how to classify foot lesions. Numerous classification systems for diabetic foot ulcers have been proposed [59] but only a few are described here.

Table 48.4 Meggitt–Wagner classification.

Grade	Description
0	No ulcer, but high-risk foot (deformity, callus, etc.)
1	Superficial ulcer
2	Deep ulcer, may involve tendons but not bone
3	Deep ulcer with bone involvement, osteomyelitis
4	Localized gangrene (e.g. toes)
5	Gangrene of whole foot

Source: Modified from Oyibo et al. 2001 [61].

The most widely used foot ulcer classification system worldwide at the time of writing is the Meggitt–Wagner grading, as shown in Table 48.4. Despite its wide use, this system lacks specificity and it does not refer to the neuropathic, ischemic or infective status of the ulcers.

The newer University of Texas (UT) wound classification system is currently widely used (Table 48.5) [60]. This is based on the Meggitt–Wagner system but with the addition of grades of ulcers and stages, each grade for the presence or absence of infection and ischemia. In a comparative study of these two systems, the UT system was shown to be a useful predictor of outcome, although the Meggitt–Wagner system was still confirmed to be useful [61]. A high-risk foot with preulcerative lesions (Wagner grade I, UT 1A) is shown in Figure 48.5. The two more recently described classification systems, S(AD) SAD system [size (area, depth), sepsis, arteriopathy, and denervation] and the PEDIS (perfusion, extent, depth, infection, sensation) systems appear to have some advantages over the earlier systems, but are not in widespread use [59]. Hence the UT system will be used to describe ulcer classification here. The most recently described WiFi system (Would ischemia, Foot infection) appears to have some advantages over the previously described systems, and has been shown to correlate with major amputation risk and time to wound healing [62].

Wound healing in the diabetic foot

Wound healing is a tissue response to injury and passes through the phases of inflammation, chemotaxis, cellular proliferation, extracellular matrix deposition, and finally wound remodeling and scarring. Diabetes may influence foot wound healing in a

Table 48.5 University of Texas ulcer classification system.

	Grade			
Stage	**0**	**1**	**2**	**3**
A	High-risk foot: no ulcer	Superficial ulcer	Deep ulcer to tendon/capsule	Wound penetrating bone/joint
B	+ Infection	+ Infection	+ Infection	+ Infection
C	+ Ischemia	+ Ischemia	+ Ischemia	+ Ischemia
D	+ Infection and ischemia	+ Infection and ischemia	+ Infection and ischemia	+ Infection and ischemia

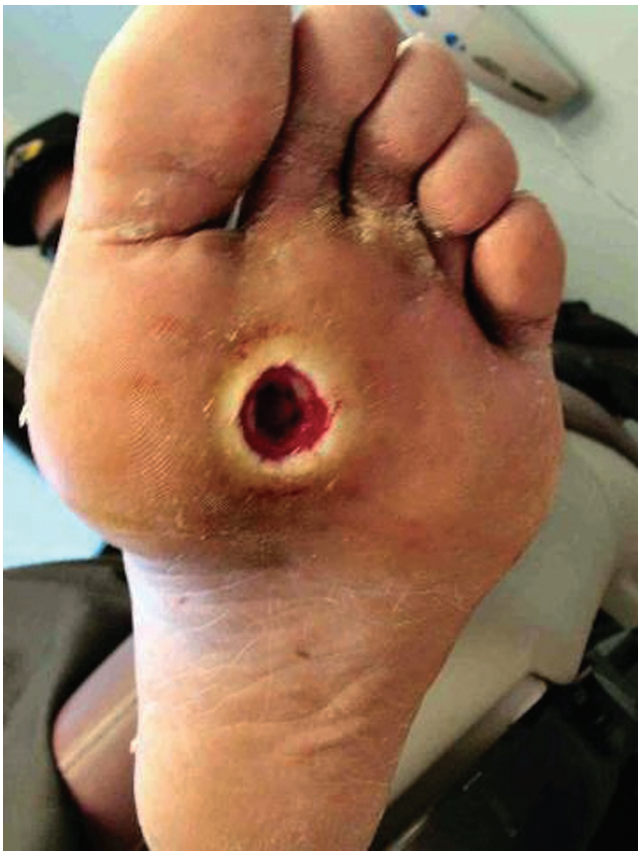

Figure 48.5 Wagner grade I ulcer, UT 1A foot ulcer, showing a rim of callus and a punched-out neuropathic ulcer in the metatarsal head region with no evidence of infection.

number of different ways, including an impairment of the peripheral circulation, altered leukocyte function, disturbed balance of cytokines and proteases, and even chronic hyperglycemia itself [4, 63]. Thus, foot ulcers in people with diabetes are recalcitrant to healing because of many cellular and molecular aberrations. Compared with normal acute wound healing, chronic foot ulcers are often stalled in the chronic inflammatory phase with impaired granulation tissue formation. Key questions are therefore, is there a fundamental impairment of wound healing in diabetes and, if so, what are the molecular/cellular impairments, and are they specific to chronic wounds? A number of studies have reported abnormalities in cytokines and growth factors in tissue from chronic diabetic foot ulcers [64–66]. Most recently, it has been suggested that levels of matrix metalloproteinases (MMPs) are important in predicting the likelihood of wound healing, and a high level of MMP-1 seems essential to wound healing [66].

Another contributory factor to impaired wound healing in diabetes appears to be repetitive pressure on the wound. The pivotal role of offloading is therefore considered in the next section.

Offloading

A normal individual with a foot wound will limp: it has been known for some time that neuropathic plantar foot wounds will heal satisfactorily when offloaded in a total contact cast (TCC) [4]. The principle of TCC management is that pressure is mitigated but, in addition, the device is irremovable, thus enforcing adherence with therapy. A number of randomized controlled trials have compared the TCC with other removable offloading devices in plantar diabetic foot ulcers, and invariably healing is most rapid in those randomized to TCC treatment [4, 67]. As it is known that removable cast walkers (RCWs) redistribute pressure in a similar manner to the TCC, however, the question remained of why the TCC usually demonstrated superiority in terms of speed of wound closure. The most likely explanation, namely non-adherence, was confirmed in a study of 20 people with plantar neuropathic diabetic foot ulcers who were provided with RCWs and their total activity was recorded both from the waist and from an activity monitor hidden in the RCW. It transpired that participants only wore the RCW for 28% of all footsteps [68]. Subsequent to this observation, it was proposed that an RCW might be rendered irremovable by wrapping it with one or two bands of plaster of Paris, therefore addressing most of the disadvantages of the TCC but preserving irremovability. A subsequent randomized controlled trial of this modified, irremovable RCW versus the TCC showed that healing times were identical [69].

The impact of appropriate offloading on the histopathological features of neuropathic diabetic foot ulcers was reported by Piaggesi et al. [70]. They confirmed that appropriate offloading resulted in the foot wound appearing more like an acute wound with reparative patterns, angiogenesis, and fibroblast proliferation and the presence of granulation tissue. In contrast, biopsies from wounds that had not previously been offloaded confirmed the presence of hyperkeratosis, fibrosis, and chronic inflammation. These observations certainly suggest that appropriate offloading is associated with changes in the histology of neuropathic foot ulcers, including the reduction of inflammatory and reactive components and the acceleration of wound healing.

Another major consideration is the importance of emotional distress (e.g. depression and anxiety) in wound healing in people with diabetes [71]. This factor may have direct and indirect effects on wound healing. The direct effects include altered catecholamine and steroid secretion in addition to an imbalance of cytokines, which might directly impair wound healing. Indirectly, those who are depressed, for example, are less likely to adhere to treatment advice such as wearing an RCW at all times when walking. These important observations have previously been neglected by clinicians, and if any person with a plantar foot ulcer treated by an RCW shows no sign of healing, consideration should be given to the extent of adherence and the possibility of rendering the RCW irremovable as noted above.

As might be deduced from the above discussion, offloading is an essential component of the management of predominantly neuropathic plantar foot ulcers. This would include most UT 1A and 2A ulcers. Casts may also be used in the presence of localized infection in neuropathic foot ulcers (Figure 48.6). There is also evidence to support the use of offloading devices in the management

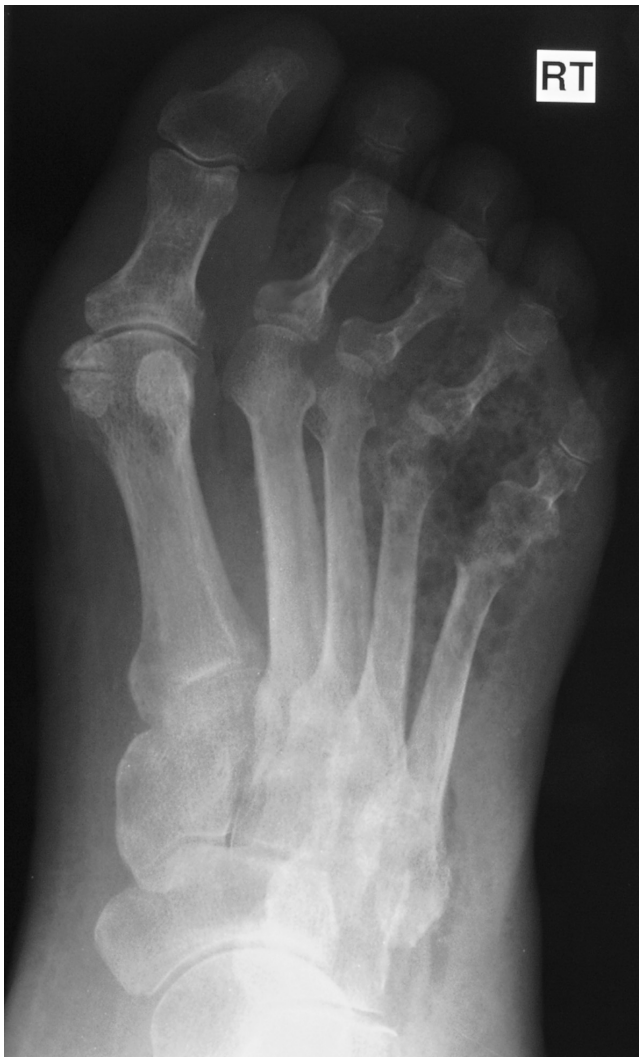

Figure 48.6 Radiograph from a person with a deep neuropathic ulcer under the right fifth metatarsal head. Gas in the tissues is not uncommon in radiographs of neuropathic foot ulcers as patients lacking pain sensation are able to walk despite the ulcer, "pumping" gas into the tissue. In this example, however, the gas makes it difficult to assess whether osteomyelitis is present.

of neuroischemic ulcers, but only if they are not clinically infected (UT 1C, 2C) [72].

For those treated with irremovable cast walkers, it is recommended that the cast be removed initially on a weekly basis for wound assessment, débridement, and cleansing. Healing can generally be a achieved in a period of 6–12 weeks in a cast; it is strongly recommended that after the plantar wound has healed, the cast be worn for a further 4 weeks to permit the scar tissue to firm up. Thereafter, the patient may be gradually transferred to appropriate footwear, which may need extra depth or, in the case of severe deformity, custom moulding.

Dressings

The danger of dressings and bandages is that some healthcare professionals may draw from them a false sense of security, believing that by dressing an ulcer they are curing it. Nothing could be further from the truth for a neuropathic ulcer. The three most important factors in the healing of a diabetic foot ulcer are freedom from pressure, freedom from infection, and good vascularity. The purpose of dressings is to protect the wound from local trauma, minimize the risk of infection, and optimize the wound environment, which should be moist in most cases. The evidence base to support the choice of any particular dressing is woefully inadequate, with few trials generally hampered by small numbers, inappropriate comparators, and poor study design [73, 74]. There is little evidence that any specific dressing will have a major impact on the rate of wound healing; indeed, a well-designed randomized trial comparing three commonly using dressings demonstrated no differences (except in cost) between them [75].

Management of infection

One of the first steps in the management of a foot ulcer is to determine whether infection is present or not: remember that all foot ulcers are colonized with potentially pathogenic organisms and it is generally accepted by the IWGDF that the diagnosis of infection in the diabetic foot ulcer remains a clinical one [76]. The presence of signs such as purulent discharge, erythema, local warmth, and swelling suggests infection requiring appropriate treatment. As recently emphasized by Abbas et al., it must be remembered that antibiotics are used to treat infection in the diabetic foot, they are not wound-healing agents [77].

Clinically non-infected ulcers

When ulcers are not infected and predominantly neuropathic (UT 1A, 2A), the use of antibiotics may be withheld, as Chantelau et al. [78] showed that with appropriate wound management, patients do equally well with or without systemic antibiotics in a randomized controlled trial. Nevertheless, frequent review, débridement, and callus removal together with offloading are essential parts of management of neuropathic foot ulcers and, should signs of infection develop, antibiotics may be needed. For those ulcers with an ischemic component that do not have gross signs of infection (UT 1C, 2C), antibiotics should probably be given in most cases as the combination of infection and ischemia in the diabetic foot is a common cause of ultimate lower extremity amputation.

Clinically infected ulcers

Non-limb-threatening infected ulcers (UT 1B, 1D, 2B, 2D) can generally be treated on an outpatient basis, and oral broad-spectrum antibiotics should be used initially until results of sensitivities are obtained. As reviewed by Lipsky's group, two sets of international guidelines have been published in recent years [76, 79, 80]. One important aspect of these recent guidelines has been the development of criteria by which to classify the severity of a diabetic foot infection. Generally, mild infections are relatively superficial and limited, moderate infections involve deeper tissues, and severe infections are accompanied by

systematic signs or symptoms of infection or metabolic disturbances [76]. Any ulcer with clinical evidence of infection should have tissue taken and sent for culture and sensitivity in the microbiology department. Although superficial swabs are commonly taken, deep (preferably tissue) specimens are preferable in terms of accuracy of diagnosis [76]. Most infective ulcers are polymicrobial, often with a mixture of anaerobes and aerobes. Unfortunately, a systematic review of antimicrobial treatments for diabetic foot ulcers revealed that few appropriately designed randomized controlled studies have been conducted, and it was difficult to give specific guidelines as to antibiotic regimens for specific infective organisms [81]; however, if there is any suspicion of osteomyelitis (signs such as a sausage-shaped toe or the ability to probe to bone may suggest this diagnosis), a radiograph of the infected foot should be taken and possibly further investigations initiated (see below and Chapter 55). The antibiotic prescription for a clinically infected non-limb-threatening foot ulcer without evidence of osteomyelitis should be guided by sensitivities after these are available from tissue specimens; when sensitivities are known, targeted appropriate narrow-spectrum agents should be prescribed. Suitable broad-spectrum antibiotics to start as soon as the clinical diagnosis of infection is made while waiting for a sensitivity result from the microbiology department would include drugs such as clindamycin or the amoxicillin–clavulanate combination [76].

Limb-threatening infection

People with limb-threatening infection usually have systemic symptoms and signs and require hospitalization with parenteral antibiotics. Deep wound and blood cultures should be taken and the circulation assessed with non-invasive studies initially, and metabolic control is usually achieved by intravenous insulin infusion. Early surgical débridement is often indicated in such cases, and initial antibiotic regimens should be broad-spectrum until sensitivities are determined from cultures. Examples of initial antibiotic regimens include clindamycin and ciprofloxacin, or flucloxacillin, ampicillin, and metronidazole. One problem with interpreting sensitivities is the question of whether the organism isolated is simply a colonizing bacterium or is a true infecting organism. One technique, the polymerase chain reaction (PCR) assay, has been shown to be effective at identifying many virulent organisms [76]. A study in France [82] showed the potential advantages of using this technique in the rapid distinction between colonizing and virulent infecting organisms.

An increasing problem in diabetic foot clinics is antibiotic-resistant pathogens such as methacillin-resistant *Staphylococcus aureus* (MRSA). In most cases, MRSA is isolated as an opportunistic colonizing organism following treatment with often inappropriate long-duration broad-spectrum antibiotics. If MRSA is felt to be an infecting organism, there are useful new agents such as linezolid [68], which can be given parenterally or orally, and are effective against such organisms. There is a suggestion that larval therapy [83] might be useful in eradicating MRSA that is contaminating diabetic foot wounds.

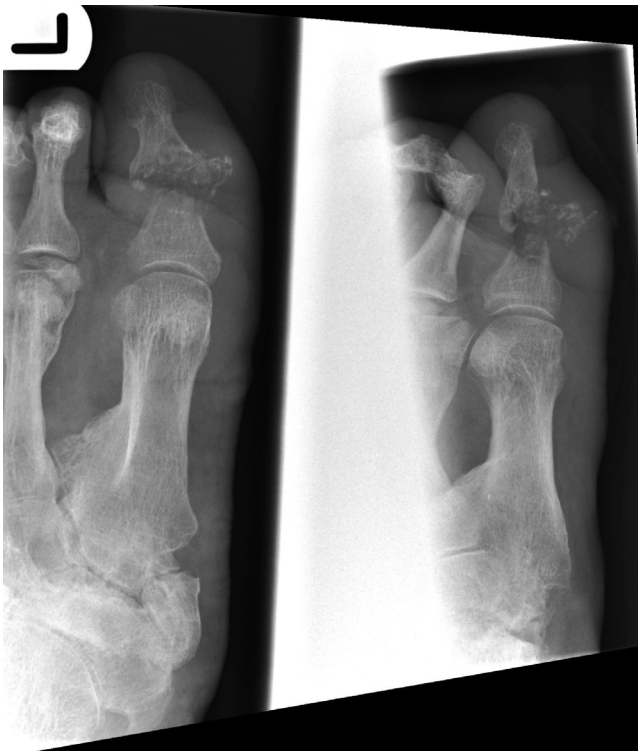

Figure 48.7 This radiograph displays two main abnormalities: (a) changes of osteomyelitis and septic arthritis involving the first metatarso-phalangeal joint, with destruction of the distal first metatarsal and proximal area of the proximal phalanx of the great toe; and (b) chronic changes of Charcot neuroarthropathy in the first cuneiform/metatarsal area.

Osteomyelitis

The diagnosis of osteomyelitis is a controversial topic, and several diagnostic tests have been recommended. Amongst these, "probing to bone" has been shown to have a relatively high predictive value whereas plain radiographs are insensitive early in the natural history of osteomyelitis. In most clinical cases, however, the diagnosis is ultimately made by a plain X-ray of the foot (Figure 48.7). Magnetic resonance imaging (MRI) is playing an increasing role in the diagnosis as it has high sensitivity [84]. The combination of an ulcer area >2 × 2 cm, a positive probe to bone test, an elevated sedimentation rate, and an abnormal radiograph are most helpful in diagnosing the presence of osteomyelitis in the diabetic foot, whereas a negative MRI scan makes a diagnosis much less likely [85]. A combination of clinical and laboratory findings together can significantly improve diagnostic accuracy for osteomyelitis in the diabetic foot: the specific combination of ulcer depth with serum inflammatory markers appears to be particularly sensitive [86]. Contrary to traditional teaching, it is increasingly recognized that some cases of localized osteomyelitis can be managed by long-term (10–12 weeks) antibiotic therapy, and this has recently been confirmed in a randomized controlled trial [87]; however, localized bony resection after appropriate antibiotic therapy remains a common approach. Those cases with osteomyelitis confined to one bone without involvement of a joint

are most likely to respond to antibiotic therapy, particularly in the absence of peripheral vascular disease. It must be pointed out that data to inform treatment choices in osteomyelitis of the diabetic foot for randomized controlled trials are limited and further research is urgently needed [88].

Adjunctive therapies

A number of newer approaches to promote more rapid healing in diabetic foot lesions have been described over the last two decades. Some of those are mentioned below but many have also been reviewed by the IWGDF [89].

Growth factors

A number of growth factors and other agents designed to modify abnormalities of the biochemistry of the wound bed or surrounding tissues have been described, but there is still no consensus on their place in day-to-day clinical practice [89]. One example is platelet-derived growth factor (PDGF), which is available for clinical use in a number of countries. Although there is some support for their use for randomized clinical studies [90], their expense, together with the fact that most neuropathic ulcers can be healed with appropriate offloading, have limited their use. Unfortunately, PDGF together with other topically applied agents such as epidermal growth factor do not have sufficient robust data to support their day-to-day use in routine clinical practice.

Hyperbaric oxygen

Hyperbaric oxygen has been widely promoted for the management of non-healing diabetic foot ulcers, particularly in the USA, for some years. Many of the reported studies have been poorly designed or anecdotal and have given rise to serious concerns about the widespread use of this treatment [91]; however, there have been well-designed randomized controlled trials to assess the efficacy of hyperbaric oxygen in ischemic diabetic foot wounds [92]. Whereas a recent systematic review that considered hyperbaric oxygen accepted that there was some evidence to support its use, it is clear that more data are required from larger controlled trials not only to confirm efficacy but also to clarify which wounds might best benefit from this expensive treatment [89, 93]. These data might be forthcoming in 2017, when the largest ever controlled trial of hyperbaric oxygen in diabetic foot wounds from multiple Dutch centers should be reported [94].

Negative pressure wound therapy

In recent decades, negative pressure wound therapy using vacuum-assisted closure has emerged as a commonly employed option in the treatment of complex wounds of the diabetic foot [95]. Earlier work suggested that the application of negative pressure optimizes blood flow, decreases local tissue edema, and removes excessive fluid and proinflammatory exudates from the wound bed. Subsequently, controlled trial evidence emerged for the use of negative pressure wound therapy in both local postoperative wounds in the diabetic foot [96] and, more recently, in the management of complex but non-surgical diabetic foot ulcers [97]. It is clear that this treatment helps promote the formation of granulation tissue, but its cost will limit its use to those complex diabetic foot wounds not responding to standard therapies. However, a more recent Cochrane review concluded that, because of the risk of bias in recent studies, further well-designed trials are required to help identify who might benefit from this therapy [98].

Bioengineered skin substitutes

Similarly to other treatments in this group of adjunctive therapies, although there is some evidence to support the use of bioengineered skin substitutes in non-infected neuropathic ulcers, its use is somewhat restricted by cost [89]. A systematic review on this topic concluded that the trials assessed were of questionable quality and until high-quality studies were performed, recommendations for the use of these skin substitutes could not be made [99].

Charcot neuroarthropathy

Charcot neuroarthropathy is a non-infective arthropathy that occurs in a well-perfused insensate foot. Although the exact mechanism underlying the development of Charcot neuroarthropathy remains unclear, progress has been made in our understanding of the etiopathogenesis of this disorder in the last two decades. It is clear that the classic neurotraumatic and neurotrophic theories for the pathogenesis of acute Charcot neuroarthropathy in diabetes do not address certain key features of the disease [100]. If the former theory were correct, Charcot neuroarthropathy would be much more common and should be symmetrical; in fact, acute Charcot neuroarthropathy is relatively rare among people with neuropathy and is usually asymmetric, although there is an increased risk of developing Charcot neuroarthropathy in the contralateral foot some years later.

Charcot neuroarthropathy occurs in a well-perfused insensate foot. Typically, patients present with a warm, swollen foot and, contrary to reports in some of the earlier texts, may be accompanied by pain or at least discomfort in the affected limb. The affected person tends to be slightly younger than is usual for individuals presenting with a diabetic foot ulcer and typically presents with a warm, swollen foot that may or may not be painful. Although a history of trauma may be present, the trauma is rarely of sufficient severity to account for the abnormalities observed on clinical examination (Figure 48.7). Although Charcot neuroarthropathy is characterized by increased local bone resorption, the exact cellular mechanisms that contribute to this condition remain unresolved. Fairly recently, receptor activator of nuclear factor κB ligand (RANKL) was identified as an essential mediator of osteoclast formation and activation. It has been hypothesized that the RANKL/osteoprotegerin (OPG) pathway may play an important part in the development of acute Charcot neuroarthropathy [100]. It has subsequently been confirmed that peripheral blood monocytes isolated from people with Charcot neuroarthropathy and cultured in the presence of macrophage colony-stimulating factor led to increased osteoclast formation compared with healthy and diabetic controlled monocytes [101].

These observations suggested that RANKL-mediated osteoclastic resorption occurs in acute Charcot neuroarthropathy. Hence the RANKL-dependent pathway is important in the pathogenesis of acute Charcot neuroarthropathy, suggesting that in the future, inhibition of RANKL might be useful in management. Other inflammatory markers, including tumor necrosis factor alpha and interleukin-6, have also been shown to be elevated in the acute phase of Charcot neuroarthropathy, showing significant reduction on resolution, suggesting that these could be used as potential markers of Charcot neuroarthropathy activity [102].

As discussed in Chapter 53, the treatment of the foot in CN depends upon the stage in which the disease is diagnosed. In the acute phase, that offloading of the affected foot by use of a plaster cast is the most effective method of reducing disease activity and local inflammation. Use of the cast should continue until the swelling and hyperemia have resolved and the skin temperature differential is 1 °C or less, at which time custom-moulded shoes with appropriate insoles are indicated [103]. The role of medical treatments has still to be clarified and none is currently recommended.

The management of advanced Charcot neuroarthropathy with bone deformity requiring reconstructive surgery is beyond the scope of this chapter and the reader is referred to recent reviews, e.g. [104].

Conclusions

There can be no doubt that despite our efforts in early identification, prevention, and aggressive treatment of diabetic foot problems, the incidence of diabetic foot disease is likely to increase in the next few decades with the global explosion of the prevalence in type 2 diabetes. It is also clear that diabetic foot disease carries not only a significant morbidity, but even mortality: Armstrong et al. [105] pointed out that the outlook for those with diabetic foot disease is worse than many malignant diseases. There is increasing recognition of the multifactorial nature of complications that led Young et al. [106] to review the survival of their patients with diabetic foot lesions over the previous 13 years. They reported that survival has improved and this has been accompanied by the adoption of an aggressive cardiovascular risk management policy that should be encouraged in all people with diabetic foot disease. The ultimate prognosis for the limb with a diabetic foot lesion depends upon the presence or absence of an ischemic component: it has been shown that people with higher Wagner or UT gradings and severity are more likely to end up with minor or even major amputation. Thus, neuropathic foot lesions generally carry a good prognosis, whereas those with a significant ischemic component are more likely to require the input of the vascular surgeon (see Chapter 47).

The team approach

It should be clear that the spectrum of diabetic foot problems requires the involvement of individuals from many specialties. The diabetic foot cannot be regarded as the sole responsibility of the diabetologist, and a number of reports over the last two decades or more have promoted the benefits of a multidisciplinary approach to diabetic foot care [107]. This started in the early 1990s, when the concept of the "annual review" was adopted by most national diabetes societies. This requires that all people with diabetes be screened on an annual basis for evidence of long-term complications [108]. There is increasing evidence from a number of long-term studies that the adoption of this approach not only in hospital but also in community care has been associated with a reduced incidence of foot problems [109–111]. The improved management of diabetic foot care in the district of Leverkusen, Germany, ultimately resulted in a 37% reduction in non-traumatic amputations in people with diabetes; however, this took more than 10 years after the establishment of specialist foot care [109]. Two studies from the UK [110, 111] have reported reductions of up to 60% in diabetic amputations and both of these followed either the introduction of multidisciplinary team work in the community or the improved organization of general diabetes care. Finally, a sustained reduction in major amputations over the previous 20 years was reported in a study in Sweden, suggesting that a substantial decrease in diabetes-related amputations can not only be achieved, but also maintained over a long period of time [112].

The team approach, involving diabetologists working together with surgeons (orthopedic and vascular), specialist nurses, podiatrists, orthotists, and often many other healthcare professionals is therefore strongly recommended in the management of complex lesions of the diabetic foot. It should be remembered, however, that it is the patient at risk of, or with foot ulceration, who must be regarded as the most important member of this team. Without the patient's willing participation, there is little that other team members can achieve to improve the overall outlook for the diabetic foot in the 21st century.

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49 Sexual Function in Men and Women with Diabetes

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Key points

- The prevalence of erectile dysfunction in men with diabetes increases with age and is about 35–50% overall.
- Penile erection occurs as a result of engorgement of the erectile tissue following vascular smooth muscle relaxation in the corpus cavernosum mediated by nitric oxide (NO), which is derived from both parasympathetic nerve terminals and the vascular endothelium.
- Erectile dysfunction in diabetes is largely due to failure of NO-mediated smooth-muscle relaxation secondary to endothelial dysfunction and autonomic neuropathy.
- Erectile dysfunction is an early indicator of endothelial dysfunction and a marker of increased cardiovascular risk.
- Sildenafil and other phosphodiesterase 5 (PDE5) inhibitors act by inhibiting the breakdown of cyclic guanosine monophosphate (cGMP), the second messenger in the NO pathway, and hence enhance erections under conditions of sexual stimulation.
- PDE5 inhibitors are safe and effective and can be used to treat erectile dysfunction in a diabetes clinic or general practice.
- Other options for treating erectile dysfunction in diabetes are intracavernosal injection therapy, transurethral alprostadil, vacuum therapy, and surgical insertion of penile prostheses.
- In women with diabetes, sexual dysfunction is less common, but there is an increased risk of vaginal dryness and arousal disorder.
- Contraceptive advice is essential in diabetes, as unplanned pregnancies carry an increased risk of morbidity and fetal abnormalities. Most forms of contraception are safe and effective in women with diabetes, but the oral contraceptive pill is recommended, as it is reliable and well tolerated.
- Hormone replacement therapy should be considered on a short-term basis in all women with an appropriate indication, particularly if they have diabetes. It has no adverse effects on glycemic control or lipid profiles.

Male erectile dysfunction

Erectile dysfunction is one of the commonest clinically apparent complications in men with diabetes. It can cause distress and unhappiness but is usually treatable. It may also be a marker of cardiovascular risk, and so it is a condition of which all diabetes professionals should be aware and understand.

Physiology of erectile function

Tumescence is a vascular process under the control of the autonomic nervous system. The erectile tissue of the corpus cavernosum behaves as a sponge, and erection occurs when it becomes engorged with blood. As shown in Figure 49.1, dilatation of the arterioles and vasculature of the corpus cavernosum leads to compression of the outflow venules against the rigid tunica albuginea [1, 2]. Hence smooth-muscle relaxation is the key phenomenon in this process, as it leads to increased arterial inflow and reduced venous outflow [3, 4]. The process is under the control of parasympathetic fibers, which were previously known as non-adrenergic, non-cholinergic neurones, as the neurotransmitter was unknown; however, it is now clear that nitric oxide (NO) is the agent largely responsible for smooth-muscle relaxation in the corpus cavernosum. It is both produced in the parasympathetic nerve terminals and is generated by NO synthase in the vascular endothelium. Within the smooth-muscle cell of the corpus cavernosum, NO stimulates guanylate cyclase, leading to increased production of the second messenger, cyclic guanosine monophosphate (cGMP), which induces the activation of protein kinase G. This inhibits calcium release, which leads to smooth-muscle relaxation [4–6] (Figure 49.2).

There is some evidence that neuronally derived NO is important in initiation, whereas NO from the endothelium is responsible for maintenance of erection [7].

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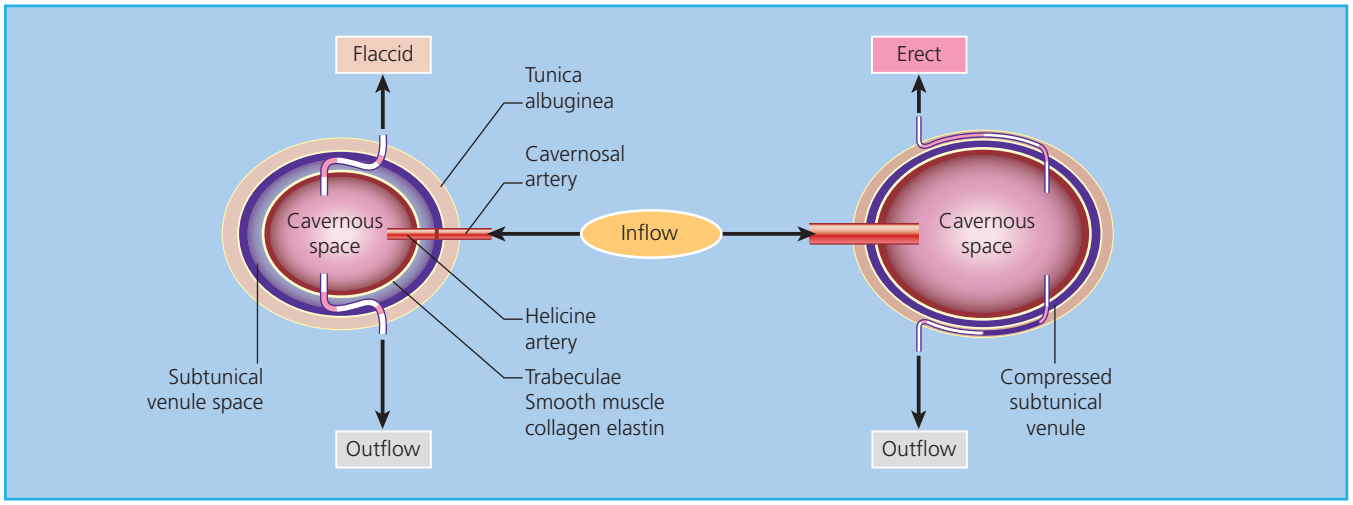

Figure 49.1 Diagrammatic representation of the corpus cavernosum. During tumescence, dilation of the helicine and cavernosal arteries produces expansion of the cavernosal space and compression of the outflow venules against the rigid tunica albuginea.

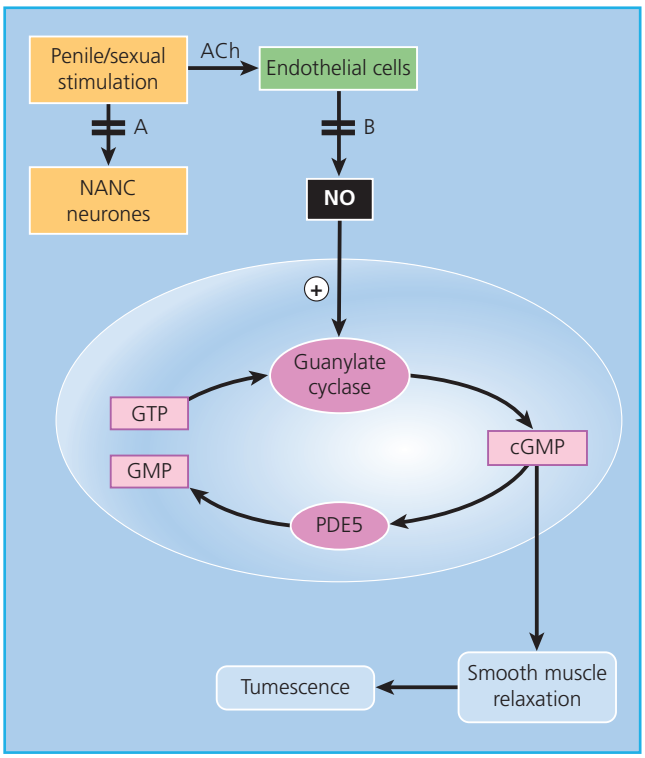

Figure 49.2 Pathophysiology of erectile function in diabetes. Diagrammatic representation of the pathways leading to the relaxation of a corpus cavernosal smooth muscle cell. In diabetes there are defects in nitric oxide mediated smooth muscle relaxation due to neuropathy of the NANC fibers (A) and endothelial dysfunction (B). Ach, acetylcholine; NANC, non-adrenergic, non-cholinergic neurones; NO, nitric oxide; PDE5, phospodiesterase type 5.

Pathophysiology of erectile dysfunction in diabetes

In men with diabetes, there is good evidence that erectile dysfunction is due to failure of NO-induced smooth muscle relaxation due to both autonomic neuropathy and endothelial dysfunction [8]. Many men with diabetes report that in the early stages they do not have a problem initially achieving an erection but that they cannot maintain it. This suggests that in these individuals failure of endothelium-derived NO occurs before significant autonomic neuropathy.

More recently, other potential abnormalities have been described that may contribute to the development of erectile dysfunction in diabetes. Endothelium-derived hyperpolarizing factor (EDHF) plays a role in endothelium-dependent relaxation of human penile arteries [9], and EDHF-mediated endothelium-dependent relaxation is significantly impaired in penile resistance arteries in men with diabetes [10]. Impaired EDHF responses might therefore contribute to the endothelial dysfunction of diabetic erectile tissue.

A further body of evidence suggests that increased oxygen free-radical levels in diabetes may reduce the vasodilator effect of NO. In particular, the formation of products of non-enzymatic glycation to produce advanced glycation end-products (AGEs) generates reactive oxygen species, which impairs NO bioactivity [11, 12]. In animal models, inhibition of AGE formation improves endothelium-dependent relaxation and restores erectile function in diabetic rats [13, 14].

Other pathophysiological changes known to occur in diabetes have been postulated to contribute to erectile dysfunction. Non-enzymatic glycation of proteins has been reported to impair endothelium-dependent relaxation of the aorta in rats [15, 16]. Other factors, not limited to diabetes, may also contribute to the development of erectile dysfunction in men with diabetes.

Structural changes associated with large-vessel disease are commonly associated with erectile dysfunction in diabetes. However, this is usually associated with functional changes of widespread endothelial dysfunction in diabetes and it is difficult to separate the relative importance of the two factors.

Testosterone has a central role in the physiology of erectile function and also in the regulation of male sexual behavior and attitudes. Hypogonadism is a well-established, and treatable, cause of erectile dysfunction. In experimental studies, androgen deficiency leads to a reduction in smooth muscle and structural abnormalities in the erectile tissue [17, 18]. In recent years, there has been a great deal of interest in a potential association between reduced levels of testosterone and type 2 diabetes mellitus (T2DM) and the metabolic syndrome. However, it is controversial whether there is a causal link between diabetes and hypogonadism, and this will be discussed later in this chapter.

Box 49.1 Medications associated with erectile dysfunction.

Antihypertensives
Thiazide diuretics
Beta-blockers
Calcium channel blockers
ACE inhibitors
Central sympatholytics (methyldopa, clonidine)
Aldosterone receptor antagonists

Antidepressants
Tricyclics
Monoamine oxidase inhibitors
(NB: Selective serotonin reuptake inhibitors can cause ejaculatory problems)

Antipsychotics
Phenothiazines
Haloperidol

Hormones
Luteinizing hormone-releasing hormone (goserilin, buserilin)
Estrogens (stilbestrol)
Antiandrogens (cyproterone)

Miscellaneous
5α-Reductase inhibitors (finasteride)
Statins (simvastatin, atorvastatin, pravastatin)
Cimetidine
Digoxin
Metoclopramide

Drugs of abuse
Alcohol
Tobacco
Marijuana
Amphetamines
Anabolic steroids
Barbiturates
Opiates

Other factors contributing to erectile dysfunction in diabetes

In addition to endothelial dysfunction and autonomic neuropathy, erectile dysfunction is associated with other conditions common in diabetes, such as hypertension and large-vessel disease [19]. Furthermore, men with diabetes are more likely to be taking medications that can impair erectile function. A list of these is given in Box 49.1. Antihypertensive agents are commonly reported to be associated with erectile dysfunction, although much of the evidence is anecdotal; β-blockers, aldosterone receptor blockers, and thiazide diuretics are the most commonly reported culprits [20]; the α-blockers perhaps have the least risk [21]. Finally, it should be remembered that there are many other potential causes of erectile dysfunction unrelated to diabetes, from which men with diabetes are not immune. The conditions associated with erectile dysfunction are listed in Box 49.2.

Box 49.2 Conditions associated with erectile dysfunction.

Psychological disorders
Anxiety about sexual performance
Psychological trauma or abuse
Misconceptions
Sexual problems in the partner
Depression
Psychoses

Vascular disorders
Peripheral vascular disease

Hypertension
Venous leak
Pelvic trauma

Neurological disorders
Stroke
Multiple sclerosis
Spinal and pelvic trauma
Peripheral neuropathies

Endocrine and metabolic disorders
Diabetes
Hypogonadism
Hyperprolactinemia
Hypopituitarism
Thyroid dysfunction
Hyperlipidemia
Renal disease
Liver disease

Miscellaneous
Surgery and trauma
Smoking
Drug and alcohol abuse
Structural abnormalities of the penis

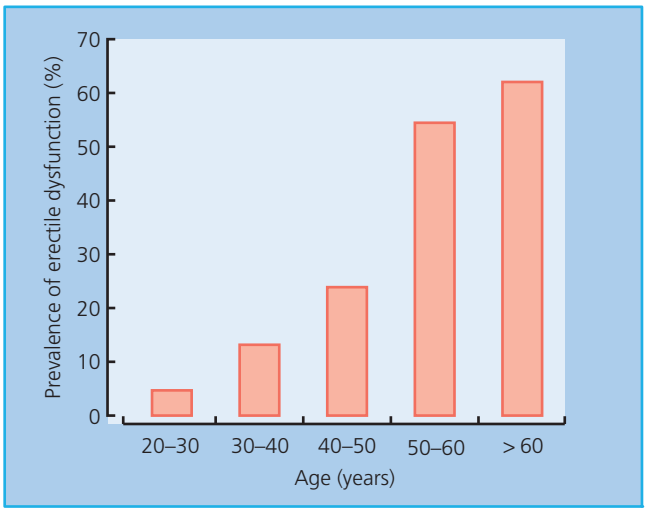

Figure 49.3 Prevalence of erectile dysfunction by age of men attending a hospital diabetes men clinic [22].

Clinical aspects of erectile dysfunction in diabetes

Erectile dysfunction becomes commoner with age. In a population-based study in Massachusetts, United States, the prevalence of complete erectile failure was reported to be 5% in men in their 40s and 15% in those over 70 years of age [19]. The prevalence in men with diabetes is significantly higher and also increases with age. In a survey of men attending a hospital diabetes clinic in the United Kingdom, the prevalence of erectile dysfunction increased from 13% among 30-year-olds to 61% among men aged over 60 years [22] (Figure 49.3). Overall, the prevalence was 38%. The prevalence of erectile dysfunction in diabetes in a general practice population was reported to be even higher, at 55% [19]. These data suggest that erectile dysfunction is the commonest clinically apparent complication of diabetes in men.

Conversely, diabetes is a common finding in men presenting with erectile dysfunction. Approximately 20% of men seen in erectile dysfunction clinics have been reported to have diabetes, of whom ~5% were previously undiagnosed [23, 24].

The presence of other medical conditions increases the risk of erectile dysfunction. A population-based survey of 600 men in Brazil, Italy, Japan, and Malaysia in 2000 examined the prevalence of erectile dysfunction and its relationship to other diseases and lifestyles. The prevalence of erectile dysfunction among men with diabetes rose from 25% at age 40–44 to 70% at age 65–70 years [25]. Cardiovascular disease increased the risk of erectile dysfunction. The prevalence was 31.7% in men with diabetes only, 40% in men with diabetes and heart disease, and 46.5% in those with diabetes and hypertension. Men with diabetes who smoked and reported below-average levels of physical activity had a fourfold increase in the prevalence of erectile dysfunction.

Erectile dysfunction as a risk factor for cardiovascular disease

There is convincing evidence of an association of between erectile dysfunction and both cardiovascular disease [26, 27] and mortality [28]. This may be because they share common risk factors. Increased waist measurement and reduced physical activity, both important risk factors for ischemic heart disease, considerably increase the risk of erectile dysfunction [29–31].

Recent studies have suggested that the association between erectile dysfunction and cardiovascular disease may be due to more than shared risk factors and may arise because they are both manifestations of endothelial dysfunction. There is considerable evidence that endothelial dysfunction has a key role in the pathogenesis and progression of atherosclerosis [32]. It is clear that the endothelium has important and complex endocrine and paracrine functions, and one of its most important products is NO (previously known as endothelium-derived relaxing factor). NO derived from both nerve terminals and the vascular endothelium has a central role in the physiology of erection. Therefore, there are theoretical grounds to believe that erectile dysfunction might be an early marker of endothelial dysfunction and hence an important risk factor for cardiovascular disease, and there is good evidence that this is the case in animal studies [33] and humans [34, 35].

Hence the association between erectile dysfunction and increased cardiovascular risk may be a case of shared "common soil," in particular endothelial dysfunction and microvascular disease. In practical terms, this means that cardiovascular risk should be assessed in any man with erectile dysfunction whether he has diabetes or not. A man with T2DM and erectile dysfunction has approximately double the risk of developing coronary heart disease compared with a similar man without erectile dysfunction [36].

Smoking and alcohol consumption

Smoking greatly increases the risk of developing erectile dysfunction. A follow-up of the Massachusetts Male Aging Study reported that cigarette smoking almost doubled the risk of developing erectile dysfunction after about 7 years [19]. A similar finding was reported by the large Health Professionals' Follow-up Study [31]. Smoking appears to exert its effects via the NO signal transduction pathway [37].

In contrast to tobacco, it is well established that moderate alcohol consumption is associated with a reduced risk of a cardiovascular event. It is interesting, that drinking alcohol in moderation also appears to reduce the risk of developing erectile dysfunction [38].

Quality of life issues

That erectile dysfunction can significantly worsen a man's quality of life is not in doubt and there is reasonable evidence to show treating erectile dysfunction improves quality of life. A large study of men with T2DM reported that erectile problems were associated with a dramatic increase in depressive symptoms [39]. In another series in general practice, 45% of men with diabetes stated that they thought about their erectile dysfunction all or most of the time, 23% felt that it severely affected their quality of life, and 10% felt that it severely affected their relationship with their partner [40]. A systematic review of randomized trials of erectile

Box 49.3 Key features in the history of erectile dysfunction in diabetes.

Onset usually gradual and progressive
Earliest feature often inability to sustain erection long enough for satisfactory intercourse
Erectile failure may be intermittent initially
Sudden onset often stated to indicate a psychogenic cause but little evidence to support this
Preservation of spontaneous and early morning erections does not necessarily indicate a psychogenic cause
Loss of libido consistent with hypogonadism but not a reliable symptom
Men with erectile dysfunction often understate their sex drive for a variety of reasons

dysfunction treatment reported improvements in self-esteem, confidence, and depression scores after treatment [41].

Assessment and investigation of erectile dysfunction in diabetes

Clinical assessment

In most cases, a man with erectile dysfunction will have taken a long time to pluck up the courage to discuss his problem with a doctor and he may be anxious. Almost invariably, however, once the subject has been broached, men with erectile dysfunction and their partners do not usually have any difficulty discussing the problem. A description of the nature of the ED should be obtained, not least to ensure that the man is complaining of erectile dysfunction and not another related problem, such as premature ejaculation. The key features in the history of erectile dysfunction are listed in Box 49.3. Ideally, the man's partner should be present, but most men attend the consultation alone. Talking to the partner without the man present can reveal interesting and useful insights into the problem.

General physical examination may give clues as to the etiology of erectile dysfunction and the choice of treatment. The key features of the physical examination are listed in Box 49.4.

Investigation of erectile dysfunction in diabetes

The suggested investigations of erectile dysfunction in diabetes are listed in Box 49.5. It is unhelpful to try to determine whether

Box 49.4 Key physical signs on examination.

Any features of hypogonadism
Manual dexterity—may preclude physical treatment
Protuberant abdomen
External genitalia:
  Presence of phimosis
  Testicular volume

Box 49.5 Investigation of erectile dysfunction in diabetes.

Serum testosterone if libido reduced or hypogonadism suspected (ideally taken at 9 a.m.)
Serum prolactin and luteinizing hormone if serum testosterone subnormal
Assessment of cardiovascular status if clinically indicated:
ECG
Serum lipids
Glycated hemoglobin, electrolytes, if clinically indicated

or not erectile dysfunction is psychogenic in origin, particularly when managing a man with diabetes and erectile dysfunction. Few investigations are needed, but it is worth excluding other treatable causes of erectile dysfunction; in practical terms, hypogonadism is the only treatable one. The relationship between diabetes and hypogonadism is a matter of much debate (see below), but gonadal function should be assessed in all men with diabetes and erectile dysfunction. Some men presenting with erectile dysfunction will not have attended any form of clinic for many years, and so the consultation provides an opportunity to address other health issues. For the reasons given above, consideration should be given to assessing the man's cardiovascular status. The consultation also provides an opportunity to address the management of the man's diabetes.

General advice

Most men with diabetes and their partners seeking treatment for erectile dysfunction are middle-aged, have been married for many years, and require only simple, common-sense advice. Specialist psychosexual counseling is not needed for most couples; several series have reported that diabetologists can offer an effective service for the treatment of erectile dysfunction without the support of psychosexual counselors [42–45]. It is important that the cause of the erectile dysfunction is explained, as many men will blame themselves. They should be advised that if they wish to resume sexual relations they will require long-term treatment, as spontaneous return of erectile function in diabetes occurs only rarely [46].

Treating erectile dysfunction in an attempt to save a failing relationship is rarely successful and may make the situation worse. The assistance of a suitably qualified psychosexual counselor should be considered in this situation. Referral to a counselor should also be considered if there is any suggestion of severe anxiety, loss of attraction between partners, or marked performance anxiety. Any other medical problems should be addressed. Improving poor metabolic control may help general well-being, but poor control should not be used as a reason to refuse or delay treatment. Men who smoke should be advised to stop for reasons of general health, although there is no good evidence that stopping smoking will improve erectile function in a man with diabetes.

Many men with diabetes will be taking medication known to cause erectile dysfunction. Experience has shown that changing

Table 49.1 Characteristics of available PDE5 inhibitors.

Agent	Dosage (mg)	Onset of action (min)	Half-life (h)	Duration (h)
Sildenafil	25, 50, or 100 prn	30–60	3–5	<12
Vardenafil	5, 10, or 20 prn	30–60	4–5	<10
Tadalafil	10 or 20 prn 5 daily	60–120	17.5	<36
Avanafil	50, 100, or 200 prn		3	<6

the treatment in an attempt to improve sexual function rarely works and may cause delays and frustration for the man. It is therefore not advisable unless there is a strong temporal relationship between starting treatment and the onset of erectile dysfunction.

Treatment options

The advent of effective oral therapies has transformed the management of erectile dysfunction. These should be offered as first-line therapy to men with diabetes and erectile dysfunction, and the other treatment options should be reserved for those in whom oral therapy is contraindicated or ineffective.

Oral agents

Phosphodiesterase 5 inhibitors

Phosphodiesterase type 5 (PDE5) is an enzyme found in smooth muscle, platelets, and the corpus cavernosum. During tumescence, there is an increase in the intracellular concentration of NO, which produces smooth-muscle relaxation via the second messenger cGMP. This is broken down in turn by PDE5. Hence PDE5 inhibitors can enhance erections under conditions of sexual stimulation.

Sildenafil was the first PDE5 inhibitor and early small trials showed it to be a highly effective treatment for erectile dysfunction in men with and without diabetes [47, 48]. The first large study was published in 1998. A total of 532 men with erectile dysfunction of mixed etiology were studied. In the group given sildenafil, 69% of all attempts at intercourse were successful, compared with 22% in those given placebo [49]. Other studies in men with erectile dysfunction of mixed etiology have shown success rates between 65 and 77% [50, 51]. Studies of sildenafil in other patient groups have reported success rates of ~70% in hypertension [52], 76% in spinal cord injury [53], 63% in spina bifida [54], and 40% following radical prostatectomy [55].

In men with diabetes, the success rates for sildenafil have been reported to be between 56 and 59% [48, 56]. A study in elderly men reported success rates of 69% overall and 50% in men with diabetes [57]. Most of these studies of sildenafil have been short term. A trial examining the long-term efficacy of sildenafil in men with erectile dysfunction due to a variety of causes reported that only 52% continued to use it after 2 years [58]. This figure may seem surprisingly low, but it is certainly considerably higher than for any other type of erectile dysfunction treatment.

Other PDE5 inhibitors

There are currently four PDE5 inhibitors licensed for the treatment of ED: sildenafil (Viagra), tadalafil (Cialis), vardenafil (Levitra), and avanafil (Stendra). Their key characteristics are listed in Table 49.1 and adverse effects from the key trials of PDE5 inhibitors in men with diabetes are given in Table 49.2 [59–65]. All four PDE5 inhibitors have similar efficacy and safety profiles. Their side-effect profiles differ slightly, but the most notable difference is the longer half-life of tadalafil. Thus a single dose of tadalafil offers the potential to restore erectile function to normal for 2 days and thereby remove the need for medication to be taken each time prior to sexual activity. The choice between this form of treatment and on-demand dosing is largely a matter of patient choice. Patient preference studies of agents with differing dosing instructions are difficult to perform in a blinded fashion. Several have been reported and

Table 49.2 Adverse effects of PDE5 inhibitors (%). The prevalence quoted for each adverse effect is for the top dose used in each study.

Effect	Sildenafil [56–58, 61]	Tadalafil [59, 60, 62]	Vardenafil [64, 65]	Avanafil [63]
Headache	8.1–9.3	8.0–21	5–11	11.5
Flushing	7.4–8.1	3.0–9.0	5.4–10	4
Back pain	2.5	4.6–9.0	0	1
Dyspepsia	2.7–3.0	4.1–17	2.3	3
Nasal congestion	2.7–4.1	2.0–5	10	3
Dizziness	2.5	1.6		
Diarrhea	2.5	0.8		
Abnormal vision	1.4	0		1
Muscle cramps	4.1	3–7		0

have generally shown a preference for tadalafil over sildenafil [62, 66–70].

Adverse effects

The commonest adverse effects related to PDE5 inhibitors are headache, dyspepsia, and flushing. Headache and flushing might be expected, as the inhibitors are vasodilators. The dyspepsia is usually mild and may be due to relaxation of the cardiac sphincter of the stomach. Abnormal vision is experienced by about 6% of men taking sildenafil; this may be because the drug has some activity against PDE6, which is a retinal enzyme. Back pain and muscle cramps are particularly an adverse effect of tadalafil. In all the studies, the discontinuation rate due to adverse effects was low.

The cardiovascular safety of PDE5 inhibitors

The launch of sildenafil, the first PDE5 inhibitor, was soon followed by case reports of cardiovascular events and deaths associated with its use. However, there is now good evidence that PDE5 inhibitors are not associated with increased cardiovascular risk [71–74]. Restoring sexual function, however, is not completely without risk. Sexual activity, like any form of physical activity, can precipitate cardiovascular events in those at risk. A large case–control study reported the risk of a cardiovascular event in the 2 h after intercourse was increased by 2.5-fold in healthy men and by 3-fold if there was a history of previous myocardial infarction [75]. Although the absolute risk remains very small, the issue of cardiovascular safety must be addressed in all men before treating erectile dysfunction. Jackson et al. suggested a classification scheme for assessing cardiovascular risk in men undergoing treatment for erectile dysfunction; those with the highest risk should be referred for specialist cardiac evaluation whereas the lowest risk group could be managed in primary care [71].

Drug interactions with PDE5 inhibitors

PDE5 inhibitors can be used safely in men taking a wide range of other drugs, but there are several potential important interactions. They are contraindicated in the presence of any nitrate therapy (including nicorandil) as the combination can cause profound hypotension. A man taking nitrates seeking treatment for erectile dysfunction can be offered alternatives to PDE5 inhibitors or the nitrates can be stopped or changed to an alternative therapy. Nitrates are a symptomatic treatment with no prognostic implications and so this is possible in most cases, but it should be done in consultation with a cardiologist in all but the most straightforward cases.

Nitrate therapy should not be given within 24 h of taking sildenafil, avanafil, or vardenafil and at least 48 h of taking tadalafil. If angina develops during or after sexual activity following the use of a PDE5 inhibitor, the man should be advised to discontinue any sexual activity and to stand up, as this reduces the work of the heart by reducing venous return.

PDE5 inhibitors should be used with caution in men who take α-blockers because the combination may lead to symptomatic hypotension in some men. Patients should be stable on α-blocker therapy before initiating a PDE5 inhibitor, which should be initiated at the lowest dose [72].

How to use PDE5 inhibitors

These agents should be taken orally about 1 hour before sexual activity. This period can be shortened if the drug is taken on an empty stomach. After the 1-h period, there is a "window of opportunity" when sexual activity can take place. For sildenafil, avanafil, and vardenafil, this is at least 4 h but may be over 8 h [72]. For tadalafil, the window of opportunity may last 48 h. Men with diabetes usually require the maximum recommended dose. The men should be warned that the drug only works in conjunction with sexual stimulation.

Tadalafil can be prescribed as a daily 5-mg dose rather than on an as-required basis. Many men find this more acceptable as it obviates the need to "plan for sex." It is effective when taken in this way [76] and may be slightly more effective than as-required tadalafil [77], but it is more expensive.

Management of non-responsiveness of PDE5 inhibitors

It is difficult to predict whether a man will respond to a PDE5 inhibitor. Failure to respond is more likely in men with long-standing and severe erectile dysfunction [35, 41]. However, no single factor precludes a successful outcome, and in practical terms it is worth trying a PDE5 inhibitor in all men with erectile dysfunction unless there is a contraindication. It is important that men are advised on how to take their medication properly. It has been suggested that intercourse success rates reached a plateau after eight attempts, so men should try at least eight times with a PDE5 inhibitor at the maximum recommended dose before being considered a non-responder [78].

Even with the maximum dose taken correctly, a large proportion of men with diabetes will not respond to PDE5 inhibitors. Treating any underlying hypogonadism may improve the outcome in this situation, but most men should be offered an alternative treatment.

Hypogonadism

The relationship between diabetes, the metabolic syndrome, and hypogonadism has been the subject of considerable interest in recent years. The overweight middle-aged man with T2DM, sexual dysfunction, fatigue, and borderline low serum testosterone is a common clinical problem. The term "late-onset male hypogonadism" has been coined to describe this condition. Pharmaceutical companies have been quick to promote research in this area as they look to widen the market for testosterone products. It is clear that reduced serum testosterone is more common in men with the metabolic syndrome and T2DM [79, 80]. Conversely, hypogonadism is associated with a near doubling of the risk of diabetes [81]. However, a causal relationship between the two has not been established and there are many confounding factors. The US Endocrine Society Clinical Practice Guidelines offer clear advice on the management of hypogonadism. It should only be treated if there are symptoms associated with hypogonadism (such as

Figure 49.4 Alprostadil self-injection pen device.

erectile dysfunction) and unequivocal biochemical evidence of hypogonadism [82]. There is certainly insufficient evidence to support treating hypogonadism to improve glucose tolerance or cardiovascular risk.

However, a serum testosterone should always be measured in men with diabetes and erectile dysfunction, particularly in those who do not respond to PDE5 inhibitors. Hypogonadism due to confirmed pituitary or testicular disease may be an uncommon finding in this situation but it usually responds well to treatment with testosterone. In the more common group of men with "late-onset male hypogonadism," there is some evidence that testosterone replacement can improve erectile dysfunction as a sole treatment [83] and enhance the response to PDE5 inhibitors [84, 85].

Other oral therapies

Various oral agents have been tried as treatments for erectile dysfunction in the past, including apomorphine, trazodone, yohimbine, and phentolamine. The data on all of them are limited and none has stood the test of time. They have been supplanted by the PDE5 inhibitors and probably have little role in the management of erectile dysfunction in diabetes.

Intracavernosal injection therapy

The technique of intracavernosal self-injection using phentolamine was first described in 1983 by Brindley [86], although the French urologist Virag [87] reported the use of papaverine slightly earlier. Although papaverine was more effective than phentolamine, it was an unlicensed treatment and was superseded by alprostadil (prostaglandin E), which was licensed for the treatment of ED in 1996.

Alprostadil is supplied in a self-injection pen device, which is easy to use, and supplied with excellent instructions (Figure 49.4). In spite of this, most studies show that self-injection therapy has a disappointingly high long-term discontinuation rate [88–90]. Self-injection treatment carries a small risk of priapism (a sustained unwanted erection). Although an infrequent complication, priapism is important, as it must be treated within 6 h by aspirating blood from the corpus cavernosum. Men undertaking self-injection must be warned of this potential problem and given instructions on what to do should it occur (Box 49.6).

Box 49.6 Instructions to medical staff for treating prolonged erections due to prostaglandin E_1.

Do not delay treatment beyond 6 h

Using an aseptic technique, aspirate 20–25 mL of blood from the corpus cavernosum (19- or 21-gauge butterfly needle)

Repeat the above on the opposite side of the penis if detumescence does not occur

If still unsuccessful, inject 0.5–1.0 mL of a 300 mg/mL solution of phenylephrine every 5–10 min (maximum dosage 5 mL) into the corpus cavernosum. If necessary, this may be followed by further aspiration of blood through the same needle. Extreme caution is necessary in men taking monoamine oxidase inhibitors, as a hypertensive crisis may result. Use carefully in those with coronary heart disease, uncontrolled hypertension, or cerebral ischemia. Monitor pulse rate and blood pressure throughout

If the above are unsuccessful, refer for urgent surgical treatment, such as a shunt procedure

Transurethral alprostadil (MUSE)

Many men find injection therapy unacceptable because it requires injecting the penis, and transurethral administration of the vasoactive agent appears largely to overcome this problem. The principle is simple: a slender applicator is inserted into the urethra to deposit a pellet containing alprostadil in polyethylene glycol. This gradually dissolves, allowing the prostaglandin to diffuse into the corpus cavernosum. In a placebo-controlled study of 1511 men with erectile dysfunction of mixed etiology, 65% were able to have intercourse using this system [91]. The results in the 240 men with diabetes in the study were similar [92]. Penile pain was reported in 10.8% and hypotension in 3.3% of the men receiving alprostadil. Priapism and penile fibrosis were not reported. As with most non-oral erectile dysfunction treatments, the long-term usage has been disappointing [93].

Topical alprostadil cream

Alprostadil is also available as a cream (Vitaros), which is applied around the urethral meatus. It contains dodecyl 2-*N*,*N*-dimethylaminopropionate, a novel penetration enhancer to allow the prostaglandin reach the erectile tissue. Published data are limited but it seems to be well tolerated and as effective as transurethral alprostadil [94].

Vacuum therapy

Vacuum devices became widely available in the 1970s. They consist of a translucent tube, which is placed over the penis, and an attached vacuum pump (Figure 49.5). The air is pumped out of

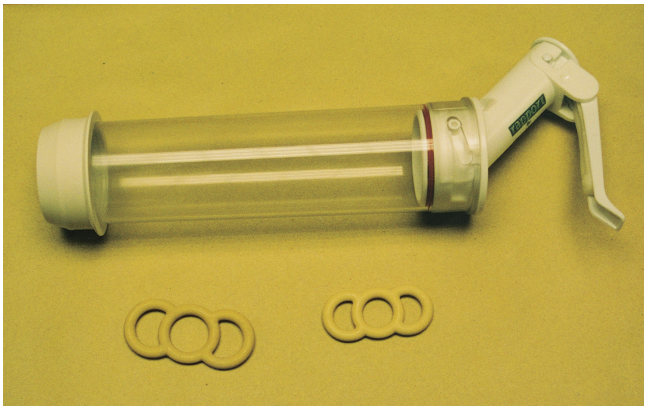

Figure 49.5 Typical vacuum device with constriction rings.

the tube, and the negative pressure draws blood into the erectile tissue, producing tumescence. A constriction band (which has previously been placed over the base of the tube) is then slipped off to remain firmly around the base of the penis so as to maintain the erection, and the tube is removed. The devices require some practice and dexterity, but most couples are able to use them satisfactorily. Trials of vacuum therapy have reported success rates of ~70% in men both with and without diabetes, suggesting that it is an effective treatment, provided that couples are prepared to use them [95–98].

Vacuum devices are safe and effective treatments, and inexpensive to use after an initial outlay (in the UK) of ~£100–250. The side effects are discomfort from the constriction band, failure to ejaculate, and a cold penis (reported by the female partner). Many couples find the use of vacuum devices unacceptable, and since the introduction of newer treatments their use has declined. They still have a role, however, in men who do not respond or who cannot use other treatments. Vacuum devices have the advantage over other erectile dysfunction treatments that they do not need repeat prescriptions and visits to a pharmacist for continued use.

Surgery

In spite of recent advances in the management of erectile dysfunction, some men will not be able to use the available treatment options. There will therefore always be a limited role for surgery.

The surgical options available are as follows:

1 The insertion of penile prostheses.

2 Corrective surgery for associated Peyronie disease or post-injection corporal fibrosis.

3 Venous and arterial surgery.

Discussion of vascular and corrective surgery of the penis is best left to a specialist urology textbook, but a general practitioner or diabetes physician needs to know which men might benefit from referral for insertion of a penile prosthesis. This form of surgery is best reserved for those in whom conventional treatments have failed and who are keen to resume full sexual activity.

Counseling of the man, and whenever possible his partner, is extremely important, particularly about the choice of prosthesis. The man's or couple's wishes are very important factors in device selection, as is the cost of the prosthesis.

The men must be warned regarding postoperative pain or discomfort and the potential for the need for reoperation. The men will need to restrict physical activity and refrain from intercourse for 4–6 weeks after the operation. They should be warned about the possible complications of infection, erosion, and prosthesis failure, and that these problems usually require device removal. It is also very important that the man and his partner are aware that the erection produced by a prosthesis is different from a normal erection, depending very much on the type of prosthesis chosen. It is useful to show examples of the prostheses and to describe how they are inserted and the mechanism of action.

There is uncertainty as to whether men with diabetes are at higher risk of infection than those without diabetes after insertion of a penile prosthesis, but there is a consensus that, should infection occur, it is more serious [99]. Good preoperative control of diabetes is important to minimize the risk. Most published series of well-selected groups of men who have undergone penile prosthesis insertion have reported acceptable results, with good levels of patient satisfaction [100].

Organization of the management of erectile dysfunction

Traditionally, erectile dysfunction has been managed in a dedicated clinic, often run by a urologist. The advent of effective oral therapies has made the management much simpler, so that erectile dysfunction in diabetes can usually be managed by any diabetologist or general practitioner. A physician considering treating erectile dysfunction will have to decide whether to run a separate clinic or to see the men in a routine diabetes clinic. Such a decision will depend on local resources and circumstances, but it is certainly possible to manage erectile dysfunction in a diabetes clinic. If this is to be done, it is advisable to have patient information literature on erectile dysfunction available. A great deal of useful patient information is produced by pharmaceutical companies and national diabetes organizations such as Diabetes UK both in printed form and online. It is often wise to let the man read this and to consider the matter, with treatment being started at a subsequent visit.

Managing erectile dysfunction in primary care

There are considerable advantages in the treatment of erectile dysfunction in primary care. A general practitioner is more likely to know and understand a man's particular circumstances. The men may be less intimidated in seeking help from their family practitioner than from a hospital specialist or sexual therapist. Little specialized equipment is required, and so there is no reason why interested general practitioners should not effectively treat the majority of men presenting with erectile dysfunction.

As with many disorders encountered in primary care, the general practitioner may choose to manage the problem in a standard consultation with the man. Others may choose to refer their patients to a fellow partner or colleague with a particular interest in erectile dysfunction or to their practice nurse, who may

have received appropriate training in the assessment of men with erectile dysfunction.

When a man presents with erectile dysfunction, there is an opportunity to consider other health issues and screen for underlying causes. Erectile dysfunction is often associated with conditions that benefit from early detection such as diabetes, hypertension, and hyperlipidemia. It is therefore important to consider general health issues and to address lifestyle factors.

The specialist erectile dysfunction service

Although most men with erectile dysfunction will be managed in primary care, there is still a role for a specialist service. It is likely that these clinics will mainly treat men who have failed to respond to oral therapies and that they will maintain expertise in the use of other treatments, such as intracavernosal injection therapy and vacuum devices, referring the men when necessary to urological surgeons for penile prosthesis insertion. Many specialist clinics are run very effectively by specialist nurses.

Conclusions on male sexual dysfunction

NO-mediated relaxation of the smooth muscle of the corpus cavernosum is the key phenomenon leading to penile erection. In diabetes, there is impairment of NO production by autonomic nerve terminals (due to autonomic neuropathy) and by endothelial cells (due to endothelial cell dysfunction). Sildenafil and other PDE5 inhibitors work by inhibiting the breakdown of cGMP, the second messenger in the NO pathway, and hence enhance erections under conditions of sexual stimulation. These agents are safe and effective treatments and can be used to treat erectile dysfunction in a diabetes clinic or in general practice.

Female sexual dysfunction

It is the universal experience of diabetes professionals that women with diabetes rarely complain of sexual problems There may be good reasons for this. In physiological terms, the female equivalent of male erectile dysfunction is reduced vasocongestion of the vulva and vagina, leading to impaired arousal and reduced vaginal lubrication. Failure to achieve an erection makes sexual intercourse impossible, but reduced vaginal lubrication is easily overcome with simple treatments such as lubricating creams and may not even be considered to be abnormal by a postmenopausal woman. Although sexual problems may not often be volunteered by women with diabetes, there is good evidence that they are more common in diabetes. Studying and managing female sexual problems is complicated by the changing and overlapping definitions of female sexual dysfunction. An in-depth review of this subject is beyond the scope of this book. For practicing diabetes professionals, the categories used by the American Psychiatric Association's *Diagnostic and Statistical Manual of Mental Disorders* (DSM-5) provide a simple and workable classification for dealing with female sexual dysfunction [101, 102]. This has reduced the number of disorders to three:

1 *Female sexual interest/arousal disorder*. A lack of sexual interest or failure to become aroused.
2 *Female orgasmic disorder*. Difficulty achieving orgasm.
3 *Genito-pelvic pain/penetration disorder*. Dyspareunia or vaginismus.

All of the reviews of female sexual dysfunction in diabetes agree that there is great variation between published studies [103–105]. It is clear, however, that female sexual dysfunction is more common in both type 1 diabetes mellitus (T1DM) and T2DM than in women without diabetes. There is a general consensus that failure of arousal is significantly more common, occurring in 14–45% of women with diabetes [103, 106]. In contrast, studies have reported conflicting results on the prevalence of orgasmic disorder [107, 108] and genito-pelvic pain in diabetes [109, 110]. It would be reasonable to summarize the results of all the studies by saying that sexual dysfunction is more common in women with diabetes and is mainly characterized by failure of arousal but orgasmic problems and dyspareunia may also occur.

The studies of sexual function in women with diabetes have reported with much greater consistency that there is poor or no correlation between sexual dysfunction and risk factors associated with diabetes, including duration of diabetes, age, body mass index, complications of diabetes, glycemic control, and menopausal status [104, 105]. In contrast, female sexual dysfunction in diabetes is closely related to psychosocial factors. Enzlin et al. reported that in women with T1DM, sexual dysfunction was related to the presence of depression and the quality of the relationship [107]. In a follow-up study of the Diabetes Control and Complications Trial (DCCT) (type 1) cohort, multivariate analysis showed that only depression and marital status predicted female sexual dysfunction [111]. A study in women with T2DM reported the same findings, that only depression and marital status predicted sexual dysfunction [112].

Anecdotally, women with severe autonomic neuropathy can have an excellent sex life, unlike men, and so it is likely that there are differences between men and women in the way in which the autonomic nervous system controls genital responses [113]. Clearly, sexual dysfunction in women with diabetes, unlike men, cannot be viewed as mainly the end result of endothelial dysfunction and autonomic neuropathy and managed as such. It is a very different disease entity in which factors such as depression and relationship status have a central role.

Management of female sexual dysfunction

Many women attending a diabetes clinic will be over 50 years of age and some will have problems associated with the menopause, including vaginal dryness and dyspareunia. It can be difficult to distinguish the effects of the menopause from those of diabetes, but in practical terms the treatment is the same. Topical estrogen or simple lubricant gels are usually effective. Managing loss of libido in women with diabetes is more complex and beyond the scope of this book. It is much more likely to be due to psychosocial and relationship, rather than somatic, problems. Similarly, anorgasmia is complex and best left to a specialist, although it is worth

remembering that selective serotonin reuptake inhibitor antidepressants are a common cause.

The mechanism of action of PDE5 inhibitors suggests that they might improve arousal and vaginal lubrication. However, trials of PDE5 inhibitors for this purpose in women with and without diabetes have shown conflicting results. Measures of genital vasocongestion and clitoral blood flow have been reported to improve, but the impact on self-reported measures of sexual satisfaction has been disappointing [114, 115]. PDE5 inhibitors probably have little role in the management of sexual dysfunction in women with diabetes.

Genitourinary infections in women with diabetes

Vaginal candidiasis is a common finding in women with diabetes, particularly if the blood glucose control is poor, probably because yeasts thrive in a glucose-rich environment. Severe infection can be very irritating and painful and can interfere with sexual intercourse. Infections usually respond to conventional antifungal creams and pessaries; resistant cases usually respond to a single oral dose of fluconazole. To reduce the chances of reinfection, attempts should be made to improve diabetic control. The male partner may also need treatment for candidiasis for the same reason.

Other genital infections also occur in women with diabetes, but probably no more frequently than in the general population. These cases should be referred to the appropriate genitourinary service.

Conclusions on female sexual dysfunction

When asked, women with diabetes admit to an increased prevalence of sexual dysfunction, vaginal dryness, and impaired arousal in particular, but these are not common problems in the day-to-day management of diabetes. Psychosocial factors are much more important than any degree of female sexual dysfunction that occurs as a result of diabetes. Arousal problems and vaginal dryness can be treated in the usual way with simple lubricants or topical estrogens. Other associated problems, such as vaginal candidiasis, should also be addressed. If there are relationship problems, referral to a counselor should be considered.

Contraception

Contraception and family planning are especially important in women with diabetes. Poor glycemic control during the first trimester of pregnancy is associated with an increased risk of fetal morbidity and mortality [116–118]. It is therefore essential that women with diabetes are advised to plan their pregnancies and achieve strict control of their diabetes prior to conception (see Chapter 61).

Contraindications to pregnancy

As medical and obstetric care has improved, the list of contraindications to pregnancy in women with diabetes has shrunk (see Chapter 61). If pregnancy is contraindicated, sterilization should be considered.

Method of contraception

Few diabetes organizations make any recommendation on the preferred method of contraception to be used in individuals with diabetes. The American Diabetes Association's recent Standards of Medical Care in Diabetes recommend that effective contraception is particularly important in women with diabetes, but the options and recommendations are largely the same as those for women without diabetes [119]. This is true, of course, but certain factors, in particular impact on risk factors and carbohydrate tolerance should be taken into consideration before choosing any particular method.

Hormonal contraception

The oral contraceptive pill (OCP) remains one of the popular methods of contraception in women with diabetes in high-income countries [120]. It is easy to understand why: it is simple to use and, most importantly, very reliable. If properly used, it has the lowest failure rate for any contraceptive method, apart from sterilization [121]. There have always been concerns, however, about the safety of hormonal contraception in women with diabetes.

Hormonal contraception, carbohydrate tolerance, micro- and macrovascular risk

There is no evidence that hormonal contraceptive affect carbohydrate tolerance or metabolic control in women with diabetes. A Cochrane review of studies examining the impact of steroidal contraception in women without diabetes reported there was minimal impact on carbohydrate metabolism and no major differences between different types of hormonal contraceptives [122]. In women with T1DM and T2DM, a more recent Cochrane review reported that there was no evidence that either combined or progestin-only contraceptives had a significantly different effect than non-hormonal contraception on metabolic control, lipid metabolism, or complications [123]. A small impact of hormonal contraception on metabolic control cannot be ruled out, but in practical terms we should not let any slight risk deter us from using it in women with diabetes.

We cannot yet be completely reassured, however, about the cardiovascular safety of hormonal contraception. Most reported studies were flawed or small. A large definitive study examining the effects on cardiovascular morbidity and mortality in women with diabetes is needed. When considering prescribing hormonal contraception to a woman with diabetes, the same factors should be considered as in a woman without diabetes. Smoking, hypertension, age, and vascular disease should be taken into account and the risks weighed for the individual woman. The World Health Organization's published criteria for contraceptive use provide useful practical advice on the choice of contraception in women with diabetes [124].

In practical terms, once the risks have been assessed, any combined or progestin-only contraceptive can be used in women with

T1DM or T2DM and patient preference should be taken into account. Any woman taking hormonal contraception should be reviewed regularly for assessment of blood pressure and serum lipids.

Combined hormonal contraceptive preparations carry an increased risk of venous thromboembolism. The risk is probably greatest (50–80% increase) with the "third-generation" progestins desogestrel and gestodene compared with preparations containing levonorgestrel [125]. The risk remains very small, however, and these are still safe preparations. There is as yet no evidence that progestin-only contraceptives are associated with an increased risk of thrombosis.

The intrauterine contraceptive device (IUD)

The IUD is a safe and effective form of contraception in women with diabetes. Early concerns about the risk of pelvic inflammatory disease in diabetes were largely unfounded; studies have suggested no increased risk of pelvic inflammatory disease in women with T1DM [126] or T2DM [127]. Similarly, early suggestions of an increased failure rate for IUDs in women with diabetes have not been borne out [126].

Barrier methods

Since the advent of acquired immune deficiency syndrome (AIDS), the condom has been widely advocated to reduce the risk of transmission of sexually transmitted diseases. It has a higher failure rate than OCPs and IUDs and for this reason is not recommended if pregnancy is contraindicated. For high-risk individuals, many genitourinary clinics recommend a combination of the OCP and condom to minimize the risk of pregnancy and sexually transmitted diseases—a technique known as "double-Dutch."

Emergency contraception

Three methods of emergency contraception are licensed in the UK and are available in many other countries: progestogen-only and combined estrogen–progesterone pills, and the copper IUD. The hormonal preparations can be taken up to 72 h after unprotected intercourse, but are most effective if taken within 24 h [128]. Nausea was reported in 23% and vomiting in ~6% of the women who used the progesterone-only regimen. Women with T1DM should be warned of these potential side effects. Little work on the use of these agents in women with diabetes has been published, but they may have a role in the prevention of unplanned pregnancies occurring at a time of poor metabolic control.

Summary

All women with diabetes of reproductive age should receive good contraceptive advice, as unplanned pregnancies occurring while glycemic control is poor carry an increased risk of morbidity and fetal abnormalities. Most forms of contraception are safe and effective in women with diabetes. The oral contraceptive pill has an important role, as it is very reliable and well tolerated.

Hormone replacement therapy

Few areas of medicine have gone through as many changes in perception in modern times as hormone replacement therapy (HRT). It was used as a treatment for osteoporosis and menopausal symptoms but had become regarded as a potential treatment to reduce cardiovascular risk, largely based on observational studies. In 2001, a survey of general practitioners and hospital doctors in the UK suggested that the majority would advise HRT for women with diabetes as prophylaxis for cardiovascular disease [129]. Attitudes changed almost overnight, however, following the publication of the Women's Health Initiative trial in 2002 [130]. This was a large, randomized study of combined estrogen and progesterone HRT that was stopped early because of increased adverse outcomes including cardiovascular disease, stroke, thromboembolism, and breast cancer. Further evidence has accumulated and now HRT is viewed largely as a short-term treatment for menopausal symptoms that does not increase cardiovascular risk but is not without risk. Many women with diabetes are postmenopausal, and so diabetes professionals need to be aware of the potential risks and benefits.

HRT and glucose tolerance

There is evidence that HRT does not worsen glucose tolerance in women with or without diabetes and may produce a slight amelioration. In women without diabetes, estradiol and low-dose conjugated estrogens are associated with an improvement and no effect on insulin sensitivity, whereas higher doses of conjugated estrogens and alkylated estrogens may cause deterioration of glucose tolerance [131–133].

In postmenopausal women with diabetes, estradiol has been reported to improve the fasting blood glucose concentration and glycated hemoglobin [134]. A larger observational study of over 15,000 women with T2DM also reported that HRT was associated with an improvement in HbA_{1c} [135]. Any potential benefit to glucose tolerance is limited to oral HRT preparations; transdermal estradiol does not appear to have any effect on glucose tolerance [136].

HRT and lipids

Like glucose tolerance, the effect of HRT on lipid profiles appears to be at worst neutral and it may be slightly beneficial. In women without diabetes, estrogens reduce total and low-density lipoprotein (LDL) cholesterol and increase high-density lipoprotein (HDL) cholesterol and triglyceride levels [137, 138]. Transdermal estrogen preparations have a beneficial effect on plasma lipids, reducing LDL cholesterol and triglycerides and increasing HDL cholesterol [139].

The effect of HRT on lipid profiles in women with diabetes has been reported in several studies. In a small, randomized crossover study of overweight women with T2DM, conjugated estrogen therapy reduced central obesity, HbA_{1c}, and total cholesterol,

and improved physical functioning [140]. In another small, randomized crossover study, conjugated estrogens reduced total and LDL cholesterol and increased HDL cholesterol in both women with and without diabetes. The addition of medroxyprogesterone acetate abolished the increase in HDL in both groups. There was no apparent effect on fasting glucose or insulin levels [141]. In the largest study, 61 postmenopausal women received combined HRT in a randomized crossover design. HRT reduced total and LDL cholesterol, but there was no change in serum HDL or triglyceride levels [142].

HRT and blood pressure

HRT can be prescribed to hypertensive postmenopausal women under careful supervision. One of the few studies of HRT and blood pressure in diabetes suggested that it can be prescribed without any adverse effect on ambulatory blood pressure measurements in hypertensive and normotensive women [143].

HRT and ischemic heart disease

Early case–control studies suggested that HRT reduces the risk of ischemic heart disease in postmenopausal women by 30–50% [144, 145]. Subsequent clinical trials, however, reported very different results, which shows the limitations of case–control studies [130, 137]. A reasonable summary of subsequent studies would be that there is certainly no evidence that HRT reduces cardiovascular risk but it probably does not increase it [146, 147]. It is, however, associated with an increase in thromboembolic disease. No large studies on the effect of HRT on the risk of ischemic heart disease in women with diabetes have been reported. Therefore, when managing a postmenopausal woman with diabetes, guidance for the general population should probably be followed. Recently published guidance from the National Institute for Health and Care Excellence (NICE) provide useful practical advice [148]. In brief, HRT should be considered as a short-term treatment for menopausal symptoms. Cardiovascular risk factors are not a contraindication provided that they are adequately managed. Transdermal preparations should be considered if there is a history of thromboembolic disease.

HRT and osteoporosis

There is evidence to suggest that women with T1DM have reduced bone mineral density at the time of diagnosis [149]. Although women with T2DM might be expected to be protected from osteoporosis because of their increased tendency to obesity, they would appear to be at increased risk of hip fracture (Chapter 53). A very large prospective cohort study of postmenopausal women in Iowa reported that women with diabetes had a 1.7-fold higher risk of hip fracture than women without diabetes [150]. Hence the benefits of HRT in reducing the risk of osteoporotic fractures would appear to be at least as great in women with diabetes as in those without diabetes, and HRT should be considered in all postmenopausal women with diabetes with osteoporosis.

Summary

HRT is can be used as a short-term treatment for the symptoms of the menopause. It has no adverse effects on glycemic control or lipid profiles and may improve both. It does not appear to increase cardiovascular risk. It should be considered in all women with diabetes with an appropriate indication.

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50 Gastrointestinal Manifestations of Diabetes

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Key points

- Diabetic enteropathy refers to all the gastrointestinal (GI) complications of diabetes, which can affect the entire gastrointestinal tract.
- GI symptoms in diabetes include dysphagia, dyspepsia, gastroparesis, abdominal pain, constipation, diarrhea, and fecal incontinence. Some GI disturbances (e.g. delayed gastric emptying) are often asymptomatic.
- Although these GI symptoms are not uncommon among persons with diabetes in clinical practice, the prevalence of GI manifestations among such people in the community is not substantially higher than in the general population.
- These GI manifestations can reduce quality of life and nutrition and also impair glycemic control.
- These symptoms are attributed to GI sensorimotor dysfunctions resulting primarily from extrinsic and intrinsic nerve (i.e. enteric) dysfunction.
- The investigations are tailored to the presenting symptoms, and require tests to exclude an organic disorder (e.g. gastric outlet obstruction in gastroparesis), to confirm GI sensorimotor dysfunctions (e.g. delayed gastric emptying), and to identify complications (e.g. small intestinal bacterial overgrowth).
- The management of GI symptoms in diabetes relies primarily upon improving control of glycemia and symptomatic measures, in addition to attention to the individual's state of hydration and nutrition.

Introduction

Although most attention has traditionally been focused on the stomach, diabetes can affect the entire gastrointestinal (GI) tract. The term *diabetic enteropathy* refers to all the GI complications of diabetes. GI involvement may be asymptomatic or manifest as symptoms, i.e. dysphagia, heartburn, nausea and vomiting, abdominal pain, constipation, diarrhea, and fecal incontinence. These manifestations may affect quality of life, impair nutrition, and affect glycemic control.

Epidemiology

Studies in selected groups, often from tertiary referral centers, suggest that GI symptoms are common in diabetes [1, 2]. However, these studies are prone to selection and other biases, which are avoided by studies conducted among people with diabetes in the community, where the prevalence of GI symptoms is either not different from or only slightly higher than for people without diabetes. Thus, in the Rochester Diabetic Neuropathy Study, only 1% of people with diabetes had symptoms of gastroparesis and only 0.6% had nocturnal diarrhea [3]. In another study from Olmsted County, Minnesota, the prevalence of GI symptoms (i.e. nausea and/or vomiting, dyspepsia, heartburn, irritable bowel syndrome, constipation, and fecal incontinence) was not significantly different between individuals with either type 1 (T1DM) or type 2 diabetes mellitus (T2DM) and age-matched people without diabetes [4]. However, people with T2DM and men with T1DM used laxatives more frequently than people without diabetes. Moreover, that study and a Finnish population-based study reported that people with T1DM had a lower prevalence of heartburn [5]. In contrast to these studies, a study in Australia found that the prevalence of several upper and lower GI symptoms was higher in 423 people with predominantly (95%) T2DM than in people without diabetes [6].

Compared with those studies, which were anchored by symptoms alone (i.e. not diagnostic tests), the cumulative 10-year incidence of gastroparesis has been estimated at 5.2% in T1DM and 1% in T2DM in a community sample of people with diabetes [7]. In that study, gastroparesis was documented by physician diagnosis based on delayed gastric emptying with scintigraphy, or by symptoms and retained food at endoscopy. However, because gastroparesis was identified only in people who presented for care, people who had an asymptomatic delay in gastric emptying may not have been identified. Hence the estimated incidence and prevalence of gastroparesis are critically dependent on definition [8].

Textbook of Diabetes, Fifth Edition. Edited by R. Holt, C. Cockram, A. Flyvbjerg and B. Goldstein.

Studies of the natural history of gastroparesis have been limited by relatively small numbers of participants, potential referral bias, or short follow-up periods. One study suggested that delayed gastric emptying and symptoms are both relatively stable over 12 or 25 years [9]. In a clinic-based study, diabetic gastroparesis was associated with severe symptoms, nutritional compromise, impaired glucose control, and a poor quality of life, independently of other factors such as age, tobacco use, alcohol use, or type of diabetes [10]. Two studies have investigated the association between diabetic gastroparesis and mortality or morbidity. The first, among 86 people with diabetes, of whom 56% had delayed emptying of solids and 28% had delayed emptying of liquids, ~25% had died by follow-up at least 9 years later. Gastroparesis was not associated with mortality after adjustment for other disorders [11]. However, this study did not ascertain the relationship between diabetic gastroparesis and other medical conditions. In another study that compared three parallel cohorts of people with diabetes (i.e. 94 with symptoms and delayed gastric emptying, 94 with classic symptoms of delayed gastric emptying but normal scintigraphy, and 94 with no symptoms of gastroparesis), diabetic gastroparesis was associated with cardiovascular disease, hypertension, retinopathy, and increased hospitalization [12]. Compared with those with GI symptoms alone, people with diabetic gastroparesis also had more hospital days; mortality was also greater, but differences were not statistically significant. In the National Institute of Diabetes, Digestive and Kidney Diseases Gastroparesis Clinical Research Consortium, the incident death rate was significantly higher in persons with diabetes compared with idiopathic cases (0.0266 vs. 0.0094), and in those with delayed compared with normal gastric emptying (0.0189 vs. 0.0031) [13].

Taken together, these data suggest that GI manifestations are not uncommon among persons with diabetes presenting for care. However, in the general population, the prevalence of GI manifestations is not substantially higher among people with diabetes, perhaps partly because the prevalence of GI symptoms, mostly attributable to functional GI disorders (e.g. irritable bowel syndrome), among people without diabetes in the community is relatively high, and approaches 20%. Among people with GI symptoms, the gastric emptying assessment can identify those with a worse prognosis. Whether this increased morbidity is driven by gastroparesis is unknown. Data on long-term natural history in the community are lacking.

Pathophysiology

Gastrointestinal dysmotility in diabetes is caused by extrinsic (i.e. sympathetic and parasympathetic) neural dysfunction, hyperglycemia, and hormonal disturbances. More recently, a role for intrinsic (i.e. enteric) neuronal dysfunctions, resulting from loss of excitatory and inhibitory neurons and interstitial cells of Cajal, has also been implicated [14]. Neural dysfunctions have been attributed to several mechanisms (e.g. oxidative stress) described below and detailed elsewhere [15].

Normal gastrointestinal motor functions

GI motor function is primarily controlled by the intrinsic or enteric nervous system (i.e. the "little brain" in the digestive tract) and modulated by the extrinsic (i.e. parasympathetic and sympathetic) nervous system (Figure 50.1) [16]. While intrinsic and extrinsic controls are independent, the prevertebral ganglia integrate afferent impulses between the gut and the central nervous system and provide additional reflex control of the abdominal viscera. The parasympathetic arm is excitatory to

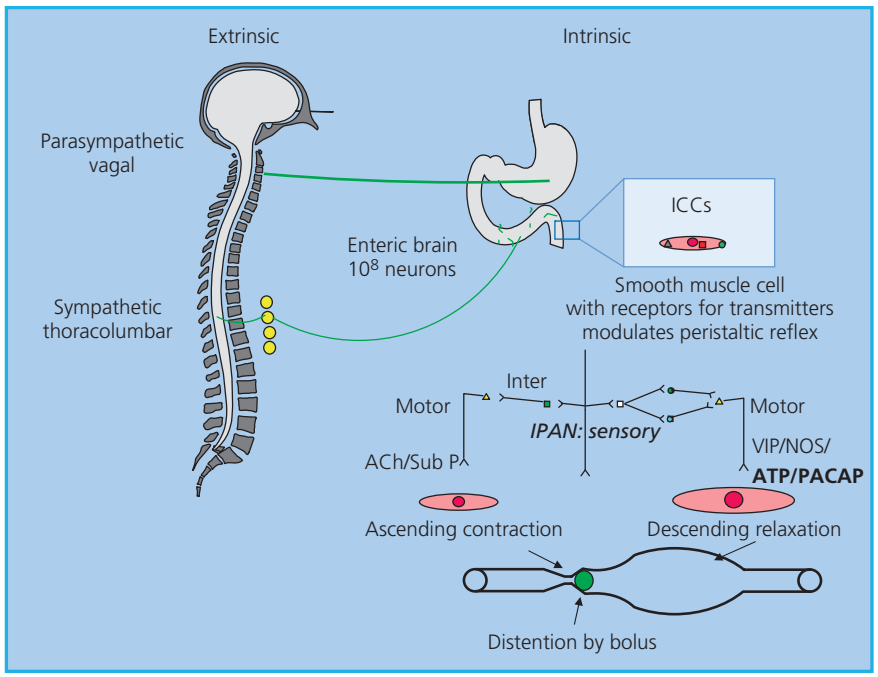

Figure 50.1 Control of gastrointestinal motility. Note that the extrinsic or autonomic nervous system modulates the function of the enteric nervous system, which controls smooth muscle cells through excitatory (i.e. acetylcholine [Ach], substance P [SubP]) or inhibitory (nitric oxide [NO], vasoactive intestinal peptide [VIP], pituitary adenylate cyclase activating peptide [PACAP]) neurotransmitters. ICC, interstitial cells of Cajal; IPAN, intrinsic primary afferent neurons. Source: Adapted from Camilleri M, Phillips SF. Disorders of small intestinal motility. *Gastroenterol Clin North Am* 1989; **18**:405–424.

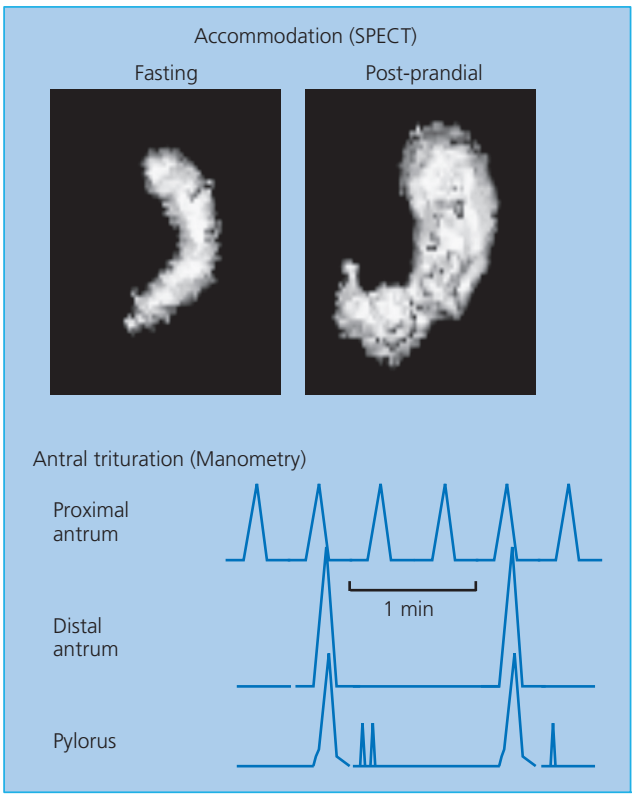

Figure 50.2 Assessment of gastric motor functions. Gastric accommodation can be assessed by measuring the postprandial change in gastric volume using single photoemission computed tomography (SPECT) (top). The stomach wall is labeled with intravenous [^{99m}Tc]pertechnetate. Food is subsequently transferred to the antrum. Manometry (bottom) demonstrates that the distal antrum and pylorus contract synchronously to grind food into smaller particles. Only particles 2 mm or smaller can be emptied through the pylorus.

non-sphincteric muscle and inhibits sphincters. The sympathetic component has opposite effects. The enteric nervous system consists of 100 million neurons that are organized in distinct ganglionated plexi, including the submucous plexus, which is primarily involved in absorption and secretion, and the myenteric plexus, which regulates motility. The interstitial cells of Cajal serve as pacemakers and also convey messages from nerve to smooth muscle. As with the somatic and autonomic nerves elsewhere, the gut's autonomic and enteric nervous system can be affected in diabetes. Derangements of the extrinsic nerves at any level may alter GI motility and secretion [17].

GI digestion and absorption require GI motility, gastric and pancreatic secretion, and GI hormonal release, which in turn modulate motor, secretory, and absorptive functions in the upper gut [18]. Traditionally, these processes are considered in three phases, i.e. cephalic, gastric, and intestinal, which are integrated and overlap. Normally, liquids, particularly non-caloric liquids, empty rapidly from the stomach in a linear fashion. In contrast, gastric emptying of solids follows an exponential pattern. During the first 45-min postprandial period (i.e. the lag phase), the gastric antrum grinds solids into particles smaller than 2 mm in size, so they can be emptied through the pylorus. During the lag phase, the stomach relaxes or accommodates, providing room for digestion to occur (Figures 50.2 and 50.3). Thereafter, solids are emptied in a linear fashion, with ~50% emptying in 2 h and 100% emptying in 4 h.

Pancreatobiliary secretions and mechanical processes ensure small intestinal digestion, which precedes absorption. The small intestine transports solids and liquids at approximately the same rate; the head of the column of liquid chyme may reach the cecum as early as 30 min after ingestion. As a result of the lag phase for the transport of solids from the stomach, liquids typically arrive in the colon before solids. However, it takes about 150 min for half the solid and liquid chyme of similar caloric density (assuming solids are presented in a triturated form to the small bowel) to traverse the small bowel. Complex carbohydrates or fat in the distal small intestine exert feedback control of proximal small intestinal motility (i.e. the small intestinal brake). Chyme is transferred from the ileum to colon in intermittent boluses. On average, it takes 36 h, with an upper limit of 65 h, to transfer contents from the cecum to the rectum. Compared with the stomach and small intestine, colonic transit is relatively prolonged, permitting digestion (i.e. fiber) and absorption (i.e. of water and electrolytes) to be completed.

Pathophysiology of diabetic enteropathy: insights from animal studies

In animal models, extrinsic neural dysfunction has been primarily ascribed to a loss of myelinated and unmyelinated fibers without much neuronal loss [19, 20]. The loss of nerve fibers is often multifocal, suggestive of ischemic injury. Within the enteric nervous system, reduced neuronal staining and, to a lesser extent, neuronal loss, particularly inhibitory neurons expressing nitric oxide synthase (NOS), have been described in several animal models of diabetes [15]. In theory, this reduction in nitrergic inhibitory functions may contribute to impaired gastric accommodation and accelerated intestinal transit in diabetes. Reduced sympathetic inhibition may also contribute to accelerated intestinal transit. Since nitric oxide (NO) is a mediator of pyloric relaxation, loss of NOS may impair pyloric relaxation, and thereby retard gastric emptying. Loss of interstitial cells of Cajal, documented in several animal models and case reports of diabetes, may also contribute to gut dysmotility [14, 21]. In addition, loss of interstitial cells of Cajal and increase in CD45 and CD68 immunoreactivity are the most common enteric neuropathological abnormalities in diabetic and idiopathic gastroparesis [22, 23].

Several mechanisms, including apoptosis, oxidative stress, advanced glycation end products, and neuroimmune mechanisms, may be responsible for neuronal loss and gut dysmotility [15]. The loss of interstitial cells of Cajal has been attributed to a reduction in heme–oxygenase (HO-1) and other protective mechanisms against hyperglycemia [14]. The effects of diabetes on neuronal morphology and functions are reversible. Insulin or pancreas transplantation improved glycemic control and the axonopathy affecting autonomic nerves in rats with diabetic

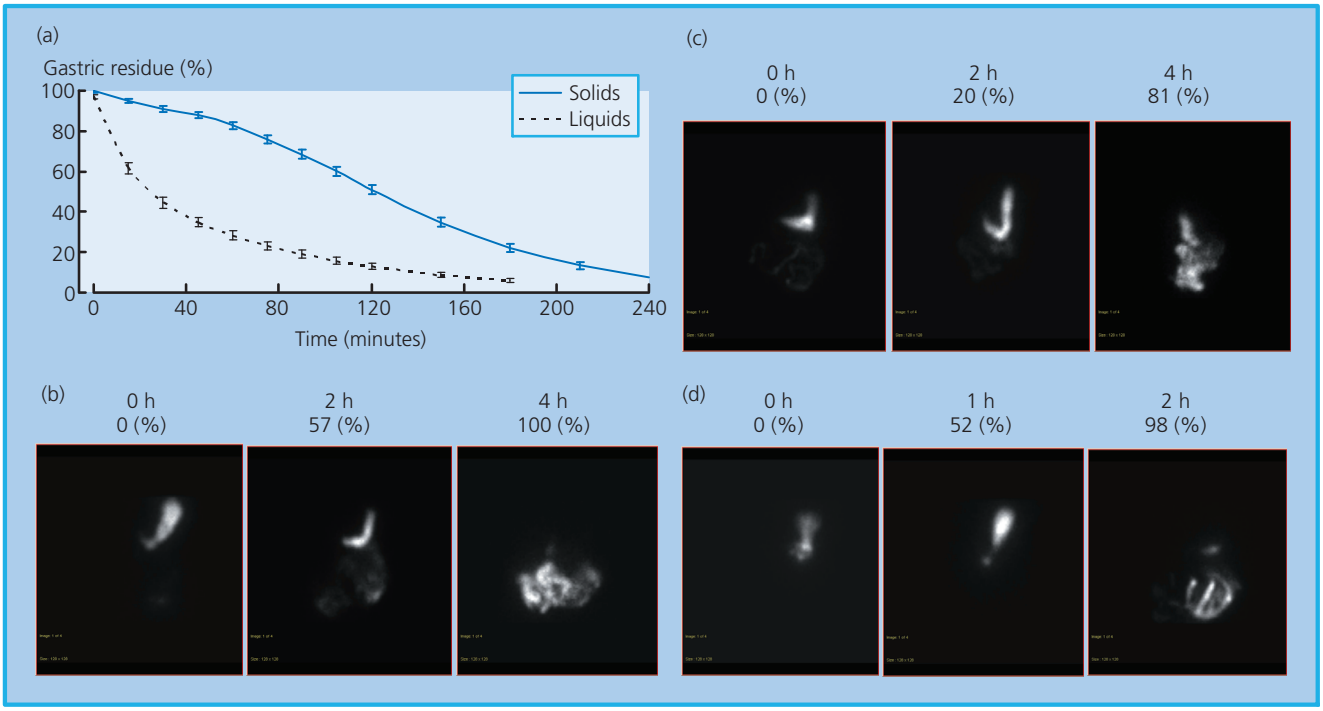

Figure 50.3 Assessment of gastric emptying by scintigraphy. Normally liquids are emptied in a linear manner whereas solid emptying has an exponential profile, characterized by an initial lag phase, followed by a more rapid, linear emptying (a). The lag phase corresponds to the time required for antral trituration and gastric accommodation, during which ~10% of solids are emptied (b), (c), (d). Representative examples of normal, delayed, and accelerated gastric emptying, respectively, of an egg meal, labeled with ^{99m}Tc, in people with diabetes. At time 0 (i.e. first image in each panel), the entire meal was in the stomach. Thereafter, the normal ranges for gastric emptying are 11–39% at 1 h, 40–76% at 2 h, and 84–98% at 4 h.

autonomic neuropathy [24]. Insulin also restored expression of NOS and gastric emptying in animal models of diabetes whereas insulin and insulin-like growth factors prevented the loss of interstitial cells of Cajal in cultures [25, 26]. Since interstitial cells of Cajal do not express receptors for either hormone, these effects are perhaps mediated by smooth muscle secretion of stem cell factor, which is the most important growth factor for interstitial cells of Cajal, rather than directly by insulin and insulin-like growth factors [14]. Overexpression of glial cell line-derived neurotrophic factor, a trophic factor for enteric neurons, in transgenic mice reversed hyperglycemia-induced apoptosis of enteric neurons and improved gastric emptying and intestinal transit [27].

Pathophysiology of diabetic enteropathy in humans

Gastric dysfunctions

Neuropathy

Diabetes is associated with accelerated or delayed gastric emptying, increased and reduced gastric sensation, and impaired gastric accommodation (Figure 50.4). A vagal neuropathy can cause antral hypomotility and/or pylorospasm, which may delay gastric emptying [28]. The pathophysiology of rapid gastric emptying in diabetes is less well understood. Conceivably, impaired gastric accommodation resulting from a vagal neuropathy [29] may increase gastric pressure and thereby accelerate gastric emptying of liquids. However, the relationship between rapid gastric emptying and impaired gastric accommodation has not been substantiated. The relationship between vagal neuropathy and impaired postprandial accommodation is unclear, since accommodation may be preserved even in persons with diabetes with vagal neuropathy [30], perhaps reflecting non-vagal adaptive mechanisms involving enteric neurons [31]. Some persons with diabetes and gastroparesis also have small intestinal dysmotility, more frequently characterized by reduced than by increased motility [32]. Small bowel dysmotility may also contribute to gastric stasis.

Hyperglycemia

Acute hyperglycemia delays gastric emptying in healthy individuals and in people with T1DM [33–36]. These effects may be explained by hyperglycemia-induced suppression of antral motility and migrating motor activity (i.e. the intestinal "housekeeper") [37–39]. However, the effects of acute hyperglycemia on gastric emptying are modest. Indeed, even in T1DM, severe acute hyperglycemia (i.e. 16–20 versus 4–8 mmol/L) prolonged the gastric emptying half-time by only 17 min (i.e. from 124 to 141 min). Acute modulation of blood glucose within the physiological postprandial range (4–8 mmol/L) can also delay gastric emptying, to a lesser extent [36]. Cross-sectional studies suggest that higher glycated hemoglobin concentrations are associated with a higher prevalence of GI symptoms and slower gastric emptying among

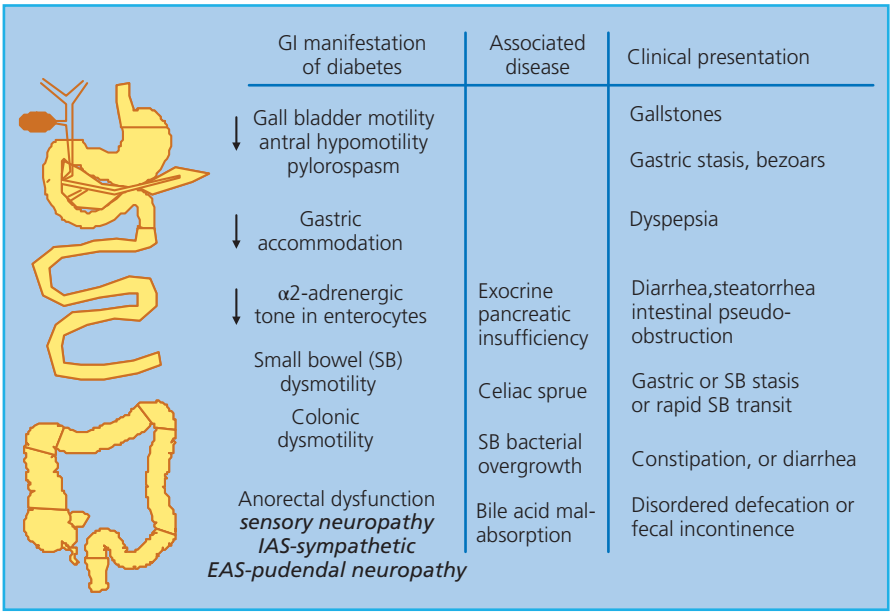

Figure 50.4 Pathophysiology of diabetes enteropathy in humans. IAS, internal anal sphincter; EAS, external anal sphincter. Source: Adapted from Camilleri M. Gastrointestinal problems in diabetes. *Endocrinol Metab Clin North Am* 1996; **25**:361–378.

people with diabetes in the community [6, 40]. Although strict glycemic control improves neural, renal, and retinal functions in diabetes, the impact on gastric emptying is unclear [41]. Indeed, in the only study that addressed this question, improved glycemic control did not improve gastric emptying 1 week later in 10 people with T2DM [42]. In addition to hyperglycemia, electrolyte imbalances due to diabetic ketoacidosis (e.g. hypokalemia) and uremia may also aggravate impaired motor function in persons with diabetes. Iatrogenic gastroparesis may result from treatment with amylin analogs such as pramlintide [43] or GLP-1 receptor agonists (such as liraglutide and exenatide). The latter has been documented in the literature in the gastric emptying of liquids [44, 45], with preliminary data proving clinically relevant delays in the gastric emptying of solids [46].

Diabetic diarrhea

It is useful to categorize the pathophysiology of diabetic diarrhea into conditions that are or are not associated with malabsorption (Figure 50.5). Involvement of sympathetic fibers, which normally inhibit motility and facilitate absorption via α_2-adrenergic

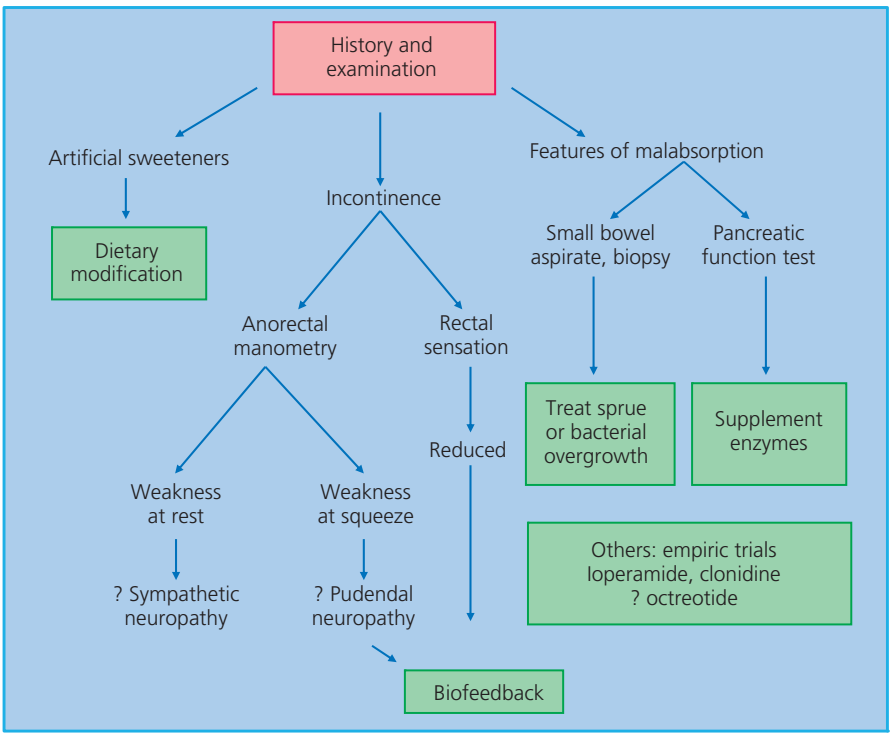

Figure 50.5 Management of diarrhea in diabetes mellitus. Source: Adapted from Camilleri M. Gastrointestinal problems in diabetes. *Endocrinol Metab Clin North Am* 1996; **25**:361–378.

receptors, can result in accelerated small intestinal transit and cause diarrhea [47]. Artificial sweeteners such as sorbitol may also contribute to diarrhea. People with rapid ileal transit may have bile acid malabsorption [48, 49] and deconjugated bile acids induce colonic secretion.

Features suggestive of malabsorption such as anemia, macrocytosis, or steatorrhea should prompt consideration of bacterial overgrowth, small bowel mucosal disease, or pancreatic insufficiency. Small intestinal dysmotility predisposes to bacterial overgrowth, which can cause bile salt deconjugation, fat malabsorption, and diarrhea. Although T1DM is associated with celiac disease, most people with celiac disease and T1DM in the community are asymptomatic [50]. Chronic pancreatic insufficiency may result from pancreatic atrophy, disruption of cholinergic enteropancreatic reflexes, or elevated serum hormonal levels of glucagon, somatostatin, and pancreatic polypeptide, which reduce pancreatic enzyme secretion [51]. However, the association between chronic pancreatic insufficiency and diabetes is uncommon. Moreover, because there is sufficient pancreatic reserve, only 10% of pancreatic function is sufficient for normal digestion.

Fecal incontinence

Loose stools and anorectal dysfunctions contribute to fecal incontinence in diabetic diarrhea. Compared with continent persons with diabetes and people without diabetes, people with diabetes and fecal incontinence have a higher threshold for rectal perception of balloon distention (i.e. reduced sensation) [52, 53]. A sympathetic neuropathy may impair internal anal sphincter functional and anal resting pressures and a pudendal neuropathy may result in reduced anal squeeze pressure.

Constipation

The mechanisms of constipation in diabetes have not been carefully studied and are poorly understood. Clinical observations suggest that, similarly to idiopathic chronic constipation, both colonic dysmotility and anorectal dysfunctions (i.e. impaired anal sphincteric relaxation during defecation) may contribute to constipation in diabetes [54]. Persons with colonic dysmotility have an impaired colonic contractile response to a meal and delayed colonic transit [55]. People with reduced rectal sensation may not perceive the desire to defecate. Compared with euglycemia, acute hyperglycemia inhibited the colonic contractile response to gastric distention and proximal colonic contraction elicited by colonic distention in healthy people without diabetes [56]. However, acute hyperglycemia did not significantly affect fasting or postprandial colonic tone, motility, compliance, and sensation, or rectal compliance and sensation in healthy people [57].

In addition to these factors, it is also important to consider the role of psychological factors in the perception of GI symptoms. Indeed, psychosomatic symptoms are significantly associated with the reporting of GI tract symptoms [4]. Several medications have GI side effects, e.g. metformin can cause diarrhea, and among other medications, verapamil and anticholinergic agents can cause constipation.

Clinical manifestations

Dysphagia and heartburn

Esophageal dysmotility, typically characterized by impaired peristalsis with simultaneous contractions, is common, may cause dysphagia, and may be related to cardiovascular autonomic neuropathy [58]. The amplitude of peristaltic contractions and basal lower esophageal sphincter pressures are generally normal. Symptoms of gastroesophageal reflux are also common, particularly in persons with impaired gastric emptying who have vomiting. Rarely, recurrent vomiting may lead to Mallory–Weiss tears and bleeding.

Dysphagia and heartburn should prompt upper GI endoscopy to exclude reflux and other incidental mucosal diseases (e.g. candidiasis, neoplasms). Although manometry may reveal esophageal peristaltic disturbances in persons with significant dysphagia that is not explained by a structural lesion, it is unlikely to alter management, except for rare people in whom another disorder (i.e. achalasia) is responsible for dysphagia. Because of the high prevalence of coronary atherosclerosis in diabetes, testing for coronary artery disease should be considered when necessary in those with chest pain.

Dyspepsia and gastroparesis

Although gastroparesis refers to a syndrome characterized by symptoms (i.e. nausea, vomiting, early satiation after meals, and impaired nutrition) and objective evidence of markedly delayed gastric emptying, gastric retention may be asymptomatic [59], perhaps because of the afferent dysfunction associated with vagal denervation [60]. Nausea and vomiting often occur in episodes lasting days to months or in cycles. Nausea and vomiting may be associated with impaired glycemic control and often cause hypoglycemia, perhaps because delivery of food into the small bowel for absorption is not sufficient to match the effects of exogenous insulin.

Consistent with the concept of a paralyzed stomach, the term gastroparesis should be restricted to people with markedly delayed gastric emptying. When the delay in gastric emptying is not severe, the term diabetic dyspepsia is perhaps more appropriate. Dyspepsia is characterized by one or more, generally postprandial, upper GI symptoms (i.e. bloating, postprandial fullness, and upper abdominal pain). Typically, vomiting is not severe, but significant weight loss secondary to reduced caloric intake is not unusual in people with dyspepsia. In addition to delayed gastric emptying, impaired gastric accommodation and abnormal (i.e. increased or decreased) gastric sensation may also contribute to symptoms in diabetes [61, 62]. Nonetheless, the distinction of dyspepsia from gastroparesis is challenging since there is no official distinction between moderately and severely delayed gastric emptying. Clinical experience suggests that gastric emptying of <65% at 4 h reflects a significant delay, as it is often associated with nutritional consequences, the need for nutritional supplementation, jejunal feeding, or gastric decompression [63].

Table 50.1 Symptoms and signs of autonomic dysfunction.

Sympathetic	Parasympathetic
Failure of pupils to dilate in the dark	Fixed, dilated pupils
Fainting, orthostatic dizziness	Lack of pupillary accommodation
Constant heart rate with orthostatic hypotension	Sweating during mastication of certain foods
Absent piloerection	Decreased gut motility
Absent sweating	Dry eyes and mouth
Impaired ejaculation	Dry vagina
Paralysis of dartos muscle	Impaired erection
	Difficulty with emptying urinary bladder
	Recurrent urinary tract infections

Gastric retention may be asymptomatic in some people, possibly owing to afferent dysfunction in the setting of vagal denervation, and delayed gastric emptying may be associated with recurrent hypoglycemia in people without upper GI symptoms.

Persons with diabetic gastroparesis frequently have longstanding T1DM with complications (i.e. retinopathy, nephropathy, peripheral neuropathy, and other forms of autonomic dysfunction, including abnormal pupillary responses, anhidrosis, gustatory sweating, orthostatic hypotension, erectile dysfunction, retrograde ejaculation, and dysfunction of the urinary bladder) (Table 50.1). In contrast, it has been suggested that rapid gastric emptying of liquids is a relatively early manifestation of T2DM [64–68]. Clinicians have relied on these manifestations, and on certain symptoms (e.g. vomiting of undigested food eaten several hours previously and weight loss) and signs (e.g. a gastric succussion splash or features of an autonomic neuropathy) to predict delayed gastric emptying in people with diabetes who present with upper and GI symptoms. However, several studies have shown that symptoms are of limited utility for predicting delayed gastric emptying in diabetes [69–75]. Similarly, the type and duration of diabetes, glycated hemoglobin levels, and extraintestinal complications were, in general, not useful for discriminating normal from delayed or rapid gastric emptying. However, significant weight loss and a neuropathy were risk factors for delayed and rapid gastric emptying, respectively [76]. In summary, upper GI symptoms in persons with diabetes may result from accelerated gastric emptying, often in association with vagal neuropathy and impaired proximal gastric accommodation. Hence it is essential to measure gastric emptying in people with upper GI symptoms.

Persons with diabetic gastroparesis may have other features caused by autonomic neuropathy. Table 50.2 provides a summary of commonly performed autonomic tests.

In persons with upper GI symptoms, an upper GI endoscopy is necessary to exclude peptic ulcer disease and neoplasms, either of which can cause gastric outlet obstruction. Upper endoscopy may reveal gastric bezoars, which suggest antral hypomotility. Metabolic derangements, such as diabetic ketoacidosis or uremia, and medications, particularly opiates, calcium channel blockers, and anticholinergic agents, may contribute to dysmotility. Rarely, people with gastroparesis present with retrosternal or epigastric pain, and cardiac, biliary, or pancreatic disease may be considered.

Barium X-rays of the small intestine or enterography with computed tomography should be considered only when the clinical features raise the possibility of small intestinal obstruction. Gastric emptying of solids should be quantified by scintigraphy or stable isotope breath test [77, 78], and antroduodenal manometry may be considered in selected circumstances. Measurement of pressure profiles in the stomach and small bowel can confirm the motor disturbance and may facilitate the selection of patients for enteral feeding (Figure 50.6). People with gastroparesis due to predominant antral hypomotility as a result of the diabetic enteropathy may tolerate feeding delivered directly into the small bowel whereas those with a more generalized motility disorder may not.

Diarrhea and constipation

The term *diabetic diarrhea* was first coined in 1936 by Bargen at the Mayo Clinic to describe unexplained diarrhea associated with severe diabetes [79]. Diabetic diarrhea is typically chronic, may be episodic, and can be severe. Diarrhea can occur at any time but is often nocturnal and may be associated with anal incontinence, which may indicate internal anal sphincter dysfunction. Persons with diarrhea often have symptoms of delayed gastric emptying such as early satiety, nausea, and vomiting.

Constipation may occur in isolation or alternate with episodes of diarrhea. Many physicians regard constipation to be synonymous with infrequent bowel movements. It is important to characterize symptoms because many people have misconceptions about normal bowel habits. For example, it is not necessary to have a bowel movement daily—the normal range varies from three bowel movements every week to every day. Moreover, by constipation, people refer to one or more of a variety of symptoms (i.e. infrequent stools, hard stools, excessive straining during defecation, a sense of anorectal blockage during defecation, the need for anal digitation during defecation, and a sense of incomplete evacuation after defecation) [80]. Some of these symptoms (e.g. a sense of anorectal blockage during defecation) may suggest disordered evacuation. A careful rectal examination during relaxation and straining is needed to exclude rectal mucosal lesions and to detect the presence of rectal prolapse, rectocele, and disordered defecation. Normally, voluntary contraction is accompanied by upward and anterior motion of the palpating finger toward the umbilicus as the puborectalis contracts. Conversely, the puborectalis should relax and the perineum should descend (by 2–4 cm) during simulated evacuation. The rectal examination may suggest features (i.e. reduced or increased perineal descent, paradoxical contraction of puborectalis) of defecatory disorders.

Abdominal pain

Persons with diabetes are obviously susceptible to the usual causes of abdominal pain seen in the general population. There is an increased prevalence of gallstones because of altered gallbladder contractility and of mesenteric ischemia caused by generalized

Table 50.2 Commonly performed autonomic tests.

Test	Physiological functions tested	Rationale	Comments/pitfalls
Sympathetic function			
1. Thermoregulatory sweat test (% surface area of anhidrosis)	Preganglionic and postganglionic cholinergic	Stimulation of hypothalamic temp. control centers	Cumbersome, whole body test
2. Quantitative sudomotor axon reflex test (sweat output, latency)	Postganglionic cholinergic	Antidromic stimulation of peripheral fiber by axonal reflex	Needs specialized facilities
3. Heart rate and blood pressure responses			
Orthostatic tilt test	Adrenergic	Baroreceptor reflex	Impaired responses if intravascular volume is reduced
Postural adjustment ratio	Adrenergic	Baroreceptor reflex	Impaired responses if intravascular volume is reduced
Cold pressor test	Adrenergic	Baroreceptor reflex	Impaired responses if intravascular volume is reduced
Sustained hand grip	Adrenergic	Baroreceptor reflex	Impaired responses if intravascular volume is reduced
4. Plasma norepinephrine response to:			
Postural changes	Postganglionic adrenergic	Baroreceptor stimulation	Moderate sensitivity, impaired response if intravascular volume is reduced
Intravenous edrophonium	Postganglionic adrenergic	Anticholinesterase "stimulates" postganglionic fiber at prevertebral ganglia	False negatives caused by contributions to plasma norepinephrine from many organs
Parasympathetic function			
1. Heart rate (RR) variation with deep breathing	Parasympathetic	Vagal afferents stimulated by lung stretch	Best cardiovagal test available, but not a test of abdominal vagus
2. Supine/erect heart rate	Parasympathetic	Vagal stimulation by change in central blood volume	Cardiovagal test
3. Valsalva ratio (heart rate, max./min.)	Parasympathetic	Vagal stimulation by change in central blood volume	Cardiovagal test
4. Gastric acid secretory or plasma pancreatic polypeptide response to modified sham feeding or hypoglycemia	Parasympathetic	Stimulation of vagal nuclei by sham feeding or hypoglycemia	Abdominal vagal test, critically dependent on avoidance of swallowing food during test
5. Nocturnal penile tumescence	Pelvic parasympathetic7	Integrity of S2–4	Plethysmographic technique requiring special facilities
6. Cystometrographic response to bethanechol	Pelvic parasympathetic	Increase in intravesical pressure suggests denervation supersensitivity	Tests parasympathetic supply to bladder, not bowel

Source: Camilleri M, Ford MJ. Functional gastrointestinal disease and the autonomic nervous system: a way ahead? *Gastroenterology* 1994; **106**(4):1114–1118. Copyright 1994 Elsevier.

atherosclerosis. However, there is little evidence that altered gallbladder contractility per se (i.e. in the absence of gallstones) causes symptoms. Thoracolumbar radiculopathy may result in pain in a girdle-like distribution that does not cross the midline. Specific tests are indicated if the clinical features of pain suggest these disorders. It is essential to elicit a careful history.

Diagnostic tests

Typically, diagnostic testing is primarily guided by symptom pattern and severity. However, since persons with delayed gastric emptying are often asymptomatic, gastric emptying assessments should also be considered in those with unexplained hypoglycemia. After initial testing to identify disturbances of transit, more detailed testing with intraluminal techniques (i.e. manometry and/or a barostat) may be useful for characterizing motor dysfunctions and guiding therapy. Delayed gastric emptying can be documented by scintigraphy, stable isotope breath test, or the presence of a large amount of retained food in the stomach. Barium studies and scintigraphy using labeled liquid meals are of limited value for identifying dysmotility because the gastric emptying of liquids and semisolids (e.g. mashed potatoes) frequently is normal, even in the presence of moderately severe symptoms. The tests that are available to measure gastric emptying non-invasively are summarized in Table 50.3.

Assessment of solid emptying by means of a radiolabel that tags the solid phase of the meal is a more sensitive test with a well-defined normal range. The proportion of radioisotope retained in the stomach at 2 and 4 h distinguishes normal function from delayed gastric emptying with a sensitivity of 90% and a specificity of 70% [81]. The importance of obtaining scans for 4 h

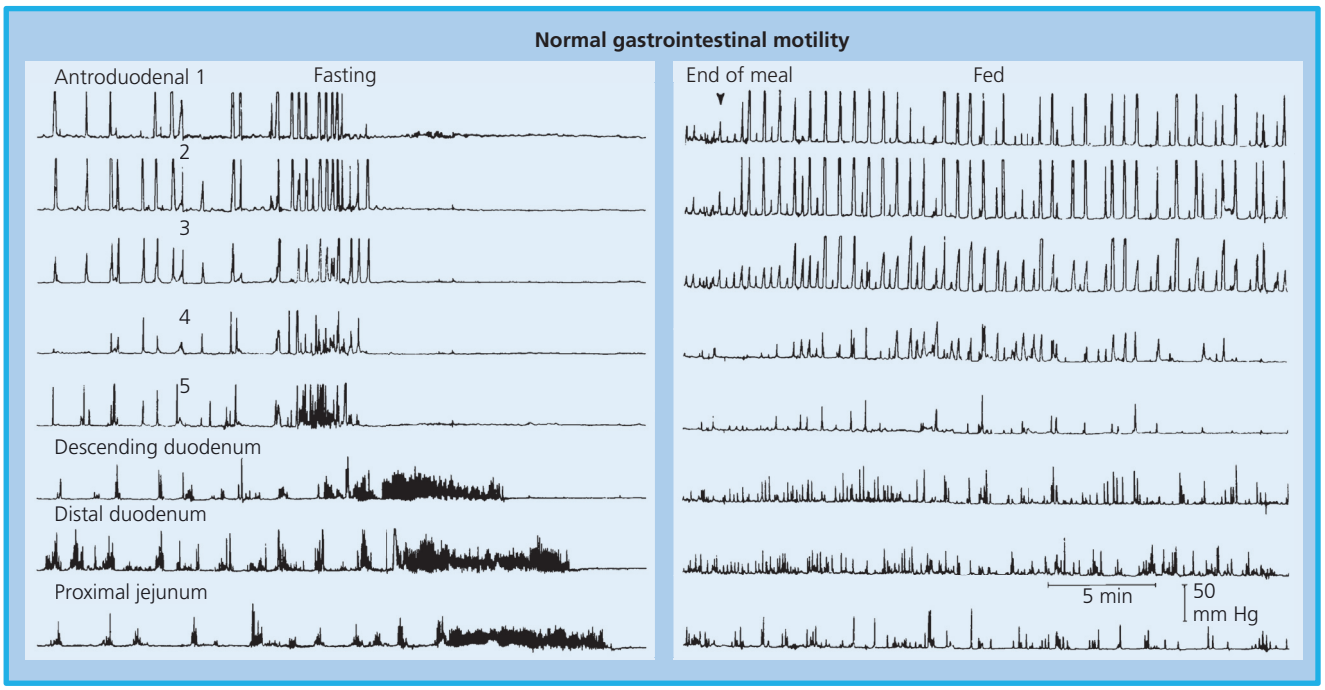

Figure 50.6 Normal manometric profile (fasting and postprandial). The migrating motor complex characteristic of fasting state is demonstrated by presence of quiescence (phase I), intermittent activity (phase II), and an activity front (phase III). The postprandial profile shows high-amplitude, irregular, but persistent phasic pressure activity at all levels. Source: Reproduced with permission from Malagelada J-R, Camilleri M, Stanghellini V. *Manometric Diagnosis of Gastrointestinal Motility Disorders*. New York: Thieme Publishers, 1986.

after a meal cannot be overemphasized. Since gastric emptying is slow initially, it is not accurate to extrapolate emptying from scans taken for a shorter duration. Another useful test for measuring solid-phase gastric emptying utilizes a standardized meal with biscuit enriched with ^{13}C, a substrate containing the stable isotope. When metabolized, the proteins, carbohydrates, and lipids of the *Spirulina platensis* or the medium-chain triglyceride octanoate give rise to respiratory CO_2 that is enriched in ^{13}C. Measurement of $^{13}CO_2$ breath content (a reflection of the amount of biscuit remaining in the stomach) by isotope ratio mass spectrometry allows the estimation of gastric emptying half-life [77, 78].

The wireless motility capsule using the SmartPill has been approved by the US Food and Drug Administration (FDA) for the evaluation of gastric emptying and colonic transit time in

Table 50.3 Non-invasive measurements of gastric emptying.

Feature	Gastric emptying by scintigraphy	Stable isotope breath test	Wireless pressure and pH capsule
Indication/function measured	Gastric emptying	Gastric emptying	Emptying and pressure amplitude
Device, assembly or special requirements	External gamma camera and isotope-labeled meal	Breath collection vials and stable isotope-labeled meal	Intraluminal capsule with miniaturized strain gauge and pH measurement
Placement of device	–	–	Capsule swallowed
Performance/versatility/ interpretation	Excellent, standardized meals, data acquisition and interpretation	Becoming standardized Performance related to mathematical analysis	Standard acquisition, delayed emptying fairly valid; pressures of unclear significance
Duration of study	Typically 4 h, could be added to small bowel and colon transit	3–4 h	6 h, could be added to small bowel and colon transit
Availability/potential use	+	+++	+
Costs	++	+	++

Source: Adapted with permission from Shin AS, Camilleri M. Diagnostic assessment of diabetic gastroparesis. *Diabetes* 2013; **62**:2667–2673. Copyright and all rights reserved. Material from this publication has been used with the permission of the American Diabetes Association.
The "+" signs signify the lowest (+) to the highest (+++) availability or potential use.

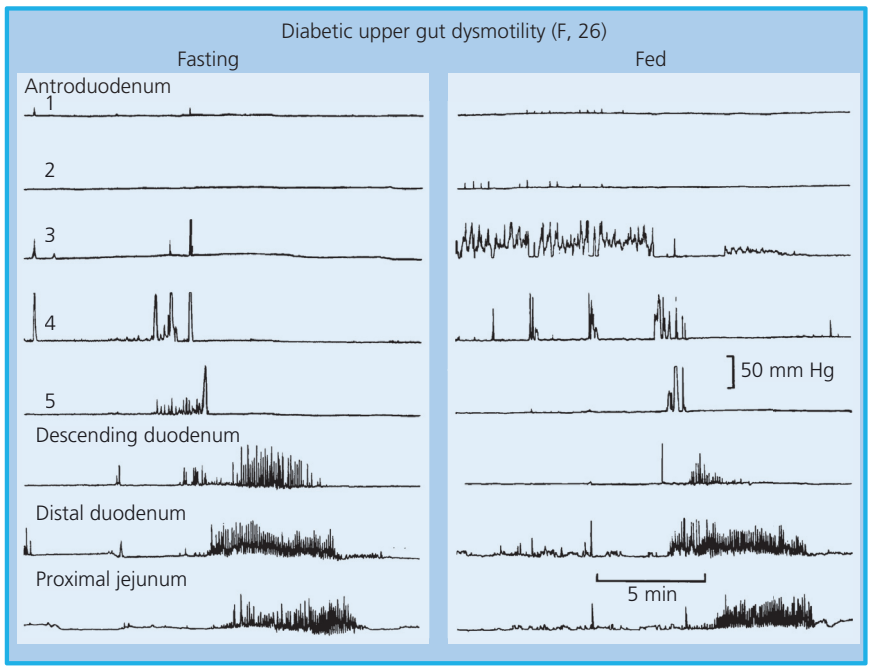

Figure 50.7 Manometric profile in a 26-year-old woman with diabetes and autonomic neuropathy, showing abnormal propagation of phase III of interdigestive motor complex and lack of a well-developed antral component in fasting tracing. Postprandially, note antral hypomotility, pylorospasm, and failure of meal to induce a fed pattern. Source: Reproduced with permission from Colemont LJ, Camilleri M. Chronic intestinal pseudo-obstruction: diagnosis and treatment. *Mayo Clin Proc* 1989; **64**:60–70.

people with suspected slow transit constipation, and for the measurement of pH, temperature, and pressure throughout the GI tract [82]; it is a safe and practical alternative to gastric electrical stimulation [83]. Sensed data are transmitted by the single-use capsule to a receiver worn by the patient, and pH values from 0.5 to 9.0, pressure activity, and temperature are recorded. Gastric emptying time is defined as the time from capsule ingestion to a rise in pH from gastric baseline to >4.0, marking the passage of the capsule from the antrum to the duodenum. Normal emptying of the capsule should occur within 5 h of ingestion. If it does not occur within 6 h, a maximum gastric emptying time value of 6 h is assigned [82]. The gastric emptying results with the wireless motility capsule are not as accurate as those using scintigraphy with a digestible solid meal. Its advantages include point-of-care use in ambulatory settings and avoidance of pitfalls of gastric electrical stimulation, such as radiation exposure, need for a gamma camera, and lack of standardized practices across centers [82]. The utility of the wireless motility capsule testing has been enhanced with data [84] showing that pressure profile measurements recorded by the capsule can differentiate persons with diabetic gastroparesis from healthy individuals by the significantly lower numbers of contractions and motility indices.

However, healthy individuals and (more likely) persons with gastroparesis may not have a phase III migrating motor complex contraction within 6 h, when the next meal is given, and capsule emptying may be inhibited by the suspension of the migrating motor complex by the meal. Other limitations include possible difficulty with capsule ingestion and the potential for capsule retention or obstruction. Use of the capsule is contraindicated in children and those with a known history of esophageal stricture.

For people with severe upper GI symptoms, antropyloroduodenal manometry is a specialized technique that assesses pressure profiles in the stomach and small bowel and also guides management. Manometry may also reveal hypomotility of the gastric antrum and/or an intestinal neuropathy (Figures 50.6 and 50.7). Individuals with selective or dominant abnormalities of gastric function may be able to tolerate enteral feeding (delivered directly into the small bowel), unlike those with a more generalized motility disorder.

Gastric accommodation in response to meal ingestion may be impaired in diabetes [85]. This may contribute to the GI symptoms of nausea, bloating, and early satiety. Imaging of the stomach wall using [^{99m}Tc]pertechnetate allows measurement of gastric volume after meal ingestion.

For persons with constipation, colonic transit, anorectal manometry, and rectal balloon expulsion tests provide a useful start. Anorectal manometry and the rectal balloon expulsion test generally suffice to diagnose or exclude defecation disorders; magnetic resonance imaging or barium proctography is required only in selected cases. Colonic transit is often delayed in people with defecatory disorders. Therefore, in those with slow colonic transit, slow transit constipation can only be diagnosed after excluding defecatory disorders. Intraluminal assessments of colonic phasic motility (by manometry) and tone (by barostat) often reveal other dysfunctions (e.g. impaired contractile responses to a meal) and/or pharmacological stimuli (e.g. bisacodyl or neostigmine) in persons with slow transit constipation. Colonic transit can be characterized by radiopaque markers, which, depending on the technique, takes 5–7 days, or by scintigraphy, which takes 24–48 h. Both techniques are equally accurate for identifying slow or rapid colonic transit.

Small intestinal dysmotility may manifest as one or more of the following features: abnormal migrating motor complexes, failure to convert from fasting to postprandial motor pattern, and/or

features of a vagal neuropathy (i.e. excessive number of fasting migrating motor complexes or persistent postprandial migrating motor complexes). Assessment of stool fat provides a useful differentiation point for diabetic diarrhea, as it indicates malabsorption as the pathophysiology leading to diarrhea. An upper endoscopy provides an opportunity to obtain duodenal aspirates for bacterial overgrowth and small bowel biopsy to exclude celiac disease. Lactose or glucose hydrogen breath tests rely on substrate metabolism by bacterial overgrowth in the small intestine with hydrogen release and breath excretion. However, studies have shown that the early peak is frequently due to rapid delivery of the substrate to the colon with bacterial metabolism by normal colonic flora rather than small bowel bacterial overgrowth [86]. To reduce the potential impact of this confounding factor (i.e. rapid intestinal transit), a more restricted definition to diagnose small intestinal overgrowth may be preferable, i.e. an early hydrogen peak (20 ppm), due to small intestinal bacteria, occurring at least 15 min before the later prolonged peak, corresponding to the passage of the remaining lactulose into the colon. However, even with more restricted definitions, the sensitivity and specificity of the lactulose hydrogen breath test in detecting small bowel bacterial overgrowth have been reported to be only 68 and 44% and for the glucose breath test 62 and 83%, respectively [86].

Management

The principles of management are to address fluid and nutritional requirements, improve glycemic control, and treat symptoms [87].

Gastroparesis and dyspepsia

Although nutritional requirements and symptoms can be addressed to a variable extent in persons with mild and compensated gastroparesis, those with severe gastroparesis often require hospitalization for one or more of the following measures: intravenous hydration and correction of metabolic derangements (ketoacidosis, uremia, hypoglycemia, hyperglycemia), nasoenteric decompression, and/or enteral nutrition to manage vomiting and nutritional requirements [63]. Parenteral nutrition may become necessary in cases of malnutrition. Bezoars may be mechanically disrupted during endoscopy, followed by gastric decompression to drain residual non-digestible particles.

Erythromycin at a dose of 3 mg/kg body weight intravenously every 8 h can accelerate gastric emptying [88, 89]. When oral intake is resumed, treatment with oral erythromycin 250 mg t.i.d. daily for 1–2 weeks is worthwhile. Thereafter, the prokinetic effects of erythromycin are limited by tachyphylaxis. Anecdotal findings suggest that erythromycin may be effective if courses are separated by a drug-free period, e.g. lasting 2 weeks. Hyperglycemia interferes with the prokinetic effect of intravenous erythromycin on gastric emptying in people with and without diabetes [39]. Since both liquids and homogenized solids are more readily emptied from the stomach than solids, liquid or blended food will be better tolerated. Frequent monitoring of blood glucose is essential during this phase but improved control of glycemia did not improve gastric emptying in people with poorly controlled T2DM [90].

For individuals with severe gastroparesis who do not respond to the measures outlined above, it may be necessary to bypass the stomach with a jejunal feeding tube. This procedure should be preceded by a trial of nasojejunal feeding for a few days with infusion rates of at least 60 mL of iso-osmolar nutrient per hour. It is preferable to place jejunal feeding tubes directly into the jejunum either by endoscopy or, if necessary, by laparoscopy or mini-laparotomy, rather than via percutaneous endoscopic gastrostomy tubes. Such tubes allow restoration of normal nutritional status but they are not without adverse effects. There is no evidence to suggest that gastrectomy relieves symptoms or enhances quality of life. People with gastroparesis often have concomitant small intestinal denervation, which is likely to cause persistent symptoms after gastrectomy [32, 91].

If the patient remains symptomatic, other prokinetic agents may be considered as adjuncts. In the United States, the only available medication is metoclopramide, a peripheral cholinergic and antidopaminergic agent. During acute administration, it initially enhances gastric emptying of liquids in diabetic gastroparesis, but its symptomatic efficacy is probably related to its central antiemetic effects. However, its long-term use is restricted by a decline in efficacy and by a troubling incidence of central nervous system side effects. Therefore, we prefer to prescribe a dose of 10 mg t.i.d., administered 30 min before meals, for a short duration; the higher dose is 20 mg t.i.d. A systematic review of trials concluded that there was limited evidence to support the use of domperidone, which is another dopaminergic antagonist not approved for use in the USA [92]. Endoscopic injection of botulinum toxin into the pylorus was not effective in controlled studies primarily of idiopathic gastroparesis [93, 94].

Although the FDA recognizes gastric electrical stimulation as a humanitarian use device for refractory gastroparesis, its use for this indication is controversial. Although published data suggest that the device reduces vomiting frequency only when the device is on, data submitted to the FDA indicated that electrical stimulation reduced vomiting frequency to a similar extent with the device turned off or on, suggesting a placebo response [95, 96]. Moreover, the device is expensive and does not accelerate gastric emptying. Between 10 and 20% of patients have device-related complications.

New motilin agonist

Although erythromycin is currently used "off-label" as a gastric prokinetic, it may induce antibiotic resistance, it is associated with tachyphylaxis [97], and it may inhibit cytochrome P-450 CYP3A4, leading to unwanted drug interactions. In addition, because erythromycin is extensively metabolized by cytochrome P-450 3A (CYP3A) isozymes, commonly used medications that inhibit the effects of CYP3A may increase plasma erythromycin concentrations, thereby increasing the risk of ventricular arrhythmias and sudden death [98]. These factors all point towards an

urgent need for a more selective motilin receptor agonist. A novel motilin agonist (camicinal) has significant promise, based on the hypothesis that the motilin receptors can be induced to preferentially signal ("biased agonism"), via particular pathways, to evoke different responses with therapeutic advantages/disadvantages, such as preferentially activating the β-arrestin pathway, enhancing the ability to recover faster from desensitization of the receptor [99].

GSK962040 (or camicinal) is a selective small-molecule motilin receptor agonist that has been shown to induce phasic contractions and increase GI motility in conscious dogs [100]. A separate study has shown that GSK962040 has a greater effect in mediating cholinergic activity in the antrum than the fundus and the small intestine [101]. Results of a phase II 28-day clinical study of effects on gastric emptying and symptoms, safety, tolerability, and pharmacokinetics in persons with T1DM and T2DM diabetes with gastroparesis are awaited.

New ghrelin agonist

Relamorelin (RM-131) is a novel pentapeptide ghrelin receptor agonist with greater potency in increasing GE in animal pharmacology studies than other ghrelin mimetics [102].

In two randomized, double-blind, placebo-controlled, crossover studies conducted in 10 people with T2DM or T1DM and prior documentation of delayed gastric emptying, relamorelin accelerated the gastric half-emptying time of solids [103, 104]. In a phase II study of persons with T1DM, relamorelin reduced upper GI symptoms, with the most impressive effects being observed in those with high baseline vomiting [105]. In individuals with chronic constipation, relamorelin also accelerated colonic transit [106].

Diabetic diarrhea

Diabetic diarrhea is treated symptomatically with loperamide, preferably administered 30 min before meals, in the dose range 2–16 mg per day. Consumption of artificial sweeteners that contain the osmotically active sugar substitute sorbitol should be reduced. Second-line approaches are clonidine, 0.1 mg orally [107] or by patch in those who do not experience significant postural hypotension. Amitriptyline, which has anticholinergic effects, may reduce intestinal cramping and transit. Octreotide (25–50 μg subcutaneously 5–10 min before meals) delays small intestinal transit [108] and may also reduce secretory diarrhea associated with rapid intestinal transit [109]. Although it has been suggested that octreotide reduces small bowel bacterial overgrowth in chronic intestinal pseudo-obstruction[110], the study assessed bacterial overgrowth by breath testing. Indeed, by delaying small intestinal transit, octreotide may predispose to bacterial overgrowth. Regulating stool consistency may also improve fecal continence. In addition, pelvic floor retraining with biofeedback therapy can improve rectal sensation and enhance coordination between perception of rectal distention and contraction of the external anal sphincter [53]. However, biofeedback therapy is less effective in people with markedly reduced rectal sensation. A descending colostomy may be required and may improve the quality of life in those with severe diarrhea associated with fecal incontinence.

Constipation

For people without pelvic floor dysfunction, chronic constipation can be generally managed with pharmacological agents (i.e. osmotic and stimulant laxatives) [111]. Pelvic floor retraining by biofeedback therapy is the cornerstone for managing defecatory disorders; laxatives are used as an adjunct to pelvic floor retraining [112]. Fiber supplementation, either with dietary supplementation or with fiber products (e.g. psyllium, 15–18 g daily), should be considered in people with inadequate fiber intake. Of the osmotic laxatives, polyethylene glycol (up to 17 g in 8 oz [225 mL] of water once or twice per day) is a widely used and safe over-the-counter agent. Although lactulose is a poorly absorbed disaccharide, lactulose syrup contains small amounts of absorbable sugars and may increase hyperglycemia. Magnesium compounds are safe, but individuals with impaired renal function may develop magnesium retention. Bisacodyl or glycerin suppositories are useful rescue agents in people who have not had a bowel movement for 2 days. If possible, suppositories should be administered 30 min after a meal to synergize pharmacological therapy with the physiological response to a meal. By activating chloride channels and inducing colonic secretion, lubiprostone accelerates colonic transit in healthy individuals and improves symptoms in functional constipation [113–115]. Although there have been no studies in people with diabetes and constipation, lubiprostone should be considered in those who have not responded to osmotic agents.

The anticholinesterase pyridostigmine is efficacious in relief of constipation in individuals with diabetes and constipation, and the effect is also observed in those with autonomic neuropathy [116, 117].

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51 Diabetes and Non-Alcoholic Fatty Liver Disease

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Key points

- Non-alcoholic fatty liver disease (NAFLD) is characterized by intrahepatic fat accumulation with varying degrees of hepatic inflammation and fibrosis.
- NAFLD is present in up to 20% of the general population worldwide.
- NAFLD is the hepatic manifestation of prediabetes and the metabolic syndrome, with strong links to obesity and type 2 diabetes (T2DM).
- There is a three- to fivefold increase in the incidence of diabetes within 5 years of the diagnosis of NAFLD.
- The spectrum of NASH includes simple steatosis, non-alcoholic steatohepatitis (NASH), and cirrhosis.
- The outcome of NAFLD varies by histologic subtype, from benign (simple steatosis) to liver failure (cirrhosis). A proportion of people with NASH progress to cirrhosis.
- Cardiovascular disease and malignancies are the main causes of death but there are increasing numbers of people developing hepatocellular carcinoma even in the absence of cirrhosis.
- The key pathogenic process involved in the transition from steatosis to NASH is hepatic lipotoxicity (especially from free cholesterol). Hepatic injury results from recruitment of inflammation through activation of pattern recognition receptors (Toll-like receptors, the NLRP3 inflammasome).
- Lifestyle measures, involving exercise and weight reduction, and optimizing metabolic control remain the cornerstone of management. Drugs such as vitamin E can improve NASH in some but not all people with NASH.
- Liver transplantation is indicated for those with end-stage liver disease.
- The disease recur in transplanted livers. Aggressive measures to optimize metabolic control are imperative to prevent this.

Introduction

Non-alcoholic fatty liver disease (NAFLD, "fatty liver") is a relatively recent addition to the list of systemic disorders associated with diabetes, although the two conditions have long been known to be pathogenically interrelated. NAFLD encompasses a spectrum of liver disorders characterized by intrahepatic fat accumulation (steatosis), with or without varying degrees of hepatic inflammation and fibrosis (non-alcoholic steatohepatitis, NASH), through to cirrhosis. These histologic features closely resemble alcoholic liver disease (hence the name "non-alcoholic") and a definition of NAFLD requires exclusion of "significant" alcohol intake.

NAFLD is important for several reasons. It is widely prevalent in the community. Though mostly benign, serious liver injury including cirrhosis and liver cancer can occur in certain subgroups (type 2 diabetes [T2DM], obesity). Fatty liver can also worsen other liver diseases including alcoholic liver disease, hemochromatosis and hepatitis C. Finally, NAFLD is an independent predictor and possible contributor to extrahepatic disorders such as ischemic heart disease and chronic kidney disease.

Definition and epidemiology

Non-alcoholic fatty liver disease is defined by hepatic fat accumulation in persons without a history of significant alcohol use [1, 2]. An operational definition of significant alcohol use restricts alcohol use to 140–210 g/week for men (2–3 standard drinks/day) and 70–140 g/week (1–2 standard drinks/day) for women [3, 4]. It is important to verify the lifetime track record of alcohol usage. Secondary causes of steatosis also need to be excluded [Table 51.1] [5].

NAFLD is the most common liver disorder worldwide [6–11] [Table 51.2]. In the USA, the community prevalence of NAFLD was initially reported as 2.8% to 8% and 18.8% to 30%,

Textbook of Diabetes, Fifth Edition. Edited by R. Holt, C. Cockram, A. Flyvbjerg and B. Goldstein.

Table 51.1 Secondary causes of hepatic steatosis.

Nutritional disorders	**Metabolic disorders**
Malnutrition	Abetalipoproteinemia
Total parenteral nutrition	Type 1 glycogen storage disease
Rapid weight loss, bulimia	Wilson disease
Celiac disease	Partial and total lipodystrophy
Drugs	**Bariatric surgery**
Amiodarone	Jejuno-ileal bypass
Perhexiline maleate	
High-dose glucocorticosteroids	**Other causes**
Tamoxifen	Chronic hepatitis C infection
Methotrexate	Toxicant-associated steatohepatitis
Highly active antiretroviral treatment	

respectively [12]. However, NAFLD was defined by criteria that are insensitive to mild steatosis (serum aminotransferases, liver ultrasound criteria). Using the more accurate method of proton magnetic resonance spectroscopy in the Dallas Heart Study (USA), up to a third of the population was shown to have NAFLD [6]. Significant ethnic differences were observed, with prevalence rates of 24%, 33%, and 45% among African Americans, non-Hispanic Whites, and Hispanics, respectively. Mirroring the global rise in obesity and T2DM, the prevalence of fatty liver now exceeds 15% in Asia and elsewhere [7, 13].

In most NAFLD studies, men outnumber women by 2 to 1 between the ages of 20 and 50 years. This trend is reversed in postmenopausal women, likely reflecting the withdrawal of a protective effect of estrogens [14]. NAFLD is also now reported (~10%) in children and adolescents [15].

NASH autopsy data show that NASH is present in 3% and 18% of lean and obese individuals, respectively [16]. Here too, there are ethnic differences. In Texas (USA), where the overall prevalence rate for NASH is ~12%, the frequencies of NASH vary among Hispanic (19.4%), non-Hispanic White (13.5%), and African Americans (9.8%), respectively [17]. These differences are partly attributed to differences in frequencies of the patatin-like phospholipase domain-containing protein 3 (PNPLA3) gene.

NAFLD and the metabolic syndrome

In most NAFLD case series, over half the individuals are obese, 30–40% have T2DM and 30% have dyslipidemia. Likewise, NAFLD is frequent in people with obesity (50%, rising to 90% in morbid obesity), T2DM (50–74%) [17], and dyslipidemia (up to 50%) [18]. NAFLD is also reported in 7–9% of lean individuals [19]. However, many of these individuals have central obesity or have been misclassified as "lean" because ethnic-specific anthropometric criteria were not used. Others may be "metabolically obese" lean individuals who have recently gained weight or become sedentary; anecdotally, most such individuals have a strong family history of T2DM.

NAFLD is the hepatic manifestation of the metabolic syndrome, with the majority (up to 87%) fulfilling criteria for the full syndrome [20]. Likewise, people with the metabolic syndrome are also 4 to 11 times more likely to develop NAFLD, which is also less likely to resolve [21]. Finally, the metabolic syndrome is a predictor of histologic severity, with an increased likelihood (OR 3.0) of NASH and advanced hepatic fibrosis (OR 3.5) [22].

NAFLD and diabetes

Type 2 diabetes

Over a third of people with NAFLD have T2DM. In people without diabetes, a family history of diabetes is obtained in over 50% and abnormalities of glucose tolerance are common [20]. In one study, 24 (33%) of 76 people with NAFLD but without diagnosed diabetes undergoing an oral glucose tolerance test had abnormalities of glucose tolerance; 7 had T2DM and 17 had impaired glucose tolerance [23]. Further, fatty liver is also an independent predictor of the future development of prediabetes [24] and T2DM (OR 3.0) [25]. The links with T2DM are important because the latter is a consistently reproducible predictor of histologic severity, including NASH (OR 2.48), any fibrosis (OR 2.94), advanced hepatic fibrosis (OR 6.03) [26], and hepatocellular carcinoma (relative risk (RR), 2.0–3.0) [27].

Table 51.2 Population-based studies assessing prevalence of non-alcoholic fatty liver disease.

Author [ref]	Year of study	Location	Sample size	Criteria used to define NAFLD	Prevalence (%)
Browning [6]	2000–2002	Dallas, USA	2287	MRS	24–45
Wong [7]	2012	Hong Kong, China	922	MRS	27
Bedogni [8]	2002–2003	Modena, Italy	3345	Hepatic ultrasound	16 (lean), 76 (obese)
Nomura [9]	1984	Okinawa, Japan	2574	Hepatic ultrasound	14; 3.6 (lean), 58 (obese)
Lazo [10]	1988–1994	NHANES III, USA	12,454	Hepatic ultrasound	19
Clark [11]	1988–1994	NHANES III, USA	15,676	Raised aminotransferases	8

MRS, proton magnetic resonance spectroscopy; NHANES III, National Health and Examination Survey III.

Type 1 diabetes

Although not as well appreciated, fatty liver is also prevalent among people with T1DM. Elevated ALT levels are seen in 10–35% of people with T1DM [28] and up to 44% have evidence of hepatic steatosis on liver ultrasound [29]. Many (48–80%) have normal ALT levels. However, ALT or ultrasound-derived prevalence data may not be accurate. Further, ultrasonography cannot differentiate hepatic steatosis from glycogenosis, a frequent finding in this group. Detailed histologic data are lacking. In Nottingham (UK), 11 (19%) of 57 people among a cohort of 4000 individuals with T1DM undergoing a liver biopsy had NAFLD. More than half (53%) had steatosis, 20% had NASH, similar to those with T2DM (54% and 35%, respectively), and one individual had cirrhosis [29].

The pathogenesis of NAFLD in T1DM is not unclear but is likely related to whole body [30] and hepatic insulin resistance [31], even in the face of insulin deficiency. Poor glycemic control is also an important contributor. Hyperglycemia promotes hepatic steatosis through activation of transcription factors involved in lipogenesis, carbohydrate response element-binding protein [32], while insulin activates sterol regulatory element-binding protein-1c (SREBP-1c) (for fatty acid synthesis), SREBP-2 (for cholesterol uptake) and upregulates glucose transporter 2 to facilitate hepatic glucose uptake [33].

Histologic subtypes

The underlying liver histologic characteristics have a strong bearing on the outcome. These include simple steatosis at one end, non-alcoholic steatohepatitis (NASH) in the middle, and cirrhosis at the other (Table 51.3) [34].

Simple steatosis is characterized by *intrahepatic fat accumulation* alone. The fat (triglyceride) deposition is predominantly macrovesicular (large fat globules) and is diffusely distributed. In severe cases, over two-thirds of all hepatocytes are involved.

NASH, the inflammatory subtype of NAFLD, is defined by hepatic steatosis *along* with *hepatic inflammation/hepatocyte injury* and varying degrees of *fibrosis* (Figures 51.1 and 51.2). Swollen hepatocytes (*ballooning*), a consequence of liver cell injury, are a characteristic finding. Some may carry eosinophilic cytoplasmic inclusions (Mallory–Denk bodies) but these are not essential for diagnosis. The hepatic inflammatory cell infiltrate is predominantly composed of lymphocytes and macrophages. The fibrotic changes are initially conspicuous in zone 3, in the vicinity of the terminal hepatic venule ("perivenular" fibrosis) and often encircle individual hepatocytes in a "chicken-wire" configuration or line the hepatic sinusoids ("perisinusoidal fibrosis"). In time, the fibrotic process involves the portal and periportal areas, leading to portal-central bridging fibrosis and cirrhosis. In children, an alternative histologic pattern with hepatic steatosis and portal fibrosis is recognized.

Hepatic nodules and diffuse hepatic fibrosis define NAFLD-associated cirrhosis. Curiously, hepatic fat or steatohepatitis may be absent, leading to mislabeling of these cases as representing "cryptogenic cirrhosis." However, people with cryptogenic cirrhosis are more often obese (55% vs. 24%) and have T2DM (47% vs. 22%) than those with other causes of cirrhosis, suggesting that these may represent cases of "burnt-out" fatty liver [35].

For accurate histologic subtyping, the pathologist's overall assessment of the liver biopsy remains critical [34]. For clinical trials, liver biopsies are also scored using a detailed scoring system [36] (Table 51.4).

Table 51.3 The spectrum of non-alcoholic fatty liver disease and definitions.

	Histologic subtype	Natural history
Simple steatosis	Fat accumulation within hepatocytes (steatosis) with no hepatocyte ballooning or fibrosis.	Mostly non-progressive.
Non-alcoholic steatohepatitis (NASH)	Hepatic steatosis with varying degrees of lobular inflammation, hepatocyte ballooning and/or fibrosis.	Can progress to cirrhosis. Associated with increased overall and liver-related mortality.
NASH cirrhosis	Cirrhosis with current or past evidence of hepatic steatosis or NASH. In cases of cryptogenic cirrhosis, features of NAFLD may be absent but NASH as the underlying cause may be suspected by the presence of obesity/type 2 diabetes and metabolic syndrome.	Usually progressive disorder leading to liver failure and liver cancer.

Why does NASH occur?

In non-alcoholic steatohepatitis (NASH), fatty liver from overnutrition is complicated by liver injury and inflammation [37, 38]. Genetic factors, as shown by ethnic differences in prevalence and familial clustering, are also important in the development of NASH. A number of candidate genes involved in aspects of innate immunity, cell metabolism, anthropometric traits, fibrogenesis, oxidative stress have been implicated. The most important of these is PNPLA3, identified by genome-wide association studies, which contributes to a threefold variation in the risk of NASH and fibrosis [13].

As discussed later, NASH confers adverse liver outcomes. This is because inflammation connects liver cell injury with fibrosis progression, the three elements of NASH pathology (vs. simple steatosis) [39]. The difference between NASH and "not NASH" NAFLD pathology is the type of lipid molecules that accumulate, and how they are processed by hepatocytes. NASH is now conceptualized as "liver lipotoxicity" [38, 39]. As informed by lipidomic analyses in NASH livers from man and mouse [40, 41], free

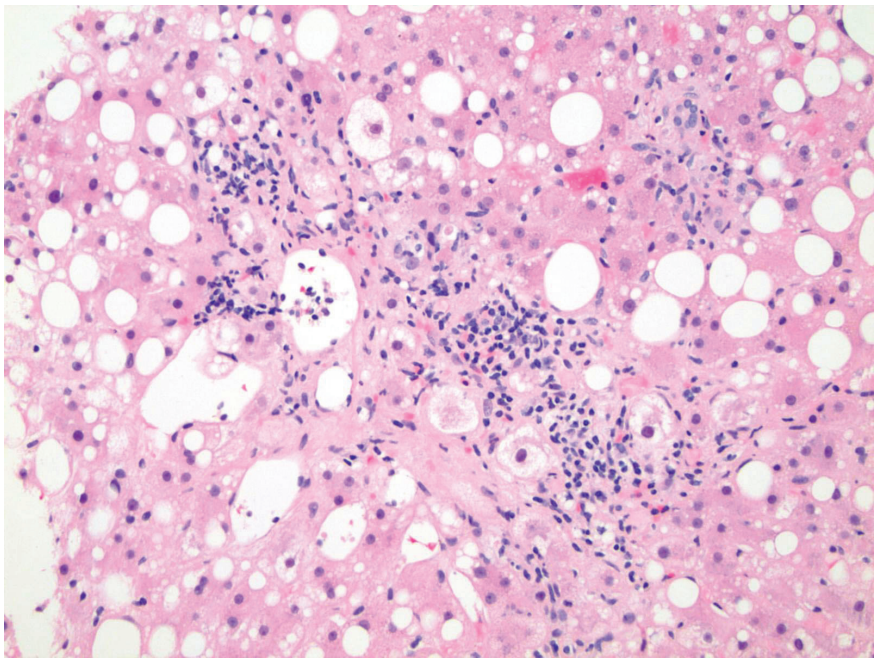

Figure 51.1 Nonalcoholic steatohepatitis. This slide illustrates diffuse hepatic steatosis, lobular inflammation, and ballooning. (H. and E. stain, × 200). Source: Slide provided by Prof. Matthew Yeh, University of Washington School of Medicine, Seattle, USA.

cholesterol seems the most likely lipotoxin [40, 42]. In obese mice with T2DM and metabolic syndrome (hypercholesterolemia, hypertension), and studies in primary hepatocytes have implicated free cholesterol in pathways to hepatocyte apoptosis and necrosis. Similar studies have shown that saturated free fatty acids and lysophosphatidylcholine exert similar lipotoxicity but the weight of evidence implicates free cholesterol as a more likely mediator of hepatocyte cell death *in vivo*. It is important to note that lipotoxicity to hepatocytes causes them to release danger associated molecular patterns (DAMPs) such as high mobility group box 1 (HMGB1), for which there is recent evidence [43]. Alternatively (or additionally) whether pathogen-associated molecular patterns (PAMPs), such as lipopolysaccharide (endotoxin) arising from a "leaky gut," are more important for inciting recruitment, and activation of macrophages to the liver in NASH is unresolved [44]. This "controversy" aside, most in this field now accept that the inflammatory response in NASH arises from innate immunity [44, 45], that is, an interaction of DAMPs and/or PAMPs with pattern recognition receptors. Greatest interest has focused on Toll-like receptors (TLRs) 4 and 9, but there is

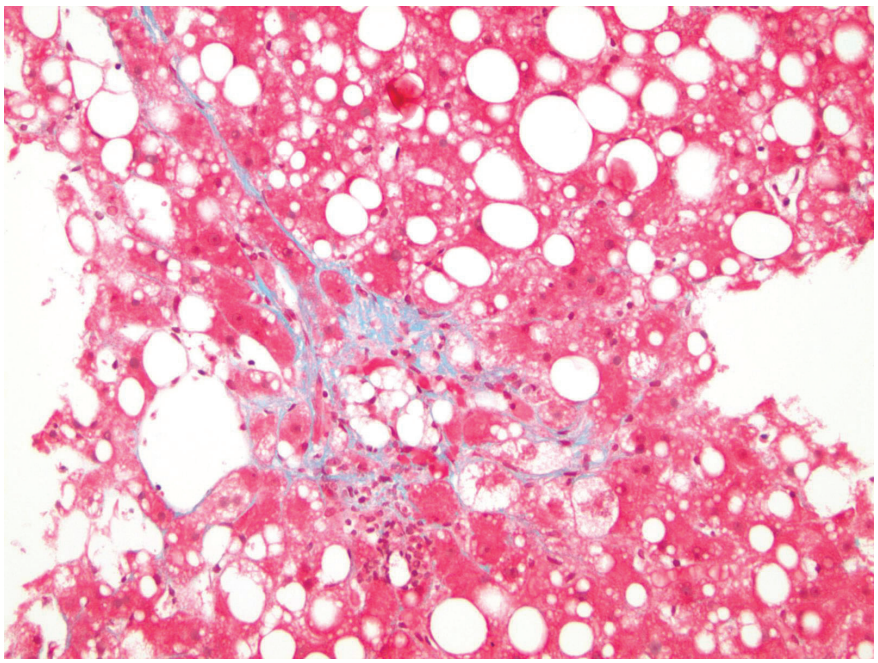

Figure 51.2 Nonalcoholic steatohepatitis. This slide shows perivenular (zone 3) and pericellular hepatic fibrosis (Masson trichrome stain, × 200). Source: Slide provided by Prof. Matthew Yeh, University of Washington School of Medicine, Seattle, USA.

Table 51.4 NAFLD histological classification developed by the Non-alcoholic Steatohepatitis Clinical Research Network.

Histological feature	Score	Category definition
Steatosis (percentage of liver parenchyma involved by steatosis under low- to medium-power evaluation)	0	<5%
	1	5–33%
	2	34–66%
	3	>66%
Hepatocyte ballooning	0	None
	1	Few ballooned cells
	2	Many ballooned cells
Lobular inflammation	0	None
	1	1–2 foci per × 200 field
	2	2–4 foci per × 200 field
	3	>4 foci per × 200 field
NAFLD activity score (NAS, 0–8) = Steatosis (0–3) + Lobular inflammation (0–3) + Ballooning (0–2)		
Fibrosis	0	No fibrosis
	1a	Zone 3, mild perisinusoidal fibrosis
	1b	Zone 3, moderate perisinusoidal fibrosis
	1c	Periportal/portal fibrosis
	2	Zone 3 + periportal/portal fibrosis
	3	Bridging fibrosis
	4	Cirrhosis
Fibrosis score 0–4		

Source: Kleiner DE, et al. 2005 [36]. Copyright © 2005 American Association for the Study of Liver Diseases. Reproduced with permission of John Wiley & Sons.
Definitive NASH, NAS ≥ 5; "Not NASH", NAS ≤ 3.

emerging evidence for inflammasome activation in NAFLD [45], as shown in alcoholic hepatitis [46].

NLRP3 (NOD-like receptor protein 3) belongs to a family of cytosolic receptors for DAMPs that facilitate aggregation of apoptosis-associated speck-like protein containing CARD (ASC) to form a scaffold for assembly and dimerization of pro-caspase-1 [47]. This activates caspase-1 to cleave pro-IL-1β and pro-IL-18. Secreted IL-18 activates macrophages. IL-1β directs neutrophil recruitment, and may activate stellate cells directly into matrix-depositing cells. NLRP3 activation has been noted in dietary models of steatohepatitis [46], while *Nlrp3*, *Asc*, or *caspase-1* deletion protects against steatohepatitis in an amino acid deficiency model. Inflammatory response to biomaterials requires plasma membrane cholesterol [48], which is increased in NASH. In atheroma, cholesterol crystals activate NLRP3 in macrophages [49]. Cholesterol crystals have recently been noted in human, as well as in obese, diabetic mice with NASH, and caspase-1 activation in the latter NASH livers co-locates with crystal-laden hepatocytes [50]. Of interest, the pattern of lobular inflammation in NASH is predominantly one of macrophages (and activated Kupffer cells) surrounding injured hepatocytes to form crown-like structures, the likely source of macrophage and neutrophil chemokines. Such macrophages likely accumulate in response to lipotoxicity and/or cholesterol crystals. Phase 2b trial of a macrophage chemokine inhibitor is currently underway.

Clinical features

Most people with NAFLD are asymptomatic, with the diagnosis being suggested by liver ultrasonography or by abnormal liver tests. Occasionally, individuals may complain of discomfort over the right upper quadrant and a soft, enlarged liver may be palpable. A firm or hard liver should raise suspicion of significant liver fibrosis. Jaundice, splenomegaly, ascites, bruising, encephalopathy are usually absent. When present, these signs are often accompanied by typical biochemical and imaging characteristics of cirrhosis.

Extrahepatic-associations of NAFLD

People with NAFLD have an increased risk (OR 2–4.0) of non-fatal and fatal ischemic heart disease, beyond what is predicted by traditional cardiovascular risk factors. An association with atherosclerosis markers (e.g. carotid intima-media thickness) has also been demonstrated [51]. Not all studies have shown an increased risk but this inconsistency may result from differences in case definition. However, the links with cardiovascular mortality have also been emphasized in hospital-based case series, which have also correlated cardiovascular risk with liver disease severity (risk for NASH > simple steatosis > matched controls) [52]. Potential contributory mechanisms include oxidative stress, and an altered cytokine, fibrinolytic, and atherogenic profile (small dense LDL, reduced HDL) [51]. Targher et al. have observed a similar relationship between NAFLD and microvascular complications of diabetes ([retinopathy, OR 3.3; 95% CI: 1.4–7.6]; nephropathy, [OR 1.87; 95% CI: 1.3, 4.1]) [53] but there have been conflicting results. Other systemic disorders that are highly prevalent among individuals with NAFLD include chronic kidney disease, obstructive sleep apnea, colorectal adenomas/cancer, and polycystic ovarian syndrome [25].

Natural history of NAFLD

The histologic subtype dictates the outcome of people with fatty liver. Individuals with simple steatosis have an excellent outcome, with a very low risk of developing cirrhosis and liver failure. In a Danish study that followed 417 people with non-alcoholic and alcoholic steatosis over 13 to 20 years, the rates of cirrhosis were 0.6% and 22%, respectively [54]. Most people with simple steatosis can be reassured and managed by primary care physicians. The only caveat is that transition of simple steatosis to NASH can occur, as can resolution of NASH to simple steatosis, but the "deterioration" transition seems uncommon (rapid weight gain

and development of diabetes could be relevant) [70]. What is clear is that the existence of liver fibrosis (any severity) is a more important predictor of progression to cirrhosis than even the presence of NASH versus "not NASH" NAFLD.

In contradistinction to simple steatosis, those with NASH can progress to cirrhosis and hepatic decompensation. Over a period of 15 years, the risk of developing cirrhosis is at least 10% (4–14%) and the overall liver-related mortality is ~7% (2.8–18%) [55, 56]. The outcome of people, with NAFLD-associated cirrhosis, who have decompensated, is similar to that observed with chronic hepatitis C and other chronic liver diseases [56]. Over a 10-year period, the mean overall and liver-related mortality is 18% (7–44%) and 25% (19–89%), respectively [55]. Overall, there is a 1.7-fold increase in standardized mortality, and liver disease ranks third among the causes of death, preceded only by cardiovascular disease and malignancy [57].

Hepatocellular carcinoma

Several studies have highlighted the association between T2DM (relative risk (RR), 2.0 to 3.0) and obesity (RR 1.89) and the risk of hepatocellular carcinoma (HCC) [27, 58]. Most HCCs are associated with viral hepatitis and alcohol-related cirrhosis but the contribution of NAFLD may have been previously underestimated in small short-term studies [56].

Most but not all NAFLD-associated HCCs arise in the setting of cirrhosis. While some tumors in "non-cirrhotic" livers could represent sampling errors (with greater degrees of fibrosis having being missed), there are strong confirmatory liver explant data. In one Japanese series, only 51% had cirrhosis, with significant gender differences (men 39%, women 70%). The risk of HCC with NAFLD-cirrhosis is lower than that for chronic hepatitis C and is estimated between 2.4% over 7 years (0.34%/year) to 13% in 3 years (4.3%) [59, 60]. This is related to differing patient characteristics (age, body weight, alcohol intake) between studies. The overall risk of HCC is still low, especially in the absence of cirrhosis, but its widespread prevalence raises concerns about a potential public health crisis. In Newcastle (UK), a third of all HCC cases are now attributed to NAFLD [61].

Over two-thirds of HCCs occur in men, with a median age of 72 years. Most of these tumors are often solitary (75%) and well differentiated, with an average size of 3 cm. Many of these people have not been on surveillance programs.

Diagnosis and assessment

It is important to seek supportive evidence to make a positive diagnosis of NAFLD (metabolic syndrome features) (Tables 51.5 and 51.6) and to exclude those that negate this possibility (Table 51.1).

Liver enzymes

The entire histologic spectrum of NAFLD has been described in people with normal liver tests [62]. Therefore, aminotransferase changes are unreliable in predicting liver histology or response to treatment. When increased, serum alanine aminotransferase (ALT) values typically exceed those of aspartate aminotransferase (AST) (unlike for alcoholic liver disease) and are usually less than 10-fold above the upper limit of normal. In cases with advanced hepatic fibrosis or cirrhosis, the AST : ALT ratio approaches 1. Cases with ALT values exceeding 1000 IU/L are unusual and suggest the possibility of viral, autoimmune, or drug-induced liver injury. Occasional people present with an isolated increase in alkaline phosphatase and/or gamma glutamyl transferase [63].

Antinuclear and/or smooth muscle antibodies can be present in 25% of cases [64] and a liver biopsy may be necessary to exclude autoimmune hepatitis. An elevated serum ferritin (with a normal

Table 51.5 Initial evaluation of a person with non-alcoholic fatty liver disease.

Anthropometry	**Serology**
Height, weight, waist circumference	Hepatitis B surface antigen, hepatitis C antibody
Blood pressure	Anti-nuclear, smooth muscle, liver-kidney microsomal and mitochondrial antibody
Liver function tests	Serum ceruloplasmin, alpha-1 antitrypsin
Full blood count, prothrombin time	**Other tests**
Serum bilirubin	Transglutaminase antibody (celiac disease)
Serum alanine aminotransferase, aspartate aminotransferase	Iron studies, thyroid function tests
Serum alkaline phosphatase, gamma glutamyl transferase	**Imaging**
Serum albumin, globulins	Abdominal ultrasound, transient elastography (if available)
Serum fasting lipids, blood glucose, insulin (optional)	
75 g oral glucose tolerance test if fasting blood glucose ≥ 5.6 mmol/L	

Table 51.6 Metabolic syndrome (as defined by the International Diabetes Federation).

The metabolic syndrome is defined by central obesity plus any two of the following:	
Central obesity	Waist circumference ≥ 94 cm (Europid men); ≥ 80 cm (Europid women); ≥ 90 cm (Asian men); and ≥ 80 cm (Asian women)
Fasting blood glucose	Elevated fasting plasma glucose ≥ 5.6 mmol/L or previously diagnosed type 2 diabetes
Elevated triglyceride level	≥1.7 mmol/L or receiving specific treatment for this lipid abnormality
Reduced HDL-cholesterol level	≤ 1.03 mmol/L (men) and ≤ 1.29 mmol/L (women) or receiving specific treatment for this lipid abnormality
Raised blood pressure	Systolic BP > 130 mmHg or diastolic BP > 85 mmHg or receiving treatment for hypertension

BP, blood pressure. Source: Alberti KG, Zimmet P, Shaw J; IDF Epidemiology Task Force Consensus Group. The metabolic syndrome – a new worldwide definition. *Lancet* 2005; **366**:1059–1062. Copyright 2005 Elsevier.

transferrin saturation) is often present in people with NASH but this is usually unrelated to iron overload [65]. Hyperferritinemia has been suggested as a marker of histologic severity and as an indication for liver biopsy but its performance is inferior to other non-invasive diagnostic methods [66] (e.g. NAFLD fibrosis score).

Imaging

Hepatic ultrasound (US), abdominal computerized tomography (CT) and magnetic resonance imaging (MRI) can all identify fatty liver and detect advanced cases of cirrhosis with portal hypertension but are insensitive to mild steatosis (<33% of hepatic steatosis) [67] and cannot differentiate simple steatosis from NASH nor accurately assess fibrotic severity.

On liver ultrasound, fatty liver is defined by increased hepatic echogenicity relative to the right kidney ("bright" liver), blurring of the hepatic vasculature and poor visualization of the diaphragm (Figure 51.3). Liver ultrasonography has high specificity (>90%) but is insensitive to mild steatosis (<33%). On abdominal CT, hepatic steatosis is defined by decreased hepatic attenuation alone or by comparison with the spleen (liver-spleen attenuation difference >10 Hounsfield units) or by the liver : spleen attenuation ratio (>1.1) [68]. On an MRI scan, the fatty liver exhibits lower signal intensity than the surrounding muscle. Magnetic resonance spectroscopy (MRS), performed on MRI systems of >1.5 Tesla, is the most accurate non-invasive method of determining quantifying liver fat content by evaluating water- and triglyceride-derived proton signals within a small liver volume (2 cm^3). MRS is expensive and remains a research tool but it has been useful in selecting an intrahepatic triglyceride fat threshold of ≥5.56% to define NAFLD [8].

Of the newer imaging modalities, *transient elastography* (TE) using a dedicated instrument (Fibroscan,™ EchoSens, Paris, France) or conventional ultrasound equipment (*acoustic radiation force imaging*, ARFI) are used in staging liver fibrosis [69]. A shear wave is generated using a cutaneous probe placed over the liver area and then velocity of its passage across a defined block of the liver is measured. This estimate of liver stiffness (*liver stiffness measurement*, LSM) correlates with the fibrosis stage. The negative predictive value for cirrhosis is high (>90%) and some liver biopsies can be avoided. However, there is a "gray" zone of LSM where there is uncertainty about the fibrosis stage and a liver biopsy is still necessary. Failure to obtain adequate readings may occur in obese individuals but a new XL probe can be useful in such cases. Also promising is the ability to detect mild steatosis (10%) and grade steatosis using the same equipment. This is scored by the *controlled attenuation parameter* (CAP), which reflects ultrasound beam attenuation by liver fat [70]. Magnetic resonance elastography is also being evaluated as a fibrosis staging tool [71].

Liver biopsy: indications and limitations

Liver histology is the "gold standard" against which other diagnostic tests are compared. The indications for liver biopsy are listed in Table 51.7. In recent years, the place of liver biopsy is being re-evaluated. Besides the inconvenience, pain, risk of bleeding, visceral injury and rarely death from this procedure, there are other technical issues. The sample size should be adequate (length 2 cm, containing at least 10 portal tracts). Fair to good agreement between observers is noted for steatosis (k = 0.79) and fibrosis (k = 0.84) but there is less agreement in interpreting ballooning (0.56) and lobular inflammation (k = 0.45) [36]. These

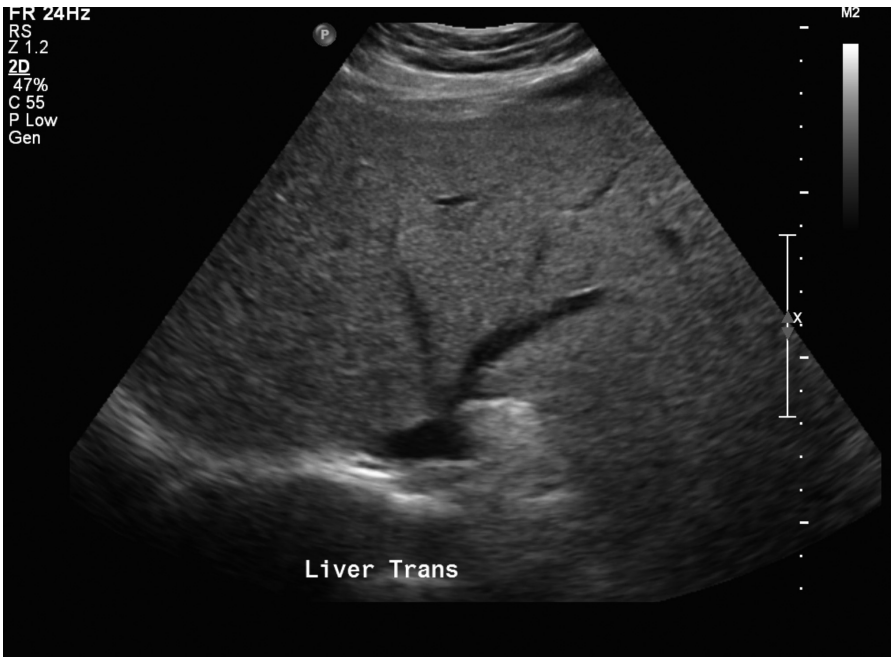

Figure 51.3 Hepatic ultrasonogram showing features of non-alcoholic fatty liver disease: bright echo texture and blurring of intrahepatic vessels. Source: Ultrasound image courtesy of Dr. Tarun Jain, Canberra Hospital, Australia.

Table 51.7 Indications for liver biopsy.

Indication	Typical settings
Presence of demographic, laboratory or imaging features that predict an higher likelihood of NASH or advanced hepatic fibrosis (age >50 years, type 2 diabetes, obesity, metabolic syndrome, hypothalamic-pituitary disease, AST : ALT ratio ≥1, low platelet count, features suggestive of cirrhosis on imaging); increasingly, derived scores (e.g. NAFLD score) or special techniques such as transient elastography have been used to assess fibrotic severity.	In some cases, the results of non-invasive tests may obviate the need for a liver biopsy. A liver biopsy is usually reserved for those cases where the stage of fibrosis cannot be determined with certainty. In other cases, where there is a high likelihood of advanced fibrosis, a biopsy is still useful if the diagnosis of cirrhosis could have an impact on managing comorbid conditions, e.g. cardiac or major surgery, renal transplantation
To exclude other liver disorders where the diagnosis is uncertain	Some examples 1. In people with chronic viral hepatitis B or C where there is suspicion that abnormal liver tests may relate to coexisting NAFLD rather than to active viral replication. 2. To exclude autoimmune hepatitis in the presence of anti-nuclear/smooth muscle antibodies, raised globulins.
In clinical trials	To document treatment response

limitations have stimulated a search for alternative assessment methods.

Non-invasive methods of assessing NAFLD

These include serum biomarkers and newer imaging techniques. There are two principal objectives: to distinguish between cases with simple steatosis from those with NASH, and to assess fibrotic severity. In addition, in population-based studies, several indices have been developed to identify people with NAFLD.

Screening for NAFLD

Neither population-screening nor screening in high-risk groups (obesity, diabetes) is officially endorsed. In population-based studies, indices that can predict NAFLD use a combination of anthropometric (body weight, waist circumference), standard (triglycerides) and non-standard (apolipoprotein A1, haptoglobin) lab tests and imaging (ultrasound). These population-based screening indices are less reliable when applied to individual cases.

Separating simple steatosis from NASH

Tests include combinations of markers of inflammation and cell death with other biologic and standard lab tests. Their applicability is limited by sample size and lack of independent validation. The limitation of serum aminotransferases has been discussed earlier. Measuring serum markers of inflammation such as highly sensitive C-reactive protein, interleukin-6, tumor necrosis factor α (TNF-α) lack sensitivity (<65%) in identifying NASH [72].

Hepatocyte apoptosis is an important mode of cell death in NASH. Its final steps involve the effector caspases 3 and 7, which also cleave a major cytoplasmic intermediate filament cytokeratin-18 (CK-18) to yield measurable serum fragments. The current CK-18 assays measure these fragments alone (M-30 assay) or as a combination of whole and cleaved CK-18 fragments (M-65 assay). The initial results were promising (area under the curve of 0.9) [73] but subsequent studies have been disappointing (sensitivity/specificity 58%/68%, AUROC 0.65), with significant overlap between cases with steatosis and those with NASH [74]. The terminal peptide of procollagen III (PIIINP) is also being evaluated as a biomarker that separates cases with simple steatosis from those with NASH and/or advanced fibrosis (AUROC of 0.85–0.87) [75].

Identifying fibrosis stages

Several different systems have been used to assess fibrotic severity, the best correlate of clinical outcome [76–82] (Table 51.8). These combine demographic variables such as age with routine laboratory tests. Of these, the NAFLD score has been extensively validated [76]. The score can be used to rule in or rule out hepatic fibrosis. A liver biopsy is needed for those with scores between -1.4 and 0.676. In the original study, over 75% of liver biopsies could have been avoided.

Another scoring system (original European liver fibrosis score, ELF Score) developed in the UK [78] includes age and three fibrosis markers: hyaluronic acid, N-terminal peptide of procollagen III (PIIINP), and tissue inhibitor of matrix metalloproteinase 1 (TIMP-1). Age was later omitted from the scoring system. More recently, PIIINP has been used as a standalone marker [75].

There are only limited data comparing individual scores. Some have found complex scores [83] to perform better than simple scores [BARD, APRI] while others have found comparable results [84]. Negative predictive values of over 90% were reported with APRI, BARD score, FIB-4, and NAFLD fibrosis score. However, 30–60% fall into the category of "indeterminate" and liver biopsy is still needed [83].

Current practice

There is no single non-invasive test that can accurately separate simple steatosis from NASH or assess fibrotic severity. In practice, combinations of serum biomarkers or clinical scores and/or transient elastography are used as "screening" tools. Liver biopsies are recommended for those who fall into the "indeterminate" and high-risk categories. Joint discussions with a gastroenterologist can help in selecting the appropriate diagnostic tests (including biopsy).

Table 51.8 Non-invasive scoring systems used in staging hepatic fibrosis.

Scoring system	Variables included	Interpretation of score	Reference
NAFLD fibrosis score	Age, BMI, IFG/diabetes, AST : ALT ratio, platelet count, albumin	2 cut-offs used. AUROC for 0.84 for advanced fibrosis. Lower cut-off has a NPV of 93% to exclude advanced fibrosis. Higher cut-off score has a PPV of 90% for ruling in advanced fibrosis	76
FibroTest	Age, alpha2-macroglobulin, total bilirubin, GGT and apolipoprotein 1	AUROC 0.75–0.86 for significant fibrosis; PPV 90% and NPV 73%	77
Original ELF score	Age, hyaluronic acid, PIIINP, TIMP-1	AUROC of 0.87; PPV 80%, NPV 95%	78, 79
(OELF)	Same as OELF except age excluded	Note: only 61 people with NAFLD included	
ELF score		AUROC same as OELF; PPV 42%, NPV 95%	
PIIINP	Serum PIIINP	AUROC 0.85–0.87 for distinguishing people with simple steatosis from those with NASH or advanced fibrosis	75
Fibrometer	Glucose, ferritin, platelet count, weight, age	AUROC 0.943 for significant fibrosis; PPV 88%, NPV 92%	79
FIB-4	Age, AST, ALT	AUROC for 0.802; NPV 90%	80
BARD	BMI > 28 kg/m^2, AST : ALT ratio, diabetes	AUROC 0.81, PPV 43%, NPV 96%	81
APRI	AST, platelet count	AUROC 0.85, NPV 93%	82

BMI, body mass index; AST, aspartate aminotransferase; ALT, alanine aminotransferase; GGT, gamma glutamyl transferase; AUROC, area under the curve; NPV, negative predictive value; IFG, impaired fasting glucose; PIIINP, N-terminal peptide of procollagen III.

Management

Diet and exercise

Lifestyle changes remain the cornerstone of management. Not only are they effective but also they are critical in managing the metabolic syndrome [85]. In fact, the "historical precedence" for lifestyle intervention in NAFLD is the structure and success of lifestyle intervention programs against T2DM among those with prediabetes (nearly all of whom will have NAFLD).

Diet

As a group, people with NAFLD consume high amounts of simple sugars (especially fructose), saturated fat, and lower amounts of omega-3 polyunsaturated fatty acids [PUFA] [86]. Therefore, dieticians recommend calorie restriction appropriate to gender, body mass index, and physical activity and restrict simple sugar and saturated fat (see Chapter 25). Pilot studies showing an improvement in NASH have encouraged consumption of PUFA-enriched diets or fish oil supplements [87]. However, a recent phase 2 placebo-controlled trial with ethyl eicosapentaenoic acid (EPA-E), a synthetic n-3 PUFA, showed no significant histologic benefits of EPA-E over placebo [88].

A 5% to 10% reduction in body weight can normalize liver tests, improve hepatic steatosis, lobular inflammation, and hepatocyte ballooning [89]. Crash diets achieving rapid weight loss (>1 kg/week) are discouraged because they can worsen steatohepatitis. Although there are initial quantitative differences in the amount of weight loss between the different diets available (e.g. low-carbohydrate, high-protein diets), these are not sustained at 2 years. Dietary adherence and an overall reduction in caloric intake are more important than macronutrient composition [90]. The effects on fibrosis are less pronounced but this may relate to the short study duration (often <1 year).

Physical activity

There is an inverse correlation between the intensity of physical activity and the risk of NAFLD. Current health recommendations are for at least 150 minutes of moderate intensity exercise a week. However, in a cross-sectional study of 813 people with NAFLD [91], only participants meeting the minimum criteria for *vigorous* exercise (75 minutes/week) were less likely to have advanced fibrosis (OR 0.53; 95% C.I: 0.29–0.97) or (NASH, OR 0.65; 95% C.I: 0.43–0.98). While increased exercise intensity is desirable, in this sedentary cohort, the target is likely to be achieved only through an incremental approach. A personal trainer and/or remote telephone or website support can help maintain adherence. When the effectiveness of such interventions were compared with a self-directed weight loss program, a greater proportion of people receiving support were successful in achieving 5% weight loss (38% to 41% vs. 5%, respectively) [92]. Whether the exercise prescription should involve aerobic or resistance training alone or a combination is unclear [93]. A pragmatic approach combines aerobic training on at least 5 days of week with two or three sessions of resistance training, with individual adjustments for comorbidities and overall conditioning.

Lifestyle intervention trials in people with NAFLD and T2DM

The Look AHEAD (Action for Health in Diabetes) study enrolled 5145 obese/overweight adults into two groups [94]. One group was assigned intensive lifestyle intervention (ILI) aimed at inducing a minimum of 7% weight loss while the other group received routine diabetes education support. An ancillary proton MRS study in 96 participants with NAFLD evaluated changes in liver fat (baseline vs. 1 year). The ILI group lost significantly more weight (8.3% vs. 0.03%), liver fat (51% vs. 23%), and had a greater reduction in HbA_{1c} (0.7 vs. 0.2%). There was a dose-response, with

the most striking reduction in hepatic steatosis confined to those showing a >10% reduction in body weight. Also, participants in the ILI arm without prior NAFLD were less likely to develop NAFLD (3% vs. 26% in the diabetes education support group).

The RAED2 trial compared aerobic exercise versus resistance training in 31 sedentary people with T2DM and NAFLD [95]. After 4 months, both groups showed improved insulin sensitivity and similar reduction in steatosis (by 26% to 32%), visceral and superficial subcutaneous adipose tissue content and HbA_{1c}. These studies endorse lifestyle measures as the first step in managing NAFLD.

Vitamin E

Oxidative stress is an important contributor to the pathogenesis of fatty liver. This has prompted randomized controlled trials of antioxidants such as vitamin E [96]. In the PIVENS study, participants were assigned to vitamin E (800 mg/day, $n = 84$), pioglitazone (30 mg/day, $n = 80$), or placebo ($n = 83$) for 96 weeks. Liver biopsies were obtained at baseline and at the end of treatment. The endpoint was an improvement in a composite score involving a combination of steatosis, lobular inflammation, and hepatocyte ballooning. The primary endpoint was only achieved by vitamin E (43% vs. 19% for placebo, $p = 0.001$). Pioglitazone also improved hepatic steatosis and lobular inflammation but not the composite score using the pre-specified p value of 0.025 (34% vs. 19% for placebo, $p = 0.04$). No significant changes in fibrosis were observed with either drug. Another pediatric trial (TONIC) comparing vitamin E with metformin and placebo [97] showed no significant inter-group differences with respect to the primary endpoint (ALT reduction) except for NASH resolution in the vitamin E group (58% vs. 28% for placebo, $p = 0.006$).

Although vitamin E is endorsed by some gastroenterology organizations, there are unresolved issues. Vitamin E has been linked to an increase in all-cause mortality, hemorrhagic strokes, and prostate cancer [4].

Thiazolidinediones ("glitazones")

Insulin resistance is also an important determinant of NAFLD. Rosiglitazone, now withdrawn, showed promise in NASH [98]. Subsequent studies have used pioglitazone (see PIVENS trial earlier). In a meta-analysis of seven randomized trials, thiazolidinediones were shown to improve steatosis, lobular inflammation and ballooning and even fibrosis. Inter-trial differences exist with regards to effects on ballooning and fibrosis [99]. Most of the benefits are seen in the first 1–2 years. Recurrence of NASH is frequent after discontinuation and side effects such as weight gain (mean 4.4 kg), an increased risk of bone fractures and bladder cancer are discouraging [4].

Metformin

Like thiazolidinediones, metformin is not recommended as a stand-alone drug for treating NASH. Small studies documented improvement in liver tests but there was little impact on liver histology as reiterated by a recent meta-analysis [100]. An emerging role is in the area of liver cancer prevention. In a meta-analysis of eight observational studies, metformin use was associated with a 50% reduction in the incidence of HCC (OR 0.5; 95% C.I: 0.34–0.73) [101]. *In vitro*, metformin (through AMP-activated kinase activation) has been shown to inhibit mTOR (mammalian target of rapamycin), a key signaling pathway that is upregulated in over 50% of HCCs [102].

Incretins

Incretin-based treatment strategies include drugs that mimic the action of endogenous glucagon-like peptide 1 (GLP-1). GLP-1 is secreted by intestinal L cells and is involved in blood glucose regulation through stimulation of glucose-dependent insulin release, decreased glucagon secretion, reduced gastric motility, and induction of satiety. Of relevance to fatty liver, GLP-1 also suppresses hepatic lipogenesis and increases hepatic fatty acid oxidation [103]. Further, an incretin-based approach to treatment is supported by the demonstration of GLP-1 receptors on hepatocytes [104] and evidence of diminished GLP-1 signaling in NAFLD.

GLP-1 has a very short half-life (1.5–2 min). Human studies involve analogs that mimic endogenous GLP-1 action (exenatide, liraglutide) or drugs that prolong its action by preventing its inactivation by dipeptidyl peptidase-4 (e.g. sitagliptin).

While preclinical data showed reduction in hepatic steatosis and studies in people with T2DM showed improvement in liver enzymes, human studies with histologic endpoints are lacking. In one 24-week study involving 10 people receiving liraglutide, a reduction in hepatic inflammation and fibrotic severity was seen in six and eight participants, respectively [105]. On the other hand, eight people with T2DM and NAFLD treated with exenatide improved their ALT levels but showed no histologic improvement [106]. Ongoing controversies relating to the risk of pancreatitis, pancreatic and thyroid cancer with these agents also need to be resolved (see Chapter 32).

Obeticholic acid (6-ethylchenodeoxycholic acid, OCA)

Lipophilic bile acids binding to farnesoid receptor X (FXR) improve insulin sensitivity, decrease hepatic gluconeogenesis and improve hypertriglyceridemia [107]. Further, a FXR agonist, such as OCA, also has antifibrotic effects and has been evaluated in human NASH. In a pilot study involving 41 people with diabetes ($n = 41$), OCA improved insulin sensitivity and ALT levels [108] and prompted a larger phase 2b randomized clinical trial (FLINT) involving 283 people with non-cirrhotic NASH [109]. Participants were randomized to OCA 25 mg ($n = 141$) or placebo ($n = 142$) daily for 72 weeks. Baseline and end of treatment liver biopsies were scheduled. The primary endpoint was an improved NAS score (Table 51.4) by 2 points without worsening of fibrosis stage. However, following an interim analysis, end of treatment biopsies were waived and ~20% did not undergo a second biopsy. Of those biopsied, an improved NAS score was noted in 45% and 21% in the OCA and placebo arms, respectively. However, resolution of NASH was modest (22% vs. 13%, $p = 0.08$). An improvement in fibrosis was also observed (35% vs. 19%) but again, there were

Table 51.9 Overview of current treatment approaches for managing NAFLD.

Treatment	Effects	Comments	Reference
Lifestyle measures (diet/exercise)	Improved aminotransferases, insulin sensitivity, and steatohepatitis	5% to 10% weight loss needed to achieve endpoints; high long-term attrition rates without supervision and reinforcement	89
Omega-3 polyunsaturated fatty acids	Improved aminotransferases, insulin sensitivity, and steatohepatitis	Not confirmed by a randomized controlled trial	88
Vitamin E	Improved aminotransferases, steatohepatitis	Concerns about increased all-cause mortality with long-term use	96
Pentoxifylline	Improved steatosis, lobular inflammation	Meta-analysis of 5 studies showed no significant histologic improvement	115
Insulin sensitizers			
Metformin	Improved aminotransferases, insulin sensitivity, weight loss	Improvement in steatohepatitis not different from placebo	100
Thiazolidinediones (pioglitazone)	Improved aminotransferases and insulin sensitivity; trend to improvement in steatohepatitis in randomized trial	Improvement in steatohepatitis not different from placebo Weight gain, need for long-term use, risk of bone fractures and heart failure	96
Glucagon-like peptide 1 agonists	Improved aminotransferases and insulin sensitivity	No randomized trials; limited data	105
Statins	Improved aminotransferases, variable effects on steatosis	No liver histology or randomized trial data Useful in managing dyslipidemia	3
Angiotensin-converting enzyme inhibitors (losartan)	Improved insulin steatohepatitis, steatohepatitis, and fibrosis	Small studies. Single randomized trial showed no benefit in comparison with rosiglitazone; no placebo arm in that study	116
Obeticholic acid	Modest improvement in steatohepatitis	Pruritus common; unfavorable effects on total/ LDL cholesterol	109
Bariatric surgery	Weight loss, steatohepatitis improved; slight worsening of fibrosis	Restricted to selected subgroups (morbidly obese); costs, side-effects need to be considered; increased risk in people with cirrhosis	113
Other agents			
Endocannabinoid antagonists (Rimonabant)	Improved aminotransferases, insulin sensitivity, and reduced steatosis	Causes depression; withdrawn	117
Ursodeoxycholic acid	Improved aminotransferases	No significant histologic benefit over placebo	118

no significant differences in the proportion of participants who had resolution of advanced (bridging) fibrosis (41% vs. 28%). Although well tolerated, pruritus was troublesome in the OCA group (23% vs. 6%, respectively). A further concern is a small increase in total and LDL cholesterol and a concomitant decline of HDL among those receiving OCA. In our opinion, these lipid changes among people with an already very high cardiovascular risk will limit enthusiasm for use of OCA in NASH.

Probiotics

The contributions of the gut microbiome to NASH (hepatic inflammasome activation by gut-derived bacterial endotoxin through TLR signaling) were alluded to earlier (also see Chapter 17). Studies have sought to manipulate the gut microbiota as a treatment strategy. In one, 48 children with NAFLD were given VSL#3 (a probiotic) or placebo for 4 months. VSL#3 contains a mixture of eight probiotic strains of Streptococcus thermophilus, Bifidobacteria, and Lactobacillus. The primary endpoint was a reduction in liver steatosis (by ultrasound). This was observed only in the VSL#3 group. At the end of treatment, there were fewer participants with moderate (9% vs. 55% at baseline) and severe steatosis (0% vs. 45%) in the VSL#3 arm [110]. Interestingly, significant weight loss and an increase in GLP-1 levels were noted in the VSL#3 arm alone. Further validation with histologic data is needed before probiotics can be recommended.

Statins and hyperlipidemia

Small case series noted improvement in serum aminotransferases and hepatic steatosis with statins. However, definitive histologic studies are lacking and therefore, they cannot be endorsed on their own for treating NAFLD.

Statins are often under-prescribed due to concerns of hepatotoxicity but these concerns are misplaced. The small increase in ALT seen in 2–3% of statin recipients is not a harbinger of serious liver injury. The latter (1/million) is very rare when considered in the context of their widespread use. Further, their safety is endorsed by studies involving people with normal or abnormal serum aminotransferases as well as those with established chronic liver disease [111]. Moreover, their impact on reducing cardiovascular events is particularly relevant to people with abnormal liver tests. In a *post hoc* analysis of the GREACE study, participants with abnormal liver tests receiving a statin had a 68% relative

risk reduction (10% vs. 30%) as compared with those not receiving them [112].

Bariatric surgery

This is currently indicated for people with a body mass index ≥40 kg/m^2 alone or ≥35 kg/m^2 with comorbid metabolic disorders. In addition to an improved metabolic profile, a reduction in hepatic steatosis and lobular inflammation are also observed. In a 5-year follow-up study of 381 people undergoing bariatric surgery, the proportion of participants with NASH was halved (14.2% vs. 27% at baseline). Some worsening of hepatic fibrosis was described but this was mostly mild (≤F1 in 96%) [113]. It should be noted that these procedures were done primarily for non-hepatic indications. People with cirrhosis were often excluded. While individuals with compensated cirrhosis are not barred from undergoing such procedures, they should be counseled about the potential for longer operating times, greater blood transfusion need, and operative risk [114].

Table 51.9 summarizes the different treatment strategies that been evaluated for NAFLD [115–118].

Managing people with cirrhosis

Patients should be monitored for signs of hepatic decompensation. They should undergo annual endoscopic screening for esophageal and gastric varices, annual bone densitometry, dietician, vaccination against hepatitis A and B, and seasonal influenza strains, and avoid hepatotoxic drugs, sedatives, complementary and alternative medicines, and non-steroidal anti-inflammatory drugs.

Hepatocellular carcinoma surveillance

The prevailing small but definite risk of HCC raises the question of routine surveillance. This is relevant because patients outside surveillance programs are more likely to present with larger tumors and receive curative treatment less often. Moreover, surveillance is cost-effective and thus recommended for people with cirrhosis [4], who should undergo 6-monthly abdominal ultrasound testing. The cost-effectiveness of HCC surveillance in the absence of cirrhosis is untested. Serum alfa-fetoprotein is insensitive (40% have normal AFP levels) and has been abandoned as a tumor marker.

Liver transplantation

People with decompensated liver disease should be referred for liver transplantation. Currently, NAFLD is the most common indication for liver transplantation in persons over 65 years. Overall, fatty liver is listed as the primary indication in ~10% of liver transplants [119] and is on course to becoming the leading indication within the next two decades. Short-term patient and graft survival rates are similar to people with alcoholic liver disease and better than that for those with chronic hepatitis C [120]. However, some studies have identified "high-risk" groups with a poor transplant outcome. Patients over 60 years, BMI ≥ 30 kg/m^2 with diabetes and hypertension had a 50% one-year mortality [121]. Moreover, recurrence of NAFLD is frequent. Nearly half will develop hepatic steatosis within 5 years. Seven to thirty percent will develop NASH and 10% will progress to cirrhosis within 10 years [121]. NAFLD is also seen in 10–20% of recipients undergoing liver transplantation for non-NAFLD indications. Therefore, aggressive preventive and treatment strategies aimed at optimizing metabolic control are critical.

Pediatric NAFLD

This is beyond the scope of this chapter and the reader is referred to recent reviews [122]. A few key points will be highlighted. The prevalence figures for NAFLD in children are ~10% (autopsy data) and 17% in adolescents [15]. Lower prevalence frequencies are reported in ALT/ultrasound-defined NAFLD studies. There are strong ties with obesity, with over half (53%) of obese children having NAFLD. Of these, up to 83% have at least one feature and up to 29% fulfill criteria for the metabolic syndrome [123]. Inherited genetic disorders presenting as steatosis are more prevalent in children than in adults and need to be considered. Indications for liver biopsy and diagnostic techniques are similar to those for adults. A typical pediatric pattern of NAFLD (hepatic steatosis with portal inflammation) is characteristically seen in up to half of the liver biopsies [34]. Natural history data with histological information are limited. While largely benign, advanced fibrosis, NASH, and cirrhosis can occur. The high frequencies of occurrence of severe disease (NASH in 84%, advanced fibrosis in 3%, need for liver transplantation) have been mostly in case series from tertiary centers and likely represent selection bias [123]. Treatment strategies are also similar with lifestyle intervention measures being the preferred approach. Although there are data (TONIC trial) supporting the use of vitamin E, long-term safety concerns preclude widespread use [97].

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52 The Skin in Diabetes

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Key points

- There are many skin manifestations associated with diabetes, some relatively specific while others are commoner amongst individuals with diabetes than those without.
- Acanthosis nigricans, pigmented papillomatous overgrowth of the epidermis seen in flexures, is associated with hyperinsulinemia.
- Many of the metabolic changes in the skin are related to glycation of structural proteins that occurs more extensively in diabetes.
- Necrobiosis lipoidica is most frequently seen in type 1 diabetes (T1DM), often on the shins in women. It remains problematic to treat.
- Thickening, loss of elasticity and yellowing of the skin are related to glycation of collagen and elastin in the skin.
- There are a number of vascular changes in cutaneous vessels with reddening and telangiectasia of the skin similar to premature degenerative aging of the skin.
- Skin infections, particularly *Candida,* may occur in poorly controlled diabetes.
- Necrolytic migratory erythema is a pathognomic sign of the rare glucagonoma syndrome.
- Reactions to recombinant human and analog insulin preparations and newer classes of antidiabetes agents are unusual.

Introduction

Many skin disorders are associated with diabetes. Some are relatively specific to the condition, usually caused by the metabolic changes in diabetes or side-effects of treatment, whilst others are non-specific but occur more frequently than in individuals without diabetes. The classification used in this chapter, including associated conditions and infections, is shown in Table 52.1.

Metabolic manifestations

This group includes a number of conditions that appear specific to diabetes (e.g. diabetic thick skin) or are much commoner than in the general population (e.g. necrobiosis lipoidica) [1]. The etiology of these conditions is largely related to the process of non-enzymatic glycation of cutaneous structural proteins or hyperinsulinemia.

Acanthosis nigricans

This condition is characterized by a velvety papillomatous overgrowth of the epidermis, which is usually hyperpigmented. The flexural areas, particularly the axillae, groins, inframammary region and neck, are most frequently affected and may become macerated or malodorous if severe [1] (Figure 52.1). Rarely, more generalized changes involve the knuckles, other extensor surfaces, palms, and soles. Histologic features include extensive hyperkeratosis, papillomatosis, acanthosis with retained keratotic material, which accounts for the dark color.

Acanthosis nigricans is associated with various endocrine disorders, which share the common features of insulin resistance and hyperinsulinemia: these include diabetes mellitus, acromegaly, Cushing disease, polycystic ovarian disease, obesity, metabolic syndrome, and genetic and autoimmune insulin receptor defects [2]. A severe malignant form is associated with gastric adenocarcinoma. It is believed that hyperinsulinemia induced by insulin resistance activates type 1 insulin-like growth factor receptors, on various tissues including epidermal cells and fibroblasts [3]. Stimulation of keratinocyte proliferation gives rise to hyperkeratosis and acanthosis (Figure 52.2).

Acanthosis nigricans, which can be disfiguring and upsetting, is most frequently seen in type 2 diabetes (T2DM) and obesity. Management is by reducing the underlying cause; particularly, weight reduction in obesity and increasing physical activity reverses the changes [4]. Topical retinoids, calcipotriol, and mild peeling agents such as salicylic acid or lactic acid may be helpful for limited involvement. Systemically metformin and rosiglitazone reduce insulin levels and give modest improvement in the condition [5].

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Table 52.1 Cutaneous manifestations of diabetes.

Metabolic manifestations:		Acanthosis nigricans Diabetic bullae Eruptive xanthomas Diabetic scleredema	Achrochordons Necrobiosis lipoidica Diabetic thick skin Yellow skin and nails
Vascular changes		Diabetic dermopathy Periungual telangiectasia Lower limb vascular changes	Facial rubeosis Perforating disorders Calciphylaxis
Infections	*Bacterial*	Staphylococcus Erythrasma Malignant otitis externa	Streptreptococcus Necrotizing fasciitis
	Fungal/Yeast	Dermatophytosis Mucormycosis	Candida
Associated conditions		Pruritus Lichen planus Clear cell syringomas	Vitiligo Glucoganoma Disseminated granuloma annulare
Iatrogenic		Insulin-induced **a** Immediate: localized/generalized **b** Delayed: lipodystrophy Reactions to oral hypoglycemic agents	

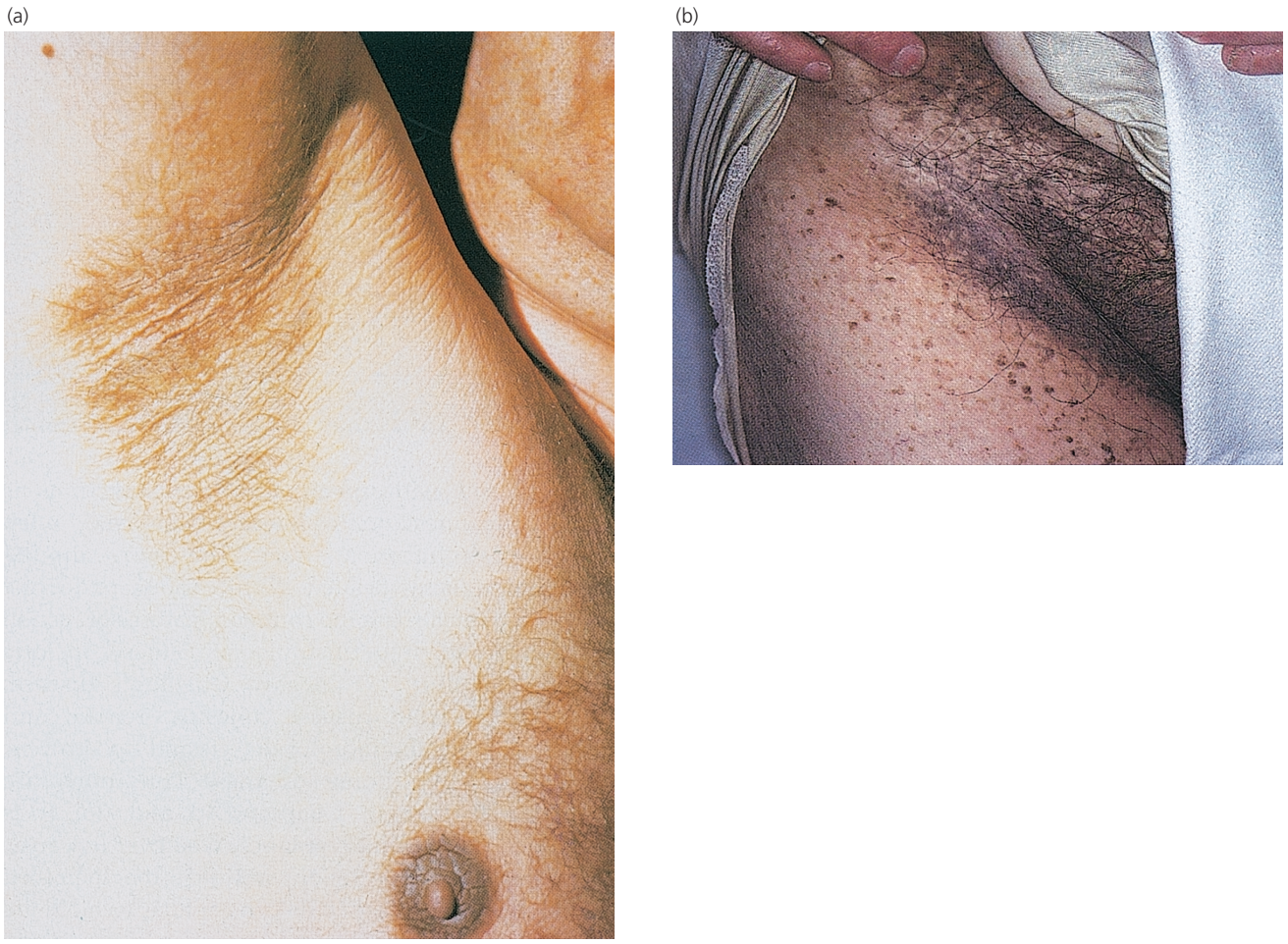


Figure 52.1 Acanthosis nigricans, showing typical dark velvety appearance: (a) in the axilla; (b) in the groin. Source: (b) Courtesy of Dr. S. Mendelsohn, Countess of Chester Hospital, Chester, UK.

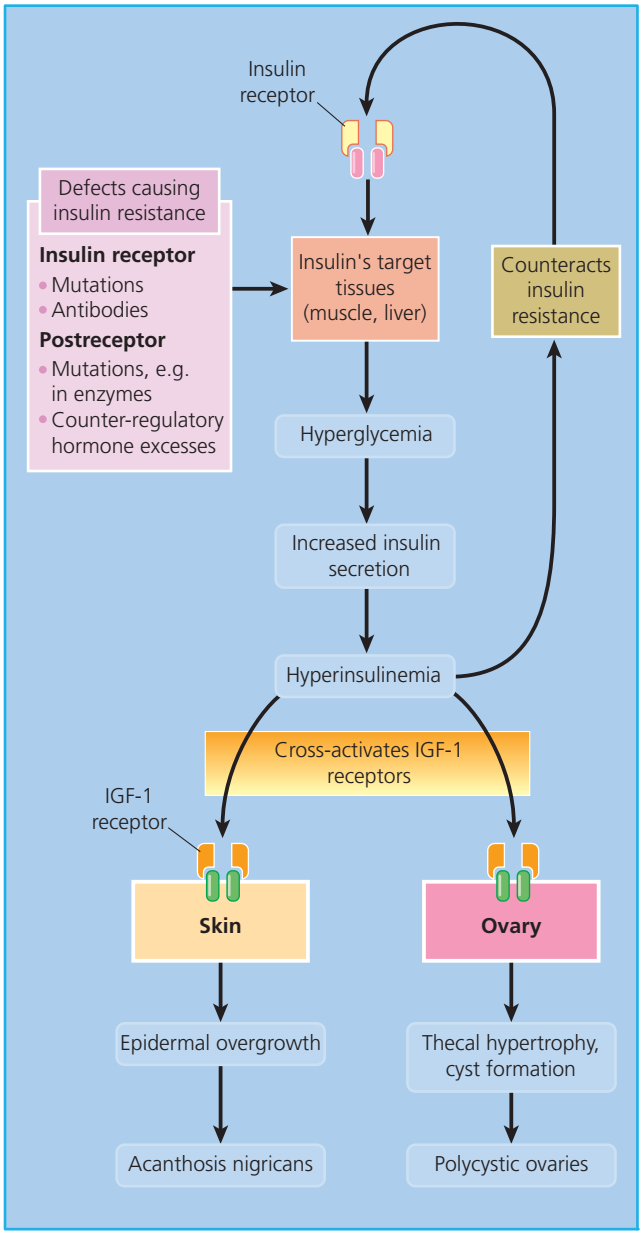


Figure 52.2 Suggested relationship of insulin resistance and hyperinsulinemia to acanthosis nigricans. Raised insulin levels may act on type 1 insulin-like growth factor receptors in the skin to cause epidermal overgrowth. Similar events in the ovary could lead to polycystic ovary disease, which is also associated with insulin-resistant states.

Achrochordons (skin tags)

Skin tags are benign, soft, fleshy skin-colored fibromas, which occur with increasing age and are particularly common in people with diabetes [6]. They may occur in at least 66% of individuals with diabetes and are probably related to the proliferative effect of hyperinsulinemia on keratinocytes and fibroblasts as in acanthosis nigricans [7]. Large numbers may be a marker of impaired glucose tolerance [8]. Skin tags occur predominantly in flexural regions around the eyes, neck, axillae, and in women in the inframammary area. Treatment is usually not required although if they cause discomfort through irritation or give cosmetic concern snip excision or electrodesiccation is effective.

Necrobiosis lipoidica diabeticorum

Necrobiosis lipoidica is a chronic granulomatous skin condition that most frequently affects the shins of those with T1DM. This is a rare condition with a 1% prevalence in people with diabetes [9, 10]. Although it is much commoner in individuals with diabetes, the relationship to diabetes and the etiology of necrobiosis lipoidica remains unclear. In a retrospective study only 22% of 65 participants with necrobiosis lipoidica had or developed diabetes in a 15-year follow-up. Necrobiosis lipoidica may precede the onset of diabetes by years, develop concurrently or years later. The presence of necrobiosis lipoidica is thus an indication for investigation of possible diabetes and future monitoring. Necrobiosis lipoidica usually develops in young adults or early middle life, but has been reported in children with T1DM [11]. Women are three times more commonly affected than men. There is no proven association with glycemic control, but people with diabetes and necrobiosis lipoidica appear to have a higher incidence of chronic diabetic complications such as retinopathy, neuropathy, and microalbuminuria [12].

Necrobiosis lipoidica has a distinctive appearance (Figure 52.3). Early lesions may be rounded, dull red, symptomless papules or plaques, which slowly progress to the typical chronic lesion—an oval or irregularly shaped indurated plaque with central atrophy. Necrobiosis lipoidica often has a shiny surface, with prominent telangiectatic vessels crossing over a waxy yellowish central area due to lipid deposition. The margin of lesions may be brownish or red and sometimes with comedo-like plugs, where necrotic material is extruded through the surface. The shin is the most commonly affected site, but the thighs, ankles, and feet may also be affected; lesions rarely occur on the trunk, upper limbs, or scalp [12]. Ulceration occurs in up to 35% of cases and may be very slow to heal. Necrobiosis lipoidica lesions are usually partially or completely anesthetic and alopecia is frequently present. Lesions are variable in number but usually few and most extend slowly over several years, sometimes coalescing with adjacent areas. Long periods of quiescence may occur or occasionally lesions may heal with scarring. The condition can lead to significant morbidity and cosmetic disfigurement. The diagnosis is usually clinical; a diagnostic skin biopsy is not normally required and may risk ulceration in atrophic lesions. The differential diagnosis of early lesions includes granuloma annulare, cutaneous sarcoid, necrobiotic xanthogranuloma, and diabetic dermopathy.

Histologically, necrobiosis lipoidica lesions consist of foci of degenerate collagen bundles with a hyalinized appearance (necrobiosis), surrounded by fibrosis, with diffuse or perivascular infiltrate of histiocytes, lymphocytes, and plasma cells. Frequently a palisading granulomatous reaction with giant cells is seen (Figure 52.4). These abnormalities occur throughout the dermis with telangiectasia and epidermal thinning [13]. There is considerable overlap between these features and those of granuloma annulare.

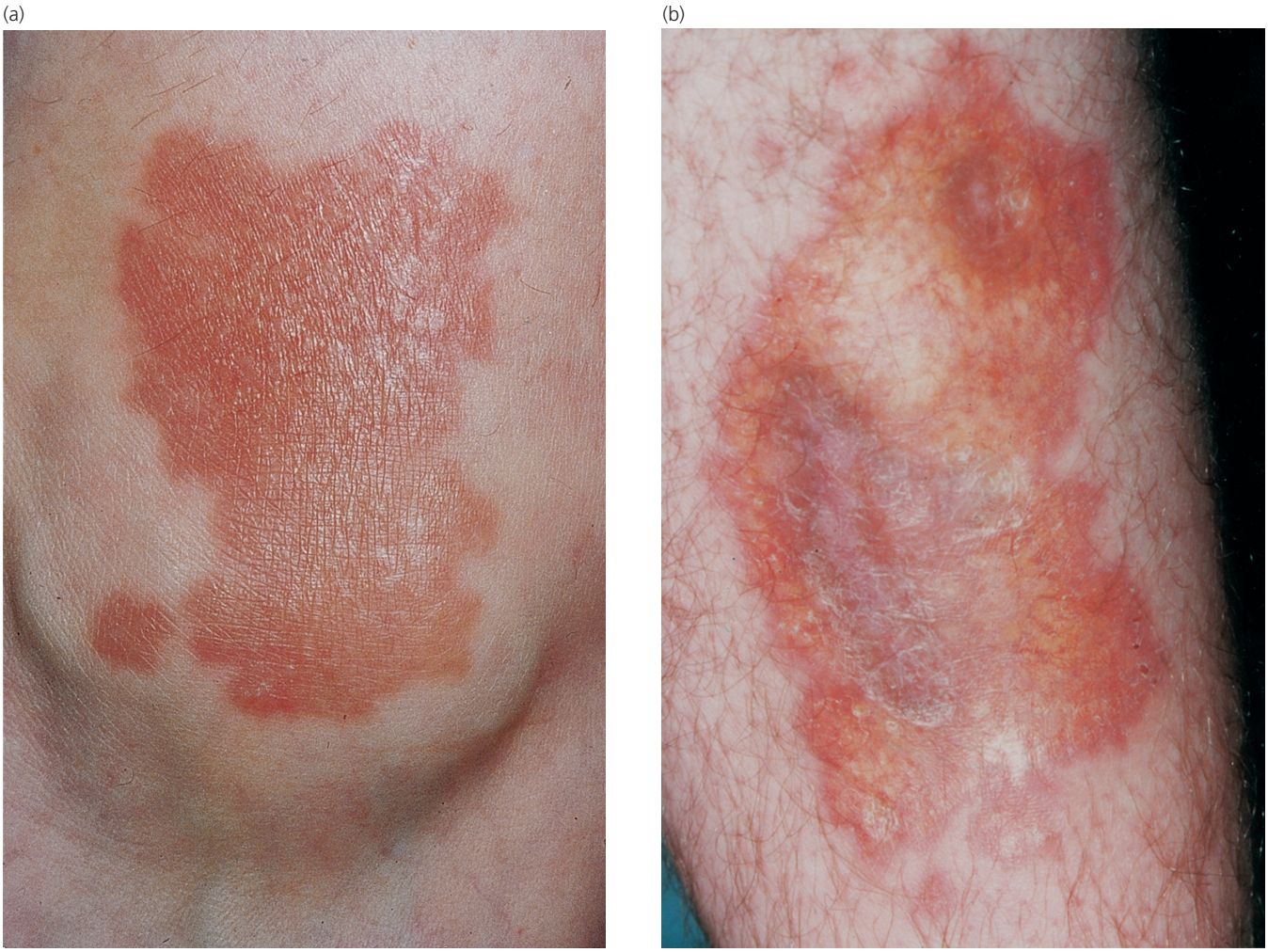


Figure 52.3 Necrobiosis lipoidica diabeticorum. (a) An early lesion on ankle showing the erythematous stage. (b) A long-standing area of necrobiosis lipoidica, note the typical yellow atrophic appearance with telangiectasia.

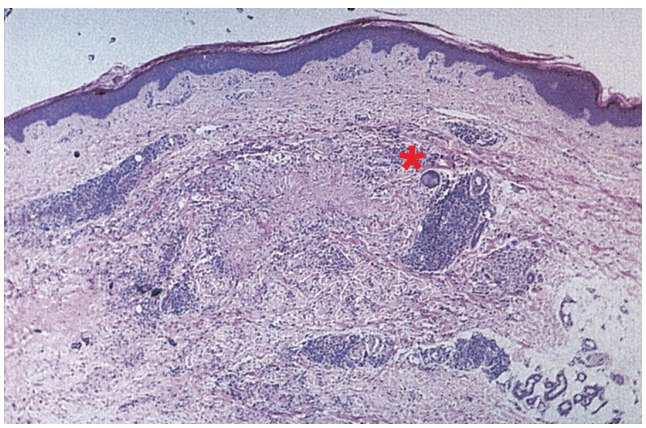


Figure 52.4 Histologic feature of necrobiosis lipoidica diabeticorum showing degeneration of the collagen (necrobiosis), associated with fibrosis and a granulomatous histiocytic infiltrate. A giant cell is indicated by an asterisk. Hematoxylin and eosin stain ×40.

The similarity contributed to the suggestion that localized granuloma annulare is associated with diabetes. Despite histologic similarities in the earlier stages of the two conditions, they run a very different clinical course and only the generalized form of granulare annulare is linked to diabetes [13].

No treatment for necrobiosis lipoidica has proved effective in double-blind placebo controlled trials and treatment remains unsatisfactory. Spontaneous remission is unusual and good diabetic control does not usually have a significant effect on the course of the condition. Patients should be encouraged not to smoke and to avoid trauma to the area, which may result in a painful and recalcitrant ulcer. The multitude of case reports of diverse treatments suggests that there is no established benefit for most of these [1]. In many cases, cosmetic camouflage may be the preferred option. Topical steroids, calcineurin inhibitors and psoralens with ultraviolet A (PUVA) are the most used therapies [14].

For early lesions corticosteroids either applied topically (perhaps under occlusion) or by intra-lesional injection may be

beneficial [15]. The inflammatory process extends beyond the clinical margins and topical steroids may halt or slow progression if applied to the periphery of lesions. Once atrophy has developed this is irreversible and topical steroids should not be used in chronic lesions because they may worsen skin atrophy. An alternative to steroids is the calcineurin inhibitor tacrolimus applied topically which will not cause atrophy. Several small open studies report an approximately 50% response rate to topical PUVA [16] while topical retinoids may be beneficial in atrophic cases [17]. Pulsed dye laser treatment may improve telangiectasia and erythema but there is a risk of skin breakdown. There are reports of good results following excision and grafting, although the disease may recur locally. The tumor necrosis factor α (TNF-α) antagonists infliximab and etanercept are reported beneficial for ulcerative necrobiosis lipoidica [18]. Most recently topical application platelet-rich plasma has shown encouraging results in ulcerated lesions. In an open study, all 15 participants showed marked reduction in ulcer size after 10 weekly applications [19].

Diabetic bullae (bullosis diabeticorum)

Diabetic bullae affect men more than women and are more common in older people and those with peripheral neuropathy [20]. The conditions usually present as tense sterile blisters, from a few millimeters up to several centimeters in size, on a non-inflammatory base, appearing rapidly and healing over a few weeks without scarring (Figure 52.5). The feet and lower legs are the commonest sites, followed by the hands. The condition is most commonly seen in long-standing T1DM with late complications. Electron microscopy studies demonstrate a subepithelial split at the level of the lamina lucida and immunofluorescence studies are negative [21]; however, the etiology of bullae is unclear. Other causes of subepithelial blisters, including the autoimmune blistering diseases porphyria cutanea tarda, pseudoporphyria, and infections such as bullous impetigo need to be excluded. Treatment is normally supportive to prevent secondary infection although surgical debridement and negative pressure dressing has been proposed [22]. Aspirating tense blisters to prevent rupture may be required and most heal within a few weeks.

Diabetic thick skin

The skin of individuals with diabetes is measurably thicker by ultrasound than in people without diabetes [23] and shows loss of elasticity [24]. Thickening is most often seen on the hands and feet and may progress to finger pebbles, groups of indurated papules on the extensor aspect of the fingers and knuckles. Milder changes are seen in a minority of older people without diabetes. The thickness of the skin is largely attributable to the filamentous proteins of the dermis, of which collagen is by far the most abundant. In people with diabetes, the collagen bundles are thickened and disorganized, as a result of irreversible non-enzymatic glycation, and cross-linking of protein. The formation of advanced glycation end-products (AGEs) damages the protein thereby reducing the ability of enzymes such as collagenase to remodel the fibers [25]. Gradual and irreversible modification of collagen, elastin and other structural dermal proteins is part of the physiologic aging process, but is accelerated in diabetes, especially if poorly controlled.

Skin thickness shows some correlation with duration of diabetes [26] and the presence of complications such as neuropathy and microangiopathy [9, 27]. Topical emollients help with the associated skin dryness, but there is no effective treatment. Tight glycemic control may slow the development of skin thickening. Whilst skin thickness is often clinically insignificant when advanced it may lead to the specific complications of "diabetic hand syndrome" and diabetic scleredema [28]. The combination of thick tight waxy skin and limited joint mobility has been called cheiroarthropathy and is present in up to a fifth of people with T1DM [29].

Diabetic hand syndrome usually occurs in those over 60 years of age (see Chapter 53) [30]. The early changes include thickening of the skin over the dorsum of the hands and digits, especially the proximal interphalangeal joints (sclerodactyly). More extreme cases present with a tight waxy appearance together with pebbly pads over the knuckles and distal fingers. The interphalangeal joints are particularly susceptible and involvement of periarticular connective tissue contributes to painful stiff fingers [31]. In a minority, the condition progresses to cause a fixed flexion deformity of the fingers and Dupuytren contracture, while soft tissue thickening of the wrist may cause carpal tunnel syndrome by compression of the median nerve.

Scleredema of diabetes

This is marked dermal thickening, commonly involving the posterior aspect of the neck and upper parts of the back, and extending to the face, arms, and abdomen with more severe involvement but sparing acral areas. It has a prevalence of 2.5–14% in diabetes and

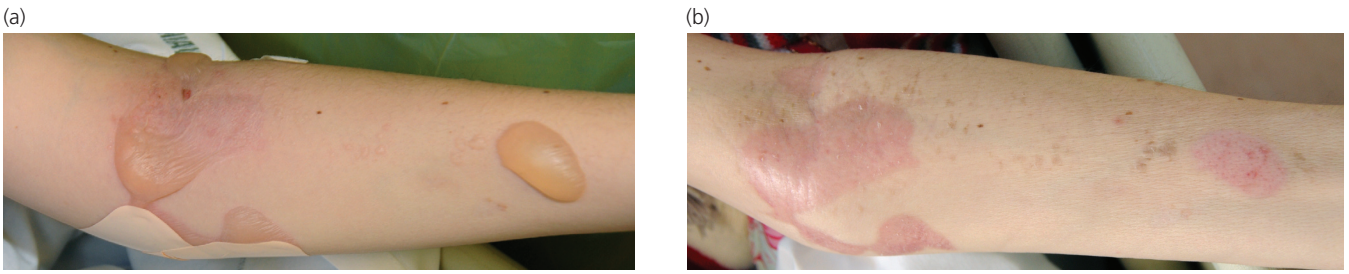


Figure 52.5 Diabetic bullae. (a) Acute bullae on an arm. (b) Resolving lesions 14 days later.

is found particularly in men with T2DM and those who are overweight and with poorly controlled diabetes [32]. The skin is hard, thick and may be indurated and erythematous. Histology of the condition shows dermal thickening that contains large collagen bundles and an increased number of mast cells [28]. Scleredema, with similar morphologic changes, may follow chronic streptococcal infection of the skin, often involving the lower legs. No therapy is very effective for scleredema although response to ultraviolet light or PUVA [33] has been reported. Strict glycemia control is recommended as this may slow the progression.

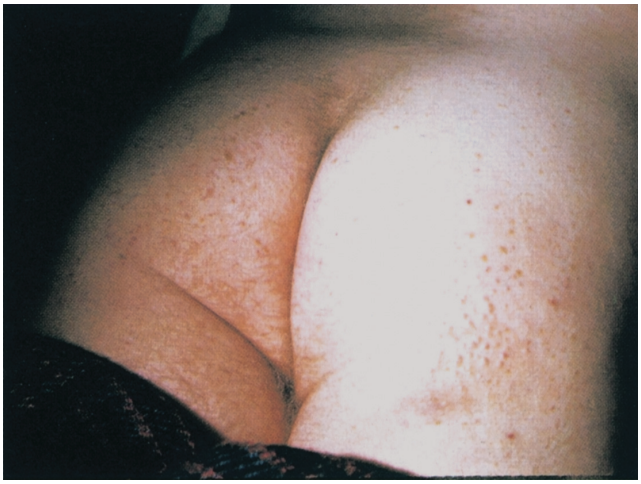
Yellow skin and nails

Individuals with diabetes develop yellowish skin and nails more frequently than the general population. This is most noticeable on the palms and soles. It has been referred to as carotenemia, but there is little evidence to support the theory that carotenoids are the cause [34]. The most probable explanation is that the discoloration is due to non-enzymatic glycation of dermal collagen. The end product 2-(2-furoyl)-4[5](2-furanyl)-1H-imidazole has a yellowish color. This occurs to a much greater extent in the hyperglycemia of diabetes compared to individuals without diabetes. Yellow nails have frequently been noted in persons with diabetes, particularly the distal hallux [35]. An early sign of diabetes may be the presence of a yellowish or brownish discoloration in the distal part of the hallux nail plate. The canary yellowish hue that can affect the toe and finger nails is distinct from the yellowish discoloration seen in association with onychomycosis. A study of fingernails has shown that people with diabetes have high levels of furosine-lysine, another marker of non-enzymatic glycation [36]. Whilst these appearances may give cosmetic concerns it is benign and there is no effective treatment.

Eruptive xanthomas

Eruptive xanthomas are rare and pathognomonic of hypertriglyceridemia. This can occur at the initial presentation of T1DM when there is insulinopenia [6]. Insulin is a stimulatory factor for lipoprotein lipase which if not activated leads to impaired clearance of very-low density lipoproteins and chylomicrons. Xanthomas present as clusters of yellowish papules of triglyceride up to 5 mm on extensor surfaces of the limbs and buttocks (Figure 52.6). The onset is usually rapid and lesions frequently occur in groups or crops with surrounding erythema initially). Men are more commonly affected. Although xanthomas may itch initially, they are usually asymptomatic. Lesions usually regress slowly within months after hypertriglyceridemia has been corrected by lipid-lowering drugs or improved glycemic control.

(a)



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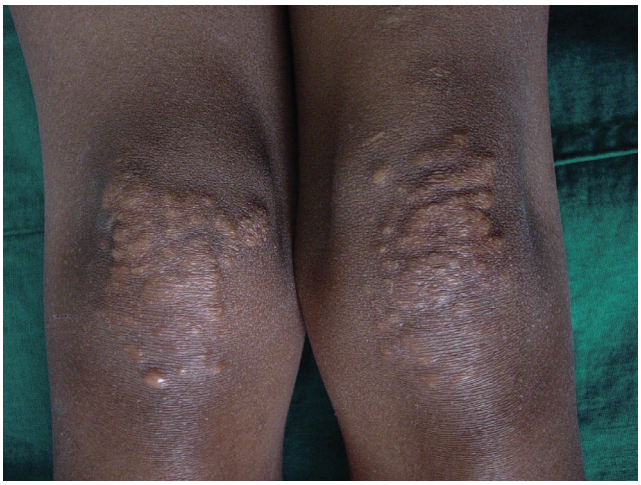

Figure 52.6 Eruptive xanthoma: (a) buttocks; (b) knees.

Vascular changes

Diabetic dermopathy (shin spots)

This is the commonest dermatological condition associated with diabetes, occurring in up to 50% of people with diabetes and nearly 3% of the adult general population, who usually have only one or two lesions. By contrast, most individuals with diabetes have four or more [37]. Men are more frequently affected. It is commoner in those over 50 years of age and in long-standing diabetes. The condition is associated with neuropathy, nephropathy, and retinopathy, and also coronary artery disease [38]. The presence of diabetic dermopathy is a subtle sign that suggests more serious complications [39]. Diabetic dermopathy does not correlate with obesity or hypertension in individuals with diabetes [40]. The presence of microvascular changes, notably thickening of arterioles and capillaries led to the term "diabetic dermopathy" [41]. It has been hypothesized that diabetic dermopathy arises from local abnormal blood flow. This was confirmed with laser Doppler technology, which revealed a functional abnormality in blood flow in 25 people with diabetes compared to 67 people without diabetes [42].

The lesions are well-circumscribed, atrophic, brownish scars often on the shins, giving the alternative name "diabetic shin spots" [37] (Figure 52.7). The forearms, thighs, and bony

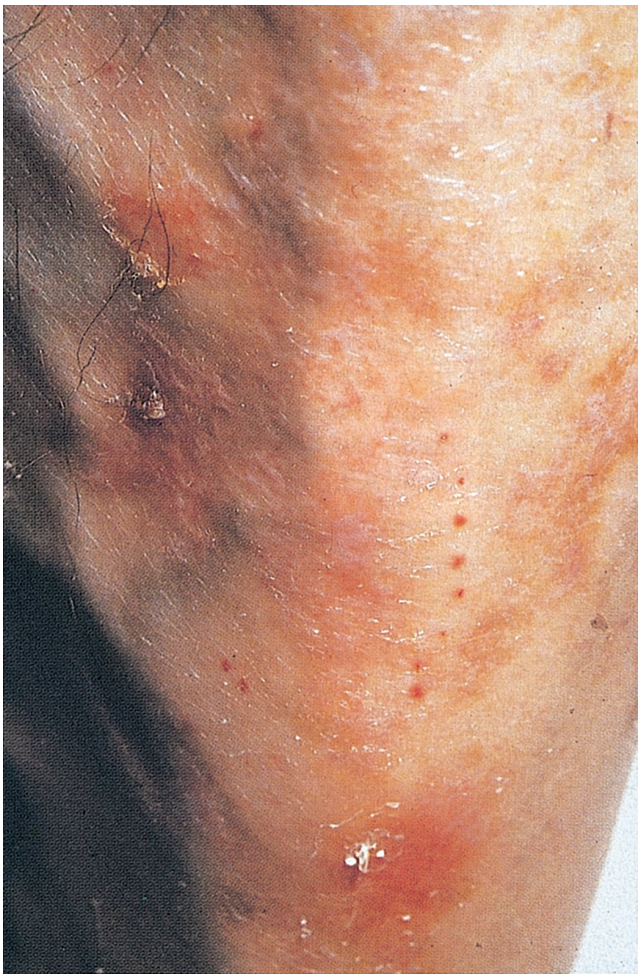

Figure 52.7 Diabetic dermopathy, "shin spots." Source: Courtesy of Professor Julian Verbov, Royal Liverpool University Hospital, UK.

prominences may also be affected [40]. The lesions are usually bilateral and may appear in crops. Early lesions are oval, red papules measuring up to 1 cm in diameter, which slowly develop scaling and a brown color due to the presence of hemosiderin-laden histiocytes and extravasated erythrocytes in the superficial dermis. There is no recommended treatment as they are usually asymptomatic and tend to resolve over 1–2 years. However, it is worthwhile screening for other microangiopathic complications of diabetes [43].

Rubeosis faciei

Rubeosis faciei is the chronic flushed appearance in the face and neck of people with diabetes [44]. The intensity of coloration is dependent on the vascular engorgement in the superficial venous plexus [45]. The changes occur due to altered vascular tone or diabetic microangiopathy. It appears more obvious in fair-skinned individuals and can be difficult to distinguish from normal facial redness in the general population. The condition may be improved with glycemic control and avoidance of vasodilators (caffeine and alcohol) [43].

Periungual telangiectasia

Erythema of the skin surrounding the nail bed resulting from the dilatation of proximal nailfold capillaries is an excellent marker of functional microangiopathy [46]. It can occur in up to 49% of people with diabetes. Even though connective tissue diseases can exhibit similar periungual telangiectases, the lesions are morphologically different. In those with diabetes, isolated homogenous engorgement of venular limbs is seen, whereas mega-capillaries or irregularly enlarged loops are observed in connective tissue disease [47].

Lower limb vascular changes

An erysipelas-like erythema with well-demarcated patches of cutaneous reddening, occurring in the legs and feet of people with diabetes is described. It can be mistaken for erysipelas, but is differentiated by the lack of associated fever, leukocytosis, or elevated erythrocyte sedimentation rate [48]. Cutaneous signs of ischemia in the lower limbs include cold or cyanosed feet, erythema, hair loss, and atrophy. A sign of large-vessel disease is dependent rubor with delayed return of color (>15 s) after pressure has been applied to the skin. Individuals with diabetes who have both venous insufficiency of the lower legs and arterial disease are particularly prone to developing non-healing ulcers; these frequently become superinfected and can be very troublesome to manage. Neuropathy, with lack of pain sensation, also contributes to lower leg injury and ulceration. Repeated trauma and increased shear forces affect the skin without the usual protective mechanisms that are impaired by peripheral neuropathy, leading to further skin breakdown [49]. Compared to people without diabetes, the risk for gangrene and amputation is higher in those with diabetes [50].

Perforating dermatoses

Reactive perforating collagenosis (folliculitis) is a condition characterized by transepidermal elimination of degenerative collagen and is seen in end-stage renal disease caused not only by diabetes, but other conditions as well [51]. It presents with pruritic hyperkeratotic papules on the extensor surfaces of the lower limbs, but can occur on the trunk and face. Histology reveals an atrophic epidermis surrounding a plug of degenerate material consisting of elastin and collagen [47]. It is thought to be a disorder of keratinization that engenders a proliferation of epidermis to eliminate abnormal tissue. Although it appears to be an inflammatory condition, microvasculopathy has been noted in the underlying dermis of biopsy specimens [52]. The lesions can be exacerbated by injury or excoriation. It is notoriously difficult to treat but may be helped by topical steroids and retinoids, failing which phototherapy is an option. Management of the underlying renal insufficiency or diabetes may be beneficial. The effectiveness of doxycycline and allopurinol has also been documented [53, 54].

Calcific uremic arteriolopathy (calciphylaxis)

Calcific uremic arteriolopathy is a small-vessel vasculopathy occurring in renal failure and, sometimes, in persons with

diabetes. It is characterized by mural calcification, intimal proliferation, fibrosis, and thrombosis [55]. The lesions start as localized areas of erythema and tenderness of the skin that become ischemic forming a livedo-reticularis pattern. This leads to the development of subcutaneous nodules and poorly healing, necrotizing skin ulcers. They can serve as a portal of entry for infectious agents. It usually affects the extremities but can involve the abdomen and buttocks as well. The prognosis in those with calciphylaxis is poor due to impaired wound healing and infection leading to sepsis. Treatment is usually unsatisfactory. Aggressive analgesic therapy may be required for ischemic pain, along with optimal blood glucose control and weight reduction [56, 57]. Newer treatments in the setting of renal failure include sodium thiosulphate [58] and cinacalcet hydrochloride [59].

Infections

Studies have shown that there is no significant increase in the prevalence of infections in most people with diabetes and the strength of previously assumed associations have been questioned (see Chapter 55) [60]. However, poor glycemic control can increase the risk of infection by causing abnormal microcirculation, decreased phagocytosis, impaired leucocyte adherence, and delayed chemotaxis [61].

Bacterial infections

Furuncles, carbuncles, folliculitis, and erythrasma were particularly frequent before the introduction of insulin and antibiotics, and skin infections due to *Staphylococcus aureus* are still probably commoner in those with diabetes.

Severe ("malignant") otitis externa is an uncommon but potentially lethal infection caused by invasive *Pseudomonas* spp. It occurs in elderly people with diabetes and manifests as purulent discharge with severe pain in the external ear. It progresses from cellulitis to osteomyelitis, meningitis, and cerebritis. Subsequent cranial nerve damage can also occur and carries a high mortality [62]. Treatment involves ear canal irrigation, skin debridement and systemic antibiotics, particularly quinolones [63].

Erythrasma, caused by *Corynebacterium minutissimum*, is rare and occurs with increased frequency in obese people with diabetes. It presents as a red, shiny or scaly patch in the intertriginous areas and with UV light exhibits a characteristic coral-red fluorescence. Topical or systemic erythromycin is curative. Unusual infections with coliforms or anaerobes occur in those with diabetes as can *Pseudomonas* infections of the toe web spaces or nail-fold (paronychia) and secondary infection of venous ulcers [64.] Anaerobic cellulitis with *Clostridium* species can occur in people with diabetic ketoacidosis, requiring aggressive debridement of devitalized tissue, and intravenous antimicrobial therapy [55].

Necrotizing fasciitis is a potentially lethal skin and soft tissue infection that is commoner in people with diabetes [65]. The infection has mixed flora including *Streptococcus pyogenes*, anaerobic *Streptococci*, *Bacteroids*, and *Stapylococcus aureus* and may arise from trivial wounds like injection sites, or begin from decubitis ulcers. It presents initially with the triad of pain, swelling, and erythema [66] and can be misdiagnosed as cellulitis (Figure 52.8). An initial clue to necrotizing fasciitis is that the pain is out of proportion to the swelling or erythema with tenderness beyond the apparent involved area. Rapid progression ensues with extensive tissue destruction and severe systemic toxicity, leading to death. Necrotizing fasciitis should be treated with extensive surgical debridement of necrotic tissue and high-dose antibiotics, with blood and tissue culture. The mortality remains high in spite of optimal treatment [67]. This condition should be considered in those with cellulitis who have associated systemic features like tachycardia, leucocytosis, marked hyperglycemia, or acidosis.

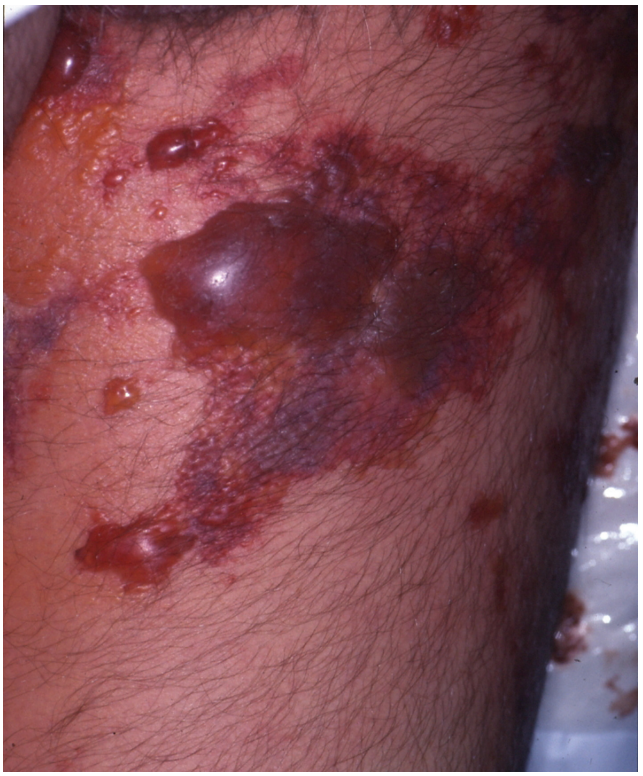

Figure 52.8 Severe infection in a person with diabetes that led to necrotizing fasciitis.

Fungal/yeast infections

Candida

Infection with *Candida albicans* may be a presenting feature of diabetes or manifest as a complication of poorly controlled diabetes. The infection appears as erythematous papules, coalescing to form glazed plaques, with satellite pustules affecting the flexural areas in the body, the vulva, and penis (Figure 52.9a). In women, vulvovaginitis is the commonest manifestation and presents with pruritus vulvae that can be intense and distressing. The vulva appears erythematous and fissured with peripheral pustulation in severe cases and may be particularly troublesome in hyperglycemia with

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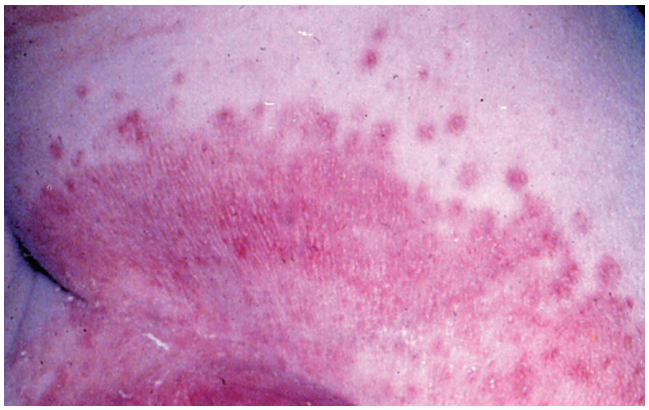

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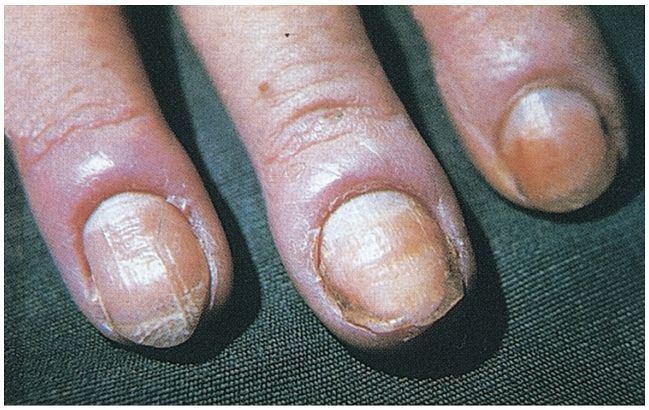

Figure 52.9 *Candida* infections in people with diabetes. (a) Flexural infection showing satellite lesions. (b) Chronic paronychia caused by *Candida albicans*. Note swollen and erythematous nailfolds.

glycosuria [65]. Candida balanitis, balanoposthitis, and phimosis occurs less commonly in men, but may be a presenting feature [68]. Candida angular stomatitis and an atrophic tongue resembling median rhomboid glossitis are oral manifestations of diabetes. Oral candidiasis occurs more commonly in people with diabetes who smoke or wear dentures [69]. Candida intertrigo occurs on opposing surfaces under the breast, in the groins and axillae, or in the folds of the abdominal skin.

Candida infection of the hands and feet are probably equally seen in people with diabetes as those without, but tends to be more severe in the former. Chronic paronychia presents as swelling and erythema around the lateral nailfold, with more severe involvement leading to onycholysis (Figure 52.9b). Microscopic examination and culture of the extruded material will confirm the infection. Less common than paronychia is infection of the web space between the middle and fourth finger (erosion interdigitale blastomycetica) [70]. Exclusion of moisture is an essential aspect to the treatment, and systemic antifungal drugs (e.g. oral fluconazole or itraconazole), rather than topical preparations may be required.

Dermatophytosis

Dermatophyte skin infections are probably not commoner in people with diabetes [60]. However, epidemiological studies have shown a higher incidence of onychomycosis in individuals with diabetes; the severity of the nail disease correlates with the duration of diabetes [71]. Fungal skin infection can serve as a portal of entry for other infectious agents, particularly in those with neurovascular complications. *Trichophyton rubrum* is the commonest pathogen, causing erythematous lesions that are often annular with scaly edges. Intertrigo or interdigital infection presents as maceration and superficial scaling. The diagnosis is confirmed by finding fungal hyphae in the superficial scale, ideally taken from the edge of the lesion. Treatment is with a topical imidazole antifungal or terbinafine, although extensive systemic itraconazole or terbinafine may be required. Severe onychomycosis can contribute to foot ulcers and hence require treatment with topical and systemic antifungal therapy, proper nail maintenance, and aggressive debridement [72].

Phycomyces infections

Poor metabolic control, resulting in hyperglycemia and ketoacidosis, may permit organisms that are normally non-pathogenic to establish infections in traumatized skin [73]. Leg ulcers or non-healing surgical wounds may have super-added phycomycete infections. Deep phycomyces infection like rhinocerebral mucormycosis is a rare but life-threatening complication of diabetes. Early manifestations include facial or ocular pain and nasal stuffiness, which progresses to fever, facial cellulitis, periorbital edema, proptosis and rarely, blindness [74]. The infection spreads along the turbinates, septum, palate, maxillary and ethmoid sinuses and can extend into the frontal lobe, cavernous sinus, or carotid artery. It should be suspected in anyone with diabetes presenting with sinusitis, purulent nasal discharge, altered mentation, and infarcted tissue in the nose or palate. Treatment involves correction of acid-base imbalance, aggressive debridement of devitalized tissue and intravenous antifungal therapy.

Associated conditions

These are a group of dermatoses that are reported more commonly in individuals with diabetes.

Vitiligo

Vitiligo is a common autoimmune condition characterized by complete loss of pigment in the skin. The exact pathogenesis is unknown. It is seen more frequently in T1DM, but can occur in type 2 diabetes as well. Polyglandular autoimmune syndrome type 2 is characterized by adrenal failure, autoimmune thyroid disease and T1DM, and can be associated with vitiligo [75]. It manifests as patchy, symmetrical depigmented areas of skin and although asymptomatic, can cause significant emotional distress.

Treatment is unsatisfactory although topical steroids and calcineurin inhibitors can be used. Patients should be advised on photoprotection.

Lichen planus

Lichen planus is an inflammatory disorder of the skin recognized by the presence of violaceous flat-topped polygonal papules, distributed in the flexural aspects of the limbs. An increased incidence of diabetes has been reported in people with lichen planus, particularly the erosive oral lichen planus variant [76, 77]. Impaired glucose metabolism is present in half of patients and 25% will have overt diabetes [78]. However, most studies have examined the presence of diabetes in those with lichen planus rather than the reverse. The link between diabetes and lichen planus is therefore still unproven, especially since both are relatively common conditions.

Pruritus

Even though there is a common assumption that itching is a symptom of diabetes, this is questionable. Studies have failed to link the presence of generalized pruritus with diabetes [79, 80]. Localized itching, particularly in the genital area, can be associated with candidal infections. The presence of xerotic skin, a feature present in individuals with and without diabetes, can also predispose to pruritus. It has been hypothesized that sympathetic nerve dysfunction leading to hypohidrosis and dry skin and peripheral sensory neuropathy can contribute to pruritus [81]. The regular use of emollients ameliorates the itch to a certain extent [82].

Clear-cell syringomas

Syringomas are adnexal non-neoplastic lesions that are derived from the intra-epidermal part of the sweat duct. They present as yellowish papules distributed around the eyes and are asymptomatic. Clear-cell syringoma is an unusual variant which has two features of note: the histological preponderance of clear cells and the frequent coexistence with diabetes mellitus [83, 84]. It has been postulated that in those affected, there may be a phosphorylase deficiency secondary to hyperglycemia that in turn results in the formation of clear cells. Generalized eruptive clear-cell syringomas have also been associated with diabetes [85].

Glucagonoma

The glucoganoma syndrome is caused by tumors of the α cells of the pancreas that secrete glucagon (Chapter 20). Even though the syndrome is rare, it needs to be considered in people with diabetes who present with diffuse atypical rashes. It consists of four major components: increased glucagon levels, diabetes (usually mild), weight loss, and necrolytic migratory erythema. Necrolytic migratory erythema occurs in 70% of cases, manifesting as an annular erythematous and figurate erythema with peripheral vesicles, pustules, and erosions (Figure 52.10). It involves the intertriginous areas and face, but can affect acral sites as well. The dermatosis can be a presenting clue, occurring 1–6 years before the diagnosis of glucoganoma [86]. It can be associated with other physical findings, including glossitis, stomatitis, dystrophic nails, and alopecia. A skin biopsy shows suprabasal acantholysis, and psoriasiform hyperplasia with pallor, ballooning and necrosis of the upper spinous layer of the epidermis [87]. The role of hyperglucagonemia in the cause of the skin eruption is unclear. Deficiency of essential fatty acids, zinc, and amino acids may be important in the pathogenesis. Resection of the pancreatic islet cell tumor clears the rash, sometimes within 48 hours. Management may also involve chemotherapy, essential amino acid and fatty acid supplementation, and the use of somatostatin or its analog octreotide, which suppresses glucagon levels and improves skin lesions.

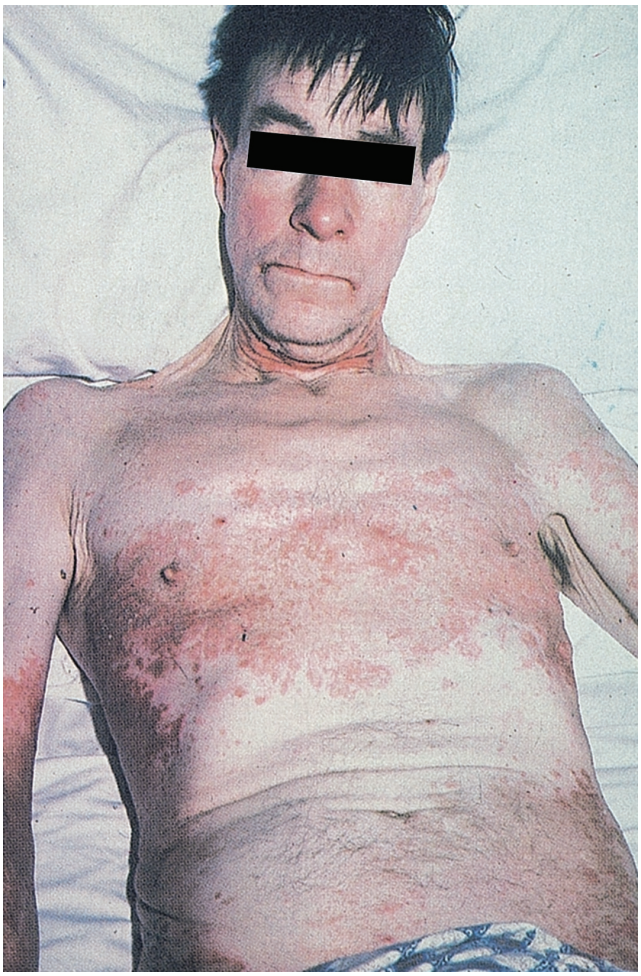

Figure 52.10 Necrolytic migratory erythema in a person with the glucagonoma syndrome. Source: Courtesy of S. Bloom, Royal Postgraduate Medical School, London, UK.

Disseminated granuloma annulare

Granuloma annulare is an inflammatory condition in the skin characterized by annular erythematous plaques with central normal skin, usually distributed in the extensor aspect of the limbs, particularly in the dorsal hands. The uncommon disseminated form of granuloma annulare has been reported with diabetes

mellitus [88, 89]. The lesions in the disseminated form are usually asymptomatic and may lack the typical annular morphology. Histology reveals granulomatous infiltration with lymphocytes and histiocytes with central areas of degenerated collagen associated with giant cells. Lesions can resolve spontaneously or persist for prolonged periods. Treatments include topical steroids, phototherapy, systemic retinoids, and topical calcineurin inhibitors [90]. The link of diabetes with generalized granuloma annulare is controversial with some authors questioning the association [91].

Iatrogenic

Reactions to insulin

Insulin allergy

Reactions to insulin were previously common due to the presence of impurities of cow or pig proteins, and preservatives or additives. The use of human and analog recombinant insulin has decreased the incidence of insulin allergy and it is now less than 1% of people with insulin-treated diabetes [55]. Allergic reactions to insulin can be classified as immediate-local, general, delayed, or biphasic. Immediate-local reactions occur within a few minutes of injection and subside within an hour. Erythema with urtication can occur and is possibly IgE mediated. Treatment of the immediate local reaction is to change the insulin to a more purified product. Systemic reactions include generalized urticaria, and rarely, anaphylaxis. Generalized urticarial reactions to purified insulins are rare [92], but a few people sensitized to animal insulins have suffered anaphylaxis with human insulin [93]. Delayed hypersensitivity reactions are the commonest, appearing about 2 weeks after the start of insulin therapy. Itchy nodules are evident at the sites of injections, 4 to 24 hours after injection. Biphasic responses have been reported in some individuals, with immediate urticaria followed by a delayed reaction several hours later. They are considered Arthus-immune complex reactions. The hypersensitivity may be to insulin itself, or to preservatives, such as aminobenzoic acid or to zinc [94]. Allergic reactions can be managed by antihistamines, addition of glucocorticoids, discontinuation of therapy, or a change in the insulin delivery system.

Lipoatrophy

Lipoatrophy occurs at sites of insulin injections and is particularly prominent with the longer-acting preparations [95]. It is characterized by a loss of subcutaneous fat and can be a cosmetic concern. This complication is less common with the advent of purer insulins. It is more common in young women with diabetes. The pathogenesis is secondary to an immunological reaction as biopsies from affected sites show immunoglobulin M and complement. Repeated injections to the same site may predispose to this problem [96].

Lipohypertrophy

Lipohypertrophy presents as soft, subcutaneous nodules or thickening at sites of repeated injections [97]. It occurs due to the lipogenic action of insulin, with repeated local stimulation of adipocytes being causative. As lipohypertrophic areas are relatively painless, young people with diabetes tend to inject the same site repeatedly, worsening the hypertrophy [10]. Insulin absorption may be delayed at such sites, potentially resulting in disruption of glycemic control [98]. It resolves spontaneously by changing the site of insulin injections. Hyperkeratotic verrucous variants of lipohypertrophy have also been described [99].

Other complications of insulin allergy

Granulomatous lesions that have a furuncular or pustular appearance can occur following insulin injections [100]. Keloids, hyperkeratotic papules, purpura, and localized pigmentation are also reported. Post-inflammatory pigmentation following insulin injection is commoner in Asian skin and may take 6–12 months to fade. Epidermal inflammation around an injection site gives hyper-pigmentation [10] and contributory factors include intradermal or intra-epidermal injections, reuse of needles, non-rotation of injection sites, and occasional injections through clothing. People using insulin pumps for subcutaneous insulin delivery can experience local infections at the site of needle insertion, contact allergy to the associated tape and tubing material, and rarely subcutaneous nodules [101]. Acanthosis nigricans can occur as

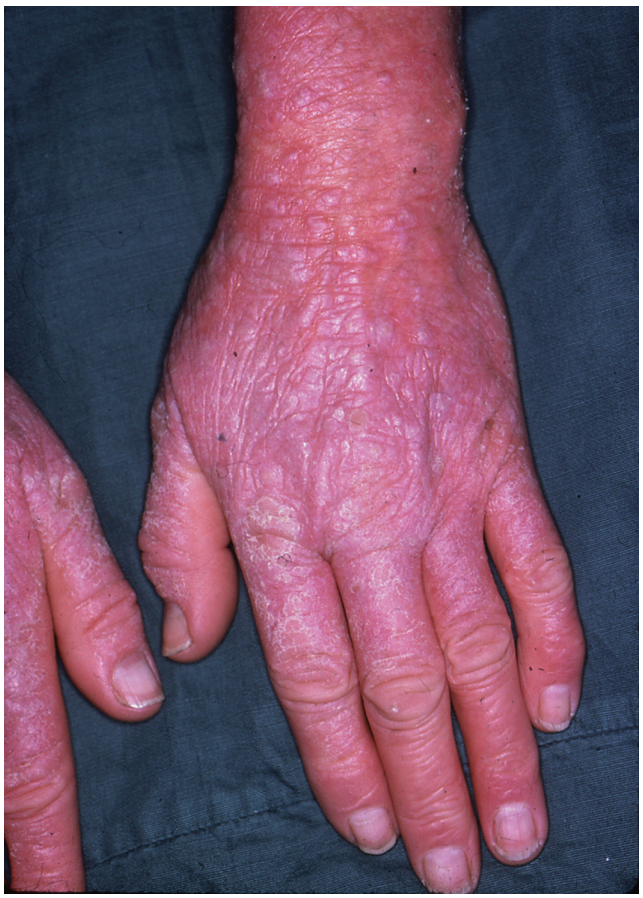

Figure 52.11 Drug rash with chlorpromazine.

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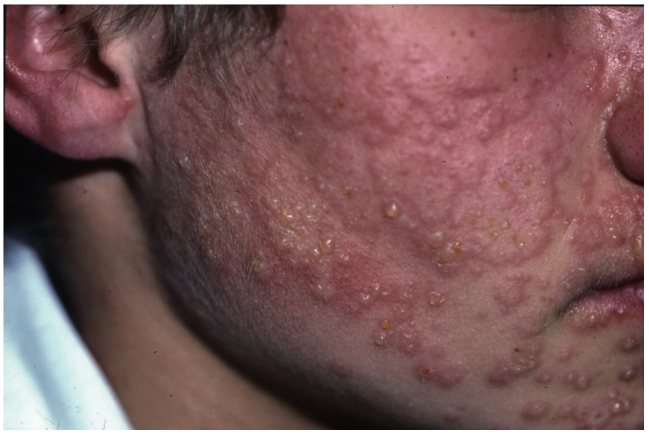

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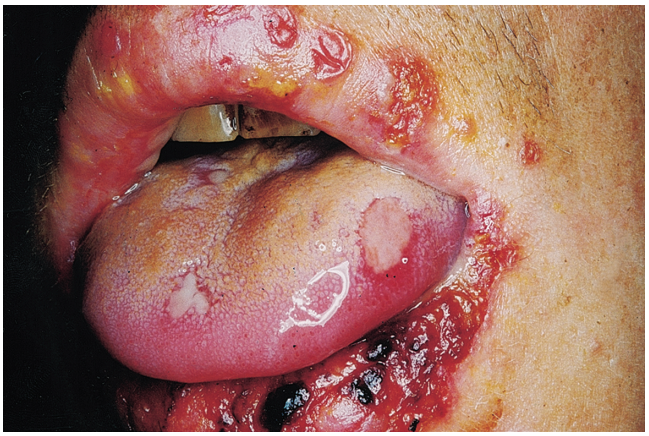

Figure 52.12 Erythema multiforme. (a) Showing the varied appearance of the condition: annular, arcuate and blistering lesions and confluent erythema on the ears. (b) Mouth ulceration in Stevens–Johnson syndrome, the severe form of erythema multiforme.

a local cutaneous side effect to insulin injections; the proliferation of the type 1 insulin-like growth factor receptor, epidermal growth factor receptor and fibroblast growth factor receptor may be causative [10].

Reaction to oral antidiabetes agents

Sulfonyureas

Sulfonylureas are the most common oral antidiabetes agents that cause skin reactions. About 1–5% of those taking first-generation sulfonyureas develop cutaneous reactions within 2 months of treatment [55]. Maculopapular, morbilliform, urticarial or generalized erythematous reactions are common and resolve with discontinuation of the medication (Figure 52.11). Photosensitive reactions, usually of the photoallergic type, as well as lichenoid eruptions have also been reported. Erythema multiforme, characterized by erythematous and hemorrhagic skin lesions associated with "target" lesions, can be a severe manifestation of drug reactions (Figure 52.12). Extensive blistering that includes the mucosal surfaces can occur and if the conjunctiva are involved, urgent ophthalmological opinion is mandatory. The chlorpropamide alcohol flush is a disulfiram-like effect occurring in 10–30% of those taking this drug. Patients experience facial erythema, headache, and palpitations about 15 minutes after drinking alcohol and it subsides in about an hour. Endogenous opioids may be important as the flush is blocked by naloxone [102]. Second-generation sulfonylureas like glipizide and glimepiride are less likely to cause cutaneous side effects. Glipizide has rarely been associated with photosensitivity, rash, urticarial, and pruritus. Glimepiride can similarly cause lichenoid skin reactions [103]. Pemphigus and psoriasiform eruptions can be precipitated by glibenclamide [104, 105].

Other oral antidiabetes agents

Rashes with other oral antidiabetes agents are much less common compared to sulfonylureas. Transient erythema or urticaria may occur with metformin. It is also reported to cause a psoriasiform drug eruption, erythema multiforme [106], photosensitivity, and leucocytoclastic vasculitis [107]. Acarbose can cause a generalized erythema multiforme. As it is minimally absorbed from the gut, it may be the degradation products of acarbose that cause the allergic reaction [108]. Acute generalized exanthematous pustulosis, a dermatosis characterized by generalized pustules all over the body, has been reported to be induced by acarbose [109]. Thiazolidinediones are not commonly associated with reactions but can cause edema, transient erythema and urticaria, as can the glinides such as repaglinide [55].

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53 Bone and Rheumatic Disorders in Diabetes

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Key points

- Musculoskeletal disorders may cause pain and disability, and adversely affect management of diabetes.
- Fibroproliferative disorders of soft tissue such as limited joint mobility, frozen shoulder, Dupuytren's contracture, trigger finger, and carpal tunnel syndrome occur more commonly in diabetes and may lead to upper limb disability.
- Charcot joint is an infrequent but serious complication of diabetic peripheral neuropathy, and is characterized by disordered osteoclastogenesis. Bisphosphonate therapy may be a useful adjunct to standard treatment.
- Individuals with diabetes are at high risk of developing gout, particularly in the presence of renal impairment and diuretic use.
- Osteoarthritis is an important cause of poor health-related quality of life in people with diabetes.
- The prevalence of diffuse idiopathic skeletal hyperostosis (DISH) is increased in people with type 2 diabetes.
- Fracture risk is increased in both type 1 and type 2 diabetes.
- Bone mineral density is decreased in type 1 diabetes, and increased in type 2 diabetes.
- Disease complications increase fracture risk by increasing risk of falls and causing regional osteopenia.
- Thiazolidinediones decrease bone formation and bone mineral density, and increase fracture risk in type 2 diabetes.
- Fracture healing may be impaired in diabetes.

Musculoskeletal disease in diabetes

Background

A variety of musculoskeletal disorders are associated with diabetes. These disorders may cause pain and disability, and influence the ability of people with diabetes to adhere to other aspects of diabetes treatment, particularly exercise and weight management. Therapies commonly used in the treatment of rheumatic disease, particularly corticosteroids and non-steroidal anti-inflammatory drugs (NSAIDs), may be particularly problematic in people with diabetes. The important bone and joint disorders associated with diabetes are discussed in this chapter and are outlined in Table 53.1.

Fibroproliferative disorders of soft tissue

Cheiroarthropathy–limited joint mobility

Limited joint mobility refers to a syndrome of joint contractures resulting in decreased passive mobility of the joints in people with diabetes [1]. Flexion contractures of the proximal interphalangeal (PIP) joints and metacarpophalangeal (MCP) joints of the hands are characteristic, with the fifth PIP joint affected first (Figure 53.1). The skin on the dorsum of the hands typically appears tight and waxy [2]. Large joints such as the wrists, elbows, ankle, and cervical spine may also be affected, and reduced lung volumes have been reported in severe cases [3, 4]. Pain is usually mild or absent early in disease, and features of synovitis such as joint swelling, effusion, warmth, and tenderness are typically absent. The disorder can be readily differentiated from systemic sclerosis by lack of Raynaud's phenomenon and other systemic features, normal nail fold capillary examination, and negative autoantibodies [5, 6].

The presence of limited joint mobility of the hands is detected clinically by assessing for the prayer sign or the table-top sign. The prayer sign is positive if patients are unable to oppose the palmar surfaces at any interphalangeal or MCP joints, when the hands are placed in the prayer position. For assessment of the table-top sign, the patient places both hands on a table top with the palms down and the fingers fanned out. The fingers are then viewed at table level. In stage 0, the entire palmar surface of the fingers makes contact with the table. In stage 1, one finger is affected (usually the fifth PIP joint of one or both hands). In stage 2, two or more fingers of both hands are affected, (usually the fourth and fifth PIP joints). In stage 3, there is involvement of all the fingers and also restricted movement in a larger joint, usually the wrist or elbow [7]. Passive joint movement should also be assessed to confirm limitation of joint mobility [8].

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Table 53.1 Bone and joint disorders in patients with diabetes mellitus.

Fibroproliferative disorders of soft tissue
Cheiroarthropathy
Frozen shoulder
Dupuytren's contracture
Stenosing tenosynovitis (trigger finger)
Carpal tunnel syndrome
Disorders of joint tissue
Charcot joint
Gout
Osteoarthritis[1]
Rheumatoid arthritis genetic risk and type 1 diabetes[1]
Disorders of bone
DISH
Osteoporosis and fractures
Disordered fracture healing

[1]Direct association not proven. DISH, diffuse idiopathic skeletal hyperostosis.

Figure 53.1 Limited joint mobility with flexion contractures affecting the finger proximal interphalangeal joints. Source: Courtesy of Dr. Tim Cundy.

Prevalence estimates for limited joint mobility in type 1 diabetes (T1DM) range from 9% to 66%, and from 25% to 75% in type 2 diabetes (T2DM) [1, 9–12]. There is some evidence that prevalence rates have declined in individuals with T1DM in the last 20 years, due to improvements in glycemic control [13].

Limited joint mobility is an important entity primarily because of its clinical associations. It is one of the earliest complications of diabetes and is strongly associated with the presence of microvascular complications such as retinopathy and nephropathy in T1DM [1, 13–16], and macrovascular complications in T2DM [10]. It is also associated with other fibroproliferative disorders affecting the upper limb such as frozen shoulder, Dupuytren's contracture, and carpal tunnel syndrome [12, 16–19]. In general, limited joint mobility does not severely impact on hand function, but combinations of these upper limb disorders may cause upper limb disability [20–22]. In addition to microvascular complications, risk factors for development of limited joint mobility in people with diabetes include older age, puberty (in T1DM), disease duration, and cigarette smoking [10, 23–25].

Advanced imaging techniques have demonstrated thickening of skin, tendons and tendon sheaths in those with limited joint mobility [26, 27]. Histological examination of the skin shows altered mucopolysaccharide distribution, elastin and collagen, and reduced vascular lumen [28]. Non-enzymatic glyclation and accumulation of collagen have been implicated in the pathogenesis [29]. Disordered glycosaminoglycan metabolism is also a feature; skin biopsies from individuals with severe limited joint mobility show pronounced hyaluronan expression in the epidermis and diminished expression in the dermis and basement membrane, compared with skin from people without diabetes and people with diabetes but without limited joint mobility [30]. In addition, increased urinary glycosaminoglycan excretion has been reported in patients with limited joint mobility [31]. Reduced circulating insulin-like growth factor 1 (IGF-1) is associated with limited joint mobility, implicating the GH-IGF axis in the pathogenesis of this complication [32]. Microvascular abnormalities also contribute to disease, with reports of disordered palmar microvascular flow in response to thermal challenge [33].

The mainstay of therapy remains obtaining excellent glycemic control, and reduced prevalence of this disorder has been reported with such interventions [13, 34]. Physiotherapy, particularly hand therapy, may be of benefit to improve joint contractures and function. Corticosteroid injection of flexor tendon sheaths has been reported to lead to resolution of finger contractures in almost two-thirds of cases related to limited joint mobility, and should also be considered [35].

Frozen shoulder

This disorder is characterized by shoulder pain, stiffness, and severely restricted range of motion in all planes [36]. Three phases of the disorder are well recognized; first, the painful freezing stage with associated nocturnal pain (lasting 4–8 months), followed by the adhesive phase with improvement in pain but severely

restricted range of motion (lasting 8–24 months), and finally the resolution phase [37]. The mean time to resolution is 30 months [37]. Plain radiographs of the shoulder are typically normal. Although the condition is usually self-limiting, some people have persistent shoulder pain and restricted range of motion many years after assessment [38, 39].

Imaging and histological studies have demonstrated that the pathological features of frozen shoulder are thickening of the capsule and synovium with contracted joint volume. Affected tissue is characterized by dense type I and type III collagen deposition with proliferating fibroblasts and a chronic inflammatory infiltrate comprising of T cells, macrophages, and mast cells [40, 41]. Disordered collagen synthesis and vascular endothelial growth factor (VEGF-1) mediated angiogenesis have also been implicated [42, 43].

Treatment is tailored to the stage of the disorder [36]. In the painful freezing stage, analgesics, including NSAIDs if tolerated, are indicated. Early use of intra-articular corticosteroids is associated with improved outcomes [44], and physiotherapy with exercise within the limits of pain is of greater benefit than more intensive physiotherapy such as stretching and mobilization [45, 46]. NSAIDs and intra-articular steroids may have similar outcomes over 6 months [47]. Although oral corticosteroids provide short-term relief in the painful freezing stage, they are not routinely recommended due to lack of long-term benefit and risk of adverse events [48]. In the adhesive phase, more intensive physiotherapy is indicated. For those who fail to respond to physiotherapy and have persistent shoulder restriction, interventions such as radiographic-guided hydrodilatation, manipulation under anesthesia, or arthroscopic release should be considered [49, 50].

Diabetes is a major risk factor for frozen shoulder. The prevalence of frozen shoulder is 11–19% of people with diabetes, compared with 2–3% age-matched controls [17, 20, 51, 52]. Individuals with diabetes are also more likely to have bilateral disease. Key risk factors for frozen shoulder in people with diabetes are older age, duration of diabetes, previous myocardial infarction, retinopathy and peripheral neuropathy [53]. The presence of other fibroproliferative musculoskeletal disorders such as limited joint mobility and Dupuytren's contracture is strongly associated with frozen shoulder in people with diabetes [53]. Furthermore, frozen shoulder in individuals with diabetes is more difficult to treat due to persistent disease and worse outcomes following surgical interventions [50, 54, 55].

Dupuytren's contracture

Dupuytren's contracture is a fibroproliferative disorder of the palmar fascia leading to formation of palmar nodules, development of a palmar aponeurosis cord with tethering of the overlying skin, and eventually flexion contractures particularly affecting the ring and little fingers [56]. Elderly men of Northern European ancestry are most frequently affected. Disordered fibroblast and myofibroblast function has been described, with deposition of type III collagen, potentially mediated by growth factors such as transforming growth factor-β (TGF-β) and basic fibroblast growth factor [57–59].

Surgical treatment is the mainstay of therapy, although nonsurgical options, particularly local injection of collagenase are promising [60]. People with diabetes have similar responses to collagenase injections as individuals without diabetes [61]. Splinting and intralesional corticosteroids are frequently ineffective [62]. Surgical referral should be considered in the presence of contracture. Various surgical approaches are available, including fasciotomy (division of the affected palmar fascia) or fasciectomy (excision of the affected palmar fascia). Percutaneous needle fasciotomy is a minimally invasive technique with good short-term outcomes, although recurrence is a frequent problem [63, 64].

Risk factors for Dupuytren's contracture include advanced age, male sex, cigarette smoking, manual labor, and alcohol consumption. Diabetes is also an important risk factor for Dupuytren's contracture, which is present in up to 26% of people with diabetes [20, 21, 65]. Age and disease duration are the major risk factors for development of Dupuytren's contracture in those with diabetes [66]. Dupuytren's contractures are also associated with microvascular complications in T1DM and macroalbuminuria in T2DM [67, 68]. Rapidly progressive contractures are less frequently seen in people with diabetes [66]. Coexistent fibroproliferative disease is frequent in individuals with diabetes-associated Dupuytren's contracture, with higher rates of limited joint mobility [68].

Stenosing tenosynovitis (trigger finger)

Trigger finger is a condition in which the flexor tendon is "prohibited from gliding through the tendon sheath because of thickening of the synovial sheath over the tendon" [69]. This disorder most frequently affects the ring finger, but may also affect the other fingers and the thumb. The patient may report a clicking sensation when moving the finger, discomfort over the palm, or overt triggering when the finger is locked in flexion [70]. Nodular or diffuse flexor tendon sheath swelling may be palpable.

The syndrome occurs due to a discrepancy between the flexor tendon and its sheath in the A1 pulley at the level of the metacarpal head [70]. The pulley becomes thickened with increased extracellular matrix and fibrocartilage metaplasia [71]. These pathological changes may be induced by repetitive trauma.

Corticosteroid injection into the tendon sheath is an effective therapy for the majority of patients, particularly in the presence of nodular disease. For people with nodular disease for less than 6 months, local injection has a reported success rate of 90% [72]. Splinting and hand therapy are useful adjuncts to local injection. If conservative therapy fails, release using a percutaneous needle approach or open surgery is indicated [73].

People with diabetes are at higher risk of trigger finger, with a lifetime risk of 10% compared with 2.6% of the general population [70]. Multiple finger involvement is also more common in people with diabetes, and is associated with presence of limited joint mobility and carpal tunnel syndrome [74]. A person's age, diabetes duration, and presence of microvascular complications

are all associated with increased risk of trigger finger in diabetes [66, 75]. Outcomes are typically worse when trigger finger is associated with diabetes, with lower responses to corticosteroid injection and greater need for surgery [76–78]. Furthermore, T1DM is associated with higher prevalence of disease, more affected digits, greater need for surgery, and higher risk of recurrence [66, 76, 78].

Carpal tunnel syndrome

Carpal tunnel syndrome is a common compressive neuropathy affecting the median nerve as it traverses with the flexor tendons through the carpal tunnel, an anatomical space comprising the carpal bones and the transverse carpal ligament [79]. The most common histological appearance is non-inflammatory tenosynovial fibrosis, with increased fibroblast number and type III collagen deposition, most likely mediated by TGF-β [80]. Compression within the carpal tunnel leads to disordered microvascular supply of the nerve, causing demyelination and axonal degeneration. The typical presentation is hand paresthesia, particularly affecting the thumb, index finger, and middle finger. Paresthesia is often more frequent at night, and may wake the patient from sleep. Wrist and hand pain may also occur, and patients frequently report hand clumsiness.

Clinical examination may be normal, but in the presence of severe and prolonged disease there may be features of median nerve denervation, including thenar wasting, weakness of thumb abduction and sensory loss over the median nerve distribution. Provocative tests including Phalen's test and Tinel's test may be positive, and if present have relatively high specificity for carpal tunnel syndrome. Phalen's test is positive if paresthesia in the median nerve distribution is reported following flexion of the wrist at 90° for 60 seconds. Tinel's test is positive if paresthesia is reported after tapping the volar wrist over the carpal tunnel. The diagnosis is confirmed by nerve conduction testing, with the typical findings of prolonged latencies and delayed conduction velocities affecting the median nerve across the wrist [81].

Treatment consists of maintaining the wrist in a neutral position using a removable wrist splint. Splinting is particularly useful for nocturnal symptoms, and may be sufficient to treat mild disease [82]. Although oral corticosteroids have short-term efficacy, side effects are usually unacceptable [83]. Local corticosteroid injection provides good short-term relief [84]. Surgical release under local anesthesia is a well-tolerated and effective therapy, which should be considered in those who have failed conservative therapy, or who have severe symptoms and signs of nerve compression [85]. Open release and endoscopic approaches have similar clinical outcomes [86].

Carpal tunnel syndrome may be caused by a number of factors including non-specific flexor tenosynovitis affecting the wrist, rheumatoid arthritis and other inflammatory synovial arthropathies, obesity, pregnancy, and disordered wrist anatomy [79]. Diabetes is one of the most common metabolic disorders associated with carpal tunnel syndrome, being present in 16% of affected patients [87]. Most studies have shown increased risk of carpal tunnel syndrome in people with T1DM or T2DM [66, 88, 89]. A survey using clinical and neurophysiological assessment reported a prevalence of carpal tunnel syndrome of 2% in a reference population without diabetes, 14% in people with diabetes but no diabetic polyneuropathy, and 30% in people with diabetic polyneuropathy [90]. Carpal tunnel syndrome is associated with duration of diabetes, and is more frequently present in those people with microvascular complications such as retinopathy, nephropathy, and polyneuropathy [66, 91]. Carpal tunnel syndrome is also more common in individuals with limited joint mobility, and it has been postulated that this disorder occurs at higher frequency in diabetes due to accelerated thickening and fibrosis of the flexor tendon sheaths within the carpal tunnel [19]. Glyclation of collagen may also reduce compliance of connective tissue within the carpal tunnel [89]. In addition, the presence of existing microvascular disease may further increase the risk of endoneural ischemia as the median nerve travels through the carpal tunnel. Carpal tunnel syndrome may be more difficult to assess in people with coexistent diabetic neuropathy, due to atypical presentation and neurophysiological assessment [90, 92]. Treatment options for those with diabetes and carpal tunnel syndrome are similar to people without diabetes, and responses to surgery are usually good [93, 94].

Disorders of joints

Charcot joint

Charcot joint is a destructive arthropathy, most commonly affecting people with diabetes in the presence of severe peripheral neuropathy. This disorder affects 0.1–0.4% of people with diabetes and may lead to severe foot deformity and disability, ulceration, and limb amputation (see Chapter 48) [95].

Several stages of disease are described [96, 97]. The developmental stage presents as acute inflammation with swelling, warmth, and erythema of the foot. Pain may be a feature, despite the presence of peripheral sensory neuropathy. Peripheral pulses are usually easily palpable. Gradually worsening deformity occurs, with bone resorption, fracture and dislocation, leading to instability of the foot and the classic rocker-bottom dislocation of the midfoot. Plain radiographs may appear normal early in the acute phase of disease (Stage 0), but MRI scans show florid bone marrow edema, subchondral cysts and microfractures, and bone scintiscan shows increased uptake on the bony phase [97]. As deformity develops, radiographs show severe osteolysis, bone fragmentation and disordered architecture (Stage 1). In the coalescence (Stage 2) phase, hyperemia resolves, swelling reduces, and skin temperature normalizes. Bone debris is resorbed and bone sclerosis may occur. The reconstructive stage (Stage 3) is characterized by remodeling of bone, ankylosis and proliferation of bone, and formation of a stable foot. The acute phase (Stages 0 and 1) typically lasts 2–6 months, and the reparative phase (Stages 2 and 3) lasts up to 24 months. During both the acute and the reparative phases of disease, bony deformity may lead to abnormal load bearing, with ulceration of overlying skin and secondary osteomyelitis.

Five separate patterns of foot involvement are identified in people with diabetes [98]: (1) affecting the forefoot with osteolysis of the MTP and IP joints of the feet, leading to the "sucked candy"

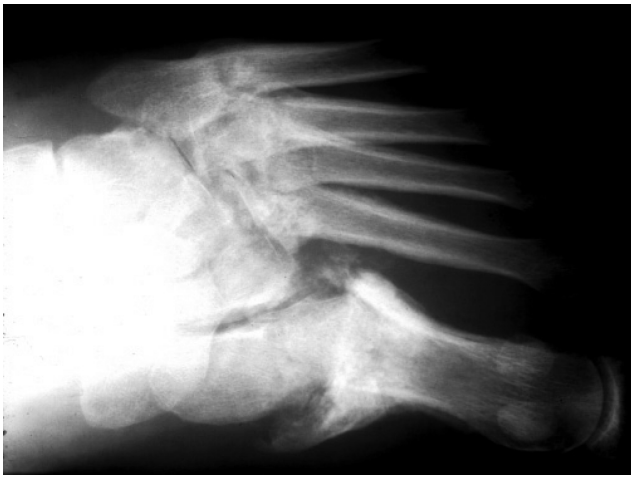

Figure 53.2 Plain radiograph of Charcot foot. Note the osteolysis, bone fragments, subluxation, and fracture affecting the tarsometatarsal joints of the foot. Source: Courtesy of Dr. Tim Cundy.

appearance on plain radiography; (2) affecting the tarsometatarsal (Lisfranc's) joint leading to instability, subluxation, and fracture (Figure 53.2); (3) dislocation and fracture affecting the midtarsal and naviculocuneiform joints; (4) affecting the ankle and subtalar joints, often with severe osteolysis; (5) affecting the calcaneus. The most common patterns are (2) and (3), and combinations of patterns may be present. Bilateral disease is present in one-quarter of patients. Rarely, other joints such as the knees, elbows, and shoulders are affected.

The etiology of the disease remains controversial [99]. Minor trauma frequently precipitates onset of disease, and may lead to subclinical bone injury that triggers an aberrant inflammatory response [100]. It is likely that disordered weight-bearing in joints affected by peripheral neuropathy leads to repetitive injury and instability (the neurotraumatic hypothesis). Additionally, autonomic dysfunction causing vasodilatation, arteriovenous shunting, and hyperemic bone resorption has been implicated (the neurovascular hypothesis). Development of osteopenia and osteolysis increases risk of fractures in the presence of abnormal load-bearing with a cycle of joint instability and fracture development, causing further abnormal load-bearing [101]. Recent work has focused on the role of local inflammation in disease pathogenesis. Advanced imaging and histological analysis have demonstrated that inflammation of synovium and bone is evident in Charcot joint, and is characterized by increased expression of the pro-inflammatory cytokines TNF-α and interleukin-1 (IL-1) [102–105]. Large numbers of osteoclasts are present within affected bone, and people with Charcot joint have greater circulating pre-osteoclast cells with increased ability to form peripheral blood-derived osteoclasts *in vitro*, compared with people with diabetes but without Charcot arthropathy and those without diabetes [105–107]. Markers of bone resorption are increased in people with acute Charcot joint [108]. Interestingly, acute phase markers are not significantly elevated, indicating an apparent dissociation between local and systemic inflammatory disease [109]. These data implicate RANKL-mediated osteoclastogenesis, driven locally by pro-inflammatory cytokines, and provide a rationale for the use of agents that target the osteoclast in treatment of the disease.

Management of Charcot joint depends on the stage of disease. Treatment during the acute phase consists of immobilization which reduces inflammation, prevents abnormal load-bearing, and stabilizes the foot in a position of least deformity. The standard immobilization method during the acute phase is a non-weight-bearing total contact cast. This treatment requires close monitoring and regular adjustment, and should be maintained until swelling and temperature normalize, and radiographs show no further bony destruction [110]. Some recent uncontrolled reports have indicated that use of a weight-bearing total contract cast may be an acceptable alternative to the non-weight-bearing option, but controlled trials are not yet available [111, 112].

The recognition that the acute phase of Charcot joint is associated with excessive osteoclast activity has led to the testing of agents targeting bone turnover for treatment of this condition. Clinical trials of bisphosphonate treatment have shown varying results, with improvement in skin temperature and bone turnover markers, but no clear benefit in immobilization rates [113]. One recently published randomized placebo-controlled trial reported increased immobilization times following zoledronate (three 4 mg infusions) [114]. A randomized trial of intranasal calcitonin demonstrated efficacy with respect to bone turnover markers, but no differences in clinical measures were reported [115]. The efficacy of TNF-inhibitors and other anti-resorptive agents such as the RANKL inhibitor denosumab has not yet been studied in Charcot joint.

Surgery is generally not considered first-line therapy, although one study has reported good surgical outcomes following débridement, open reduction, and internal fixation with autologous bone grafting in the acute phase of disease [116]. In general, surgical management is currently recommended for patients in the reparative (rather than the acute) phase of disease, and particularly for those with deformities associated with chronic foot ulcers and joint instability. Many different surgical approaches to arthrodesis have been described, including open reduction with both internal and external fixation, depending on the presence of local infection and other anatomical variables [117]. Other surgery includes exostotomy, osteotomy, intramedullary rodding, and amputation. Infection, non-union and triggering of an acute Charcot reaction are important post-operative complications, and careful post-operative management is essential.

Outcomes in people with Charcot foot are frequently poor. An analysis of 115 patients reported that non-operative management was associated with a 2.7% annual rate of amputation, a 23% risk of requiring bracing for more than 18 months, and a 49% risk of recurrent ulceration [118]. The presence of open ulcers at initial presentation or chronically recurrent ulcers is associated with increased risk for amputation.

Gout

Gout is an inflammatory arthritis caused by intra-articular deposition of monosodium urate crystals [119]. This disorder

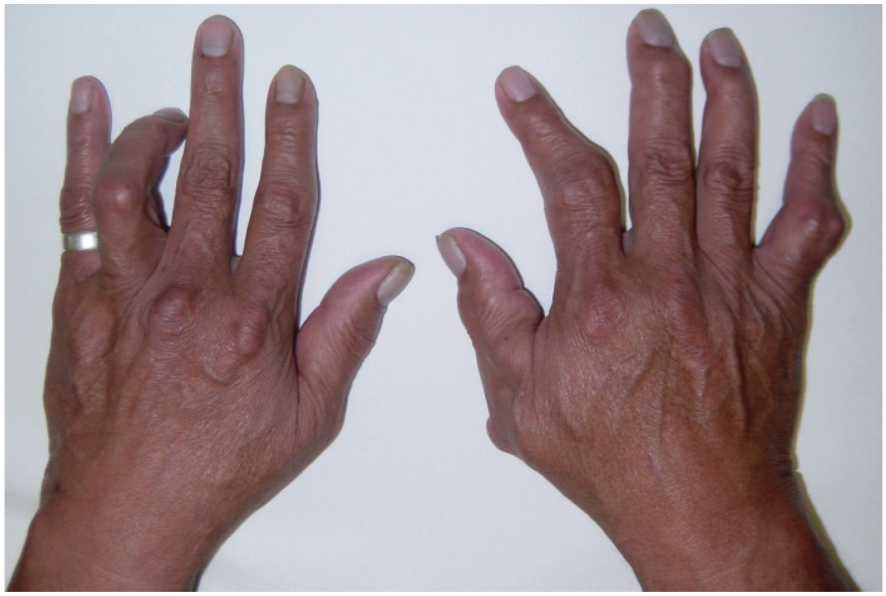

Figure 53.3 Tophaceous gout of the hands in a person with type 2 diabetes.

is the most common form of inflammatory arthritis affecting men, and affects 1–2% of the white European adult population [120]. In early disease, gout presents as recurrent episodes of self-limiting acute inflammatory attacks ("flares") of arthritis. These attacks most often affect the 1st MTP joint, midfoot, and ankle. In the presence of prolonged hyperuricemia, some individuals develop recurrent polyarticular attacks, tophaceous disease, and erosive arthritis (Figure 53.3).

The key risk factors for gout are hyperuricemia, male sex, chronic renal impairment, hypertension, obesity, diuretic use, coronary heart disease, and seafood, meat and alcohol intake [121–123]. The relationship between gout and metabolic syndrome is well recognized. Serum urate concentrations and gout are strongly associated with abdominal adiposity, and have been shown to predict the development of T2DM [124–126]. People with gout have high rates of the metabolic syndrome and T2DM compared to individuals without gout [127]. Promotion of renal tubular reabsorption of uric acid by insulin is thought to mediate this relationship [128]. Recent identification of the glucose and fructose transporter SLC2A9 as a key regulator of serum urate concentrations suggests a further etiological link between hyperuricemia and hyperglycemia [129]. The gout prevalence of up to 22% has been described in people with T2DM treated in secondary care [130]. Key risk factors for gout in this population were male sex, renal impairment, and diuretic use. Interestingly, severe hyperglycemia may reduce urate concentrations, as glycosuria has a uricosuric effect. Thus, as glycemic control improves in patients initiating treatment for diabetes, there is a potential risk of increasing serum urate concentrations and worsening gout attacks [131, 132].

Long-term urate-lowering therapy is indicated for individuals with gout who have recurrent flares, tophi, chronic kidney disease or urolithiasis [133]. Serum urate lowering to a concentration of <0.36 mmol/L (6 mg/dL) is needed to dissolve monosodium urate crystals, prevent flares and achieve tophus regression. Allopurinol is the mainstay of urate-lowering therapy, but may be ineffective at recommended doses. If the serum urate target is not achieved with allopurinol alone, further options include dose escalation of allopurinol, addition of a uricosuric agent such as probenecid or benzbromarone, or consideration of the newer xanthine oxidase inhibitor febuxostat, which provides effective urate lowering in people with diabetes and gout [134]. Options for treatment of acute gout flares include NSAIDs, corticosteroids, and/or colchicine [135]. Initiation of urate-lowering therapy is frequently associated with exacerbation of gout flares; this side effect can be avoided by commencement of urate-lowering therapy once the acute flare has resolved, gradual introduction of the urate-lowering drug, and co-prescription of low-dose colchicine.

The presence of coexistent gout has several implications for individuals with T2DM. Poorly controlled gout may hinder attempts at exercise and weight loss. For those with morbid obesity and diabetes, bariatric surgery may have beneficial effects not only on glycemic and blood pressure control, but also on control of serum urate [136]. Diuretic therapy may exacerbate hyperuricemia and should be avoided in individuals with gout unless absolutely required. Drugs such as losartan and fenofibrate have weak urate-lowering effects and may be of particular benefit in people with diabetes and gout if antihypertensive or lipid-lowering therapy is required [137, 138].

Osteoarthritis

Osteoarthritis is the most common form of arthritis and is a major cause of pain and disability worldwide. In people with diabetes, the presence of osteoarthritis leads to substantially lower health-related quality of life [139]. Increased load-bearing of articular cartilage is a key risk factor for development of osteoarthritis, and a strong positive relationship has been reported between

obesity and the risk of developing osteoarthritis [140–143]. There has been substantial uncertainty about whether T2DM is an independent risk factor for development of osteoarthritis [140, 142, 144, 145], or whether the association between T2DM and osteoarthritis is primarily mediated through increased body mass index (BMI). Recent data have suggested that diabetes itself may increase the risk for osteoarthritis independent of elevated BMI and increased joint loading. Magnetic resonance imaging studies of knee cartilage have shown that diabetes is associated with higher T2 relaxation times (indicating increased cartilage degeneration), even after adjusting for other metabolic features including abdominal circumference [146]. Diabetes is also an independent risk factor for severe osteoarthritis requiring arthroplasty, even after adjusting for BMI [147]. Furthermore, the presence of metabolic syndrome and diabetes increases the risk of knee osteoarthritis in obese women, even after adjusting for age and joint asymmetry [148]. Chondrocytes express glucose transporters and hyperglycemia has a number of deleterious direct and indirect effects on articular cartilage [149]. Inadequately controlled osteoarthritis pain is more frequently observed in people with diabetes both at the knee and hand [150, 151].

A holistic approach to osteoarthritis management is recommended, with education, exercise, and weight loss if overweight within the core management recommendations for all people with osteoarthritis [152]. Analgesic approaches include topical nonsteroidal anti-inflammatory drugs, which are generally well tolerated in people with diabetes [153]. Intra-articular steroids may provide short-term analgesia in symptomatic knee osteoarthritis, but can lead to short-lived elevations in blood glucose among people with diabetes [154]. For those undergoing hip and knee arthroplasty, diabetes is associated with higher risk of prosthetic infection, post-operative activity limitation and need for early revision [155–157].

Rheumatoid arthritis

Rheumatoid arthritis and T1DM share several genetic associations such as *PTPN22*, *HLA-DR9*, the chromosome 4q27 region, the *IDDM5* region and the *IDDM8* region [158–162]. There is evidence of familial clustering of these disorders; 2.8% of first-degree relatives of probands with rheumatoid arthritis have T1DM, compared with 0.35% of the general population [163]. The presence of T1DM is a risk factor for a particular subset of rheumatoid arthritis; anti-cyclic citrullinated peptide (CCP) positive disease [164]. Anti-CCP antibodies are associated with increased risk of persistent arthritis in patients presenting with early inflammatory arthritis [165] and development of erosive disease in those with established rheumatoid arthritis [166]. The association between T1DM and anti-CCP positive rheumatoid arthritis is in part related to the effects of *PTNP22* variants on the risk of both conditions [164].

Skeletal disease in diabetes

Diffuse idiopathic skeletal hyperostosis (DISH)

DISH is a disorder characterized by increased bone formation, particularly at the entheses (the insertions of ligaments and tendons into bone) [167]. Ossification of the anterior longitudinal ligament of the spine occurs, most commonly in the thoracic spine (Figure 53.4). Extraspinal ossification may also be identified. The prevalence has been reported to be as high as 15% in women and 25% in men over the age of 50 [168]. Patients may present with back pain and stiffness, although it remains controversial whether DISH is associated with increased back pain, and the disorder is frequently detected as an incidental finding on chest radiographs [169, 170]. Rare complications such as dysphagia, vocal cord paralysis, compression of the inferior vena cava, and neurological compression syndromes have been described in patients with florid hyperostosis [171]. Spinal fracture may occur after relatively minor injury and cause significant neurological compromise [172]. The diagnosis is made radiographically, according to the Resnick criteria, in brief: (1) presence of flowing calcification and ossification along the anterolateral aspects of at least four contiguous vertebral bodies, (2) relative preservation of intervertebral disc height and the absence of extensive degenerative disc disease, (3) absence of features of spondyloarthropathy [173].

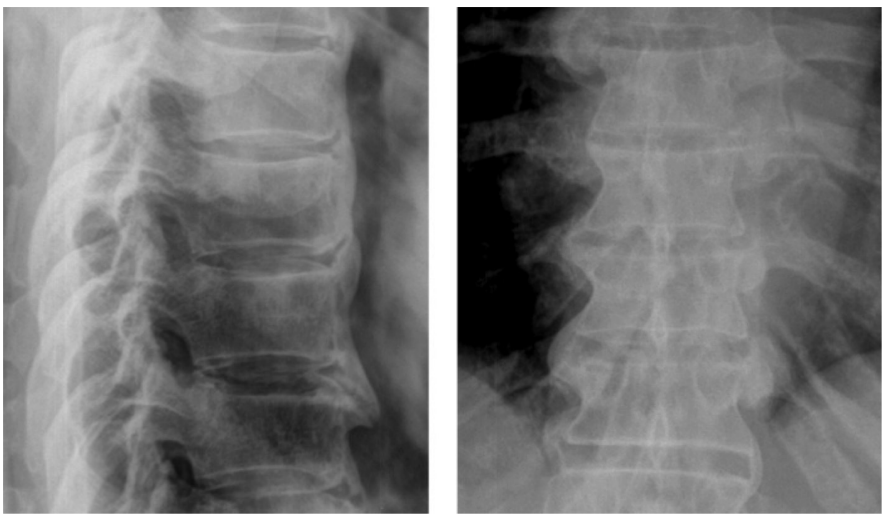

Figure 53.4 Plain radiographs of diffuse idiopathic skeletal hyperostosis (DISH) affecting the thoracic spine. Source: Courtesy of Dr. Anthony Doyle.

There have been no controlled trials of therapies in patients with DISH. For symptomatic patients, analgesics and physiotherapy are standard therapy. A small uncontrolled study of patients reported that a physiotherapy program focusing on spinal mobility, stretching and strengthening had some benefits in improving lumbar spinal mobility after 24 weeks, with no significant benefits in pain or functional outcomes [174]. Surgery is rarely required, but may be indicated for compressive syndromes caused by florid hyperostosis.

Obesity and T2DM are key risk factors for DISH [175–178]. The presence of additional metabolic disorders such as dyslipidemia or hyperuricemia further increases the risk of DISH associated with diabetes [179]. People with DISH have higher rates of hyperglycemia and higher circulating insulin levels particularly after a glucose load [176, 180]. It is likely that obesity has direct biomechanical effects, due to increased load at the entheses. Additionally, systemic factors may contribute to the development of DISH, as people with this disorder have evidence of increased bone mineral density (BMD) elsewhere in the skeleton [181, 182]. Insulin, growth hormone, and IGF-1 have been implicated in the pathogenesis of DISH, and high circulating concentrations of these hormones may contribute to the development of hyperostosis [180, 183, 184]. High expression of NF-κB, platelet-derived growth factor BB and TGF-β1 has also been reported in affected tissue in people with DISH, implicating these factors in osteoblast activation and new bone formation [185].

Osteoporosis and fractures

Background

Fragility fractures are a major cause of morbidity and public health expenditure. The most devastating fracture, that of the proximal femur, is associated with a 20% risk of dying within 6 months of the event, and a substantial risk of loss of independence [186]. Individual fractures are associated with considerable periods of disability and loss of productivity [187]. Important risk factors for fragility fracture include older age, low BMD, female gender, light body weight, previous fracture during adulthood, cigarette smoking, falls, and glucocortocoid use [186]. Dual-energy X-ray absorptiometry (DEXA) is the preferred modality for measurement of BMD. Recently, absolute fracture risk algorithms have been developed, using these risk factors, to provide 5–10-year estimates of the risk of major osteoporotic fracture, or specifically of hip fracture [188, 189].

Insight into the mechanisms by which bone loss occurs can be gained by measurement of biochemical markers of bone turnover, which reflect either osteoblast function/bone formation or osteoclast function/bone resorption. At present, bone markers are important tools in evaluating the pathogenesis and treatment of osteoporosis in clinical studies, but their utility in the management of individual patients is limited by assay variability, low predictive value for skeletal events and high cost [190].

In recent years, evidence has accrued that suggests that the risk of fragility fractures is increased in both types of diabetes, albeit perhaps by different mechanisms. In addition, attention has focused recently on the skeletal effects of treatments for T2DM, in particular the thiazolidinediones.

Fracture epidemiology in diabetes

Type 1 diabetes

Meta-analyses of observational studies have examined the relationship between T1DM and risk of fracture [191, 192]. Hip fracture is the only fracture type evaluable in these analyses, because of the paucity of studies of other fracture types. Both meta-analyses demonstrated a substantially increased (six- to ninefold) relative risk of hip fracture in T1DM [191, 192] (Figure 53.5). Studies of other fracture types in T1DM are few in number and many include only a small number of events, but they generally support the notion that non-vertebral fracture risk is increased, with relative risk estimates of 1.3–3 for any fracture [193, 194] and of 2.4 for foot fractures [195]. The only study to date to assess vertebral fractures found no increase in risk in T1DM [196].

Type 2 diabetes

Recent epidemiological studies have also suggested that fracture risk is increased in T2DM. Meta-analyses of these observational studies report increased risk of all fractures, and also those of the hip, forearm, and foot [191, 192] (Figure 53.5). Relative risk estimates for hip fracture are lower in T2DM (1.4–1.7) than in T1DM, and estimates of fracture risk at other sites in T2DM range from 1.2 to 1.4. Since the meta-analyses were published, the WHI Observational Study, which included >5000 postmenopausal women with T2DM, reported increased risks of any fracture and of fractures at several specific sites, including the hip, spine, foot, and upper arm [197]. Risk estimates ranged from 1.2 to 1.5 across the skeletal sites. The WHI study was one of the few with the capacity to evaluate vertebral fractures. Although there was an increased risk of spine fractures in the WHI study, it remains uncertain whether risk of this fracture type is higher in T2DM, as other studies have not found an association [198].

Mechanisms of skeletal fragility in diabetes

Although fracture risk appears to be increased in both T1 and T2DM, important differences might exist in the pathogenesis of skeletal fragility in the two diseases (Table 53.2). At least two mechanisms underlie the increased skeletal fragility in T1DM. The majority of cross-sectional studies of T1DM report decreased BMD throughout the skeleton, although there is no consistent association between age of participants, duration of disease, and magnitude of BMD deficit [199, 200]. Interestingly, studies performed in children and young adults demonstrate lower than normal BMD at hip and spine at the time of diagnosis [201, 202]. Taken together with the observations from longitudinal studies that BMD does not progressively decline in T1DM [203–206], and cross-sectional studies of middle-aged people with T1DM that report normal levels of markers of bone turnover [207–209], these data suggest that the observed deficit in BMD in T1DM occurs early in the course of the disease, and perhaps prior to its

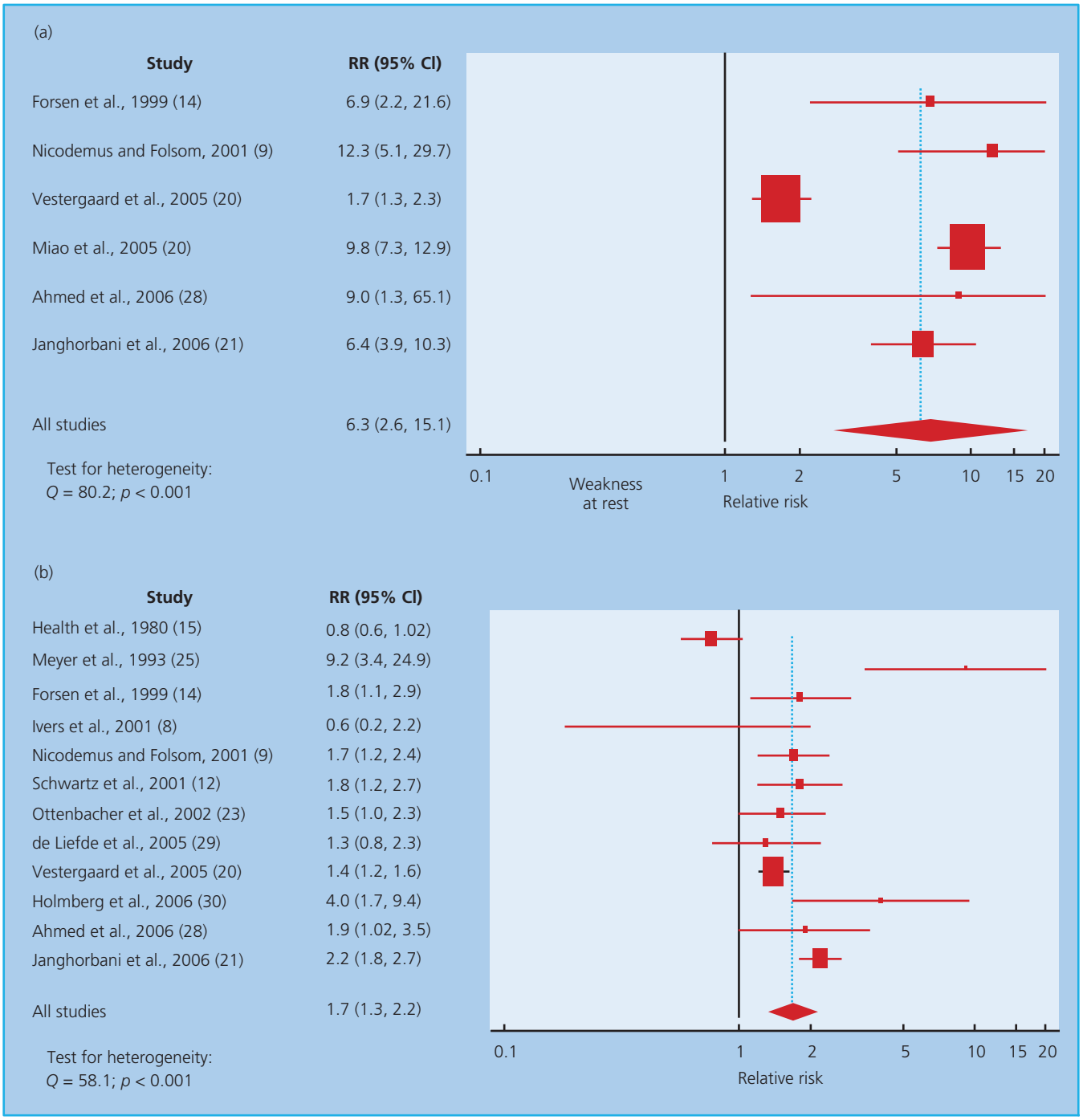

Figure 53.5 Association of type 1 diabetes (a) and type 2 diabetes (b) with hip fracture risk in meta-analyses of case–control and cohort studies. Each square shows the study-specific relative risk (RR) estimate (the size of the square reflects the study-specific statistical weight, that is, the inverse of the variance), and the horizontal line shows the related 95% CI. The diamond shows the summary RR estimate, and its width represents the corresponding 95% CI. Source: Janghorbani et al., Systematic review of type 1 and type 2 diabetes mellitus and risk of fracture, *Am J Epidemiol* 2007; **166**:495–505. Reproduced with permission of Oxford University Press.

clinical presentation. It is possible that deficiency of insulin and other pancreatic β cell hormones such as amylin and preptin, each of which has been implicated in skeletal homeostasis [210–213], contributes to the decreased BMD observed in T1DM. Recent data also implicate low levels of IGF-1 in the pathogenesis of cortical bone loss in T1DM [214]. Insulin deficiency alone is probably not sufficient to explain the lower BMD, since insulin therapy does not normalize BMD. Lower body weight may also be a factor, as

Table 53.2 Mechanisms of increased skeletal fragility in diabetes.

Type 1 diabetes	Type 2 diabetes
Decreased BMD	***Regional osteopenia***
• Lower body weight • Pancreatic β-cell hormone deficiency • Low levels of IGF-1 • Regional osteopenia secondary to neuropathy	• Secondary to neuropathy
Increased falls risk	***Increased falls risk***
• Disease complications • Hypoglycemia • Other medications	• Disease complications • Hypoglycemia • Other medications
Decreased bone quality	***Decreased bone quality***
• Advanced glycation end-products	• Advanced glycation end-products
	Disease treatment
	• Thiazolidinediones

there is a strong positive relationship between weight and BMD [215, 216].

However, the magnitude of the reduction in BMD (3–8%) is probably not sufficient to explain the higher rates of fracture in T1DM [200]. A second mechanism by which skeletal fragility is likely to be increased is via an increased propensity to falls as a result of disease complications. Neuropathy, visual impairment, cerebrovascular disease, and hypoglycemia are likely to increase falls risk. In the only study to date that has evaluated this possibility, substantially higher risks of hip fracture were observed in individuals with T1DM with a range of disease complications than in those without complications [217]. Neuropathy may also impact adversely on BMD in the distal limbs, as people with T1DM and neuropathy have lower cortical bone mass in the distal limbs than those without neuropathy [218]. Animal studies suggest that interruption of nerve supply to bone decreases regional bone mass independent of changes in mechanical loading [219]. The presence of regional osteopenia may contribute to the increased risk of distal limb and foot fractures in T1DM.

The mechanisms by which skeletal fragility is increased in T2DM is uncertain (Table 53.2). The observation that fracture risk in increased is in some ways surprising, because the higher body weight that commonly accompanies T2DM might be expected to preserve bone mass and protect against adverse skeletal outcomes. In fact, BMD in the axial skeleton *is* higher in people with T2DM than in those without diabetes [191, 197, 198]. However, BMD remains an important risk factor for fracture in T2DM, since incident fractures occur more frequently in people with T2DM and decreased BMD than in those with normal BMD [220]. The limited available evidence suggests that people with T2DM who have neuropathy and nephropathy have lower BMD than those free of these complications [191, 221].

As in T1DM, it is likely that complications of T2DM, such as neuropathy, vascular disease and impaired vision, increase the risk of falling, and thereby of fracture. In the Study of Osteoporotic Fractures, a prospective study of fracture epidemiology in older American women, participants with T2DM had a 22% higher risk of non-spine fractures than participants without diabetes [198]. Participants with T2DM who were treated with insulin had both a higher prevalence of disease complications and a higher risk of fracture than those with T2DM who were not treated with insulin. In the Health ABC study, a prospective study of older (>70 y) American men and women, there were strikingly higher prevalences of neuropathy, cerebrovascular disease, and falls in participants with T2DM who suffered a fracture, compared to those with T2DM who did not fracture [220]. Many risk factors for falls, including use of medications associated with increased falls risk, are more commonly present in populations with T2DM than in those without diabetes [222]. Low-impact falls are more frequent in individuals treated with insulin [223]. Curiously, however, adjusting for diabetes complications and/or falls risk does not necessarily attenuate the increased fracture risks observed in T2DM [198, 220].

It is possible that aspects of bone strength and/or quality that are not captured by DEXA assessment are abnormal in people with either type of diabetes, and contribute to increased bone fragility. At present, there are no validated methodologies for assessing these aspects of bone quality. Several cross-sectional studies have evaluated bone microarchitecture in small numbers of people with T2DM using high-resolution computed tomography [224–228]. Four of five studies found similar bone structural variables between participants with and without T2DM, while one reported increased porosity of cortical bone at the radius but not the tibia in the group with T2DM. In one study, microindentation analysis suggested a lower bone mechanical strength in the group with T2DM [226]. It therefore remains unclear whether abnormality of bone structure or quality exists in diabetes.

Potentially relevant to the notion that bone quality is impaired in diabetes is evidence that advanced glycation end products (AGE), products of non-enzymatic glycation, are present in greater amounts in the skeletons of diabetic animals than those of control animals [229]. The glycation of matrix proteins in bone may alter biomechanical properties in such a way as to decrease bone strength [230, 231]. *In vitro* studies suggest that AGEs inhibit differentiation of osteoblasts [229, 232] and increase differentiation of osteoclasts [233], thereby potentially altering bone remodeling and/or strength in a detrimental fashion. There may be AGE-specific effects on bone remodeling, as pentosidine decreases osteoclast development *in vitro* [234]. Mice deficient in the receptor for AGE exhibit increased bone mass and decreased osteoclast function, suggesting that the overall effect of increased AGE signaling in bone is likely to be detrimental [235]. A pivotal role for AGEs in the increased risk of fractures in diabetes implies that improved glycemic control should ameliorate the risk. However, a secondary analysis of a randomized trial of intensive glycemic control in T2DM did not find such an effect [236].

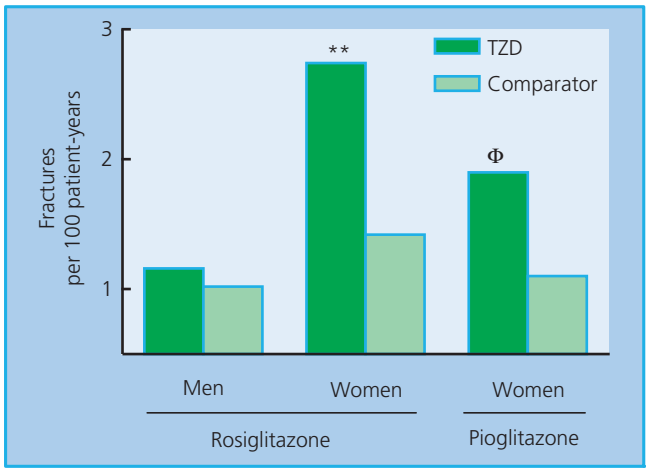

Figure 53.6 Fracture rates, captured as adverse events, in randomized, controlled trials of thiazolidinedione (TZDs). **, $p < 0.01$ vs. comparator; φ, significantly higher than comparators. Source: Reproduced with permission of A. Grey.

Finally, in T2DM, there is clear evidence that treatment with either of the currently available thiazolidinediones, rosiglitazone and pioglitazone, increases fracture risk, at least in the appendicular skeleton in women [237, 238]. Data collected as adverse events during randomized controlled trials of each thiazolidinedione in middle-aged populations with T2DM demonstrated a twofold increase in risk of distal limb fractures in women, although not in men [239–241] (Figure 53.6). However, observational data from an older cohort of individuals with T2DM suggest that fracture risk is also increased in men exposed to thiazolidinediones, and that the incidence of "classical" osteoporotic fractures (hip, forearm, humerus) is also higher in thiazolidinedione users [242].

The mechanisms underlying the adverse skeletal effects of thiazolidinediones are complex, and may involve both direct and indirect pathways (Figure 53.7). Of primary importance is the effect of the thiazolidinediones to directly inhibit bone formation, by diverting mesenchymal stem cell precursors from the osteoblast to the adipocyte lineage [237]. In addition, thiazolidinediones increase or maintain bone resorption at inappropriately elevated levels, via direct actions on osteoclast development [237, 243]. Indirect actions of thiazolidinediones that potentially contribute to their detrimental skeletal effects include decreasing systemic and skeletal production of IGF-1, modulating production of skeletally active adipokines, and decreasing levels of pancreatic β-cell hormones with known skeletal activity [238]. A substantial body of preclinical studies in rodents demonstrates that thiazolidinediones decrease bone formation and BMD *in vivo* [237]. In humans, randomized controlled trials have reported that thiazolidinediones reduce BMD over 12–18 months, although not markedly [244–247]. There was not a consistent pattern of changes in markers of bone turnover.

The skeletal toxicity of thiazolidinediones has prompted interest in the effects of other oral antidiabetes agents on bone health. At present, the available data suggest that metformin, sulfonylureas, agents that modulate glucagon-like peptide 1 signaling, and sodium-glucose co-transporter 2 inhibitors are neutral in regard to the skeleton [248].

Investigation and management of osteoporosis in diabetes

Diabetes of either type should be regarded as a risk factor for fragility fracture, and included in clinical fracture risk assessment, along with recognized risk factors such as age, gender, body weight, previous fracture, cigarette smoking, glucocorticoid use, and BMD. Recently developed fracture risk algorithms assist determination of an individual's short- to medium-term absolute fracture risk [188, 189], although they may underestimate risk in populations with diabetes [228]. Although BMD is on average

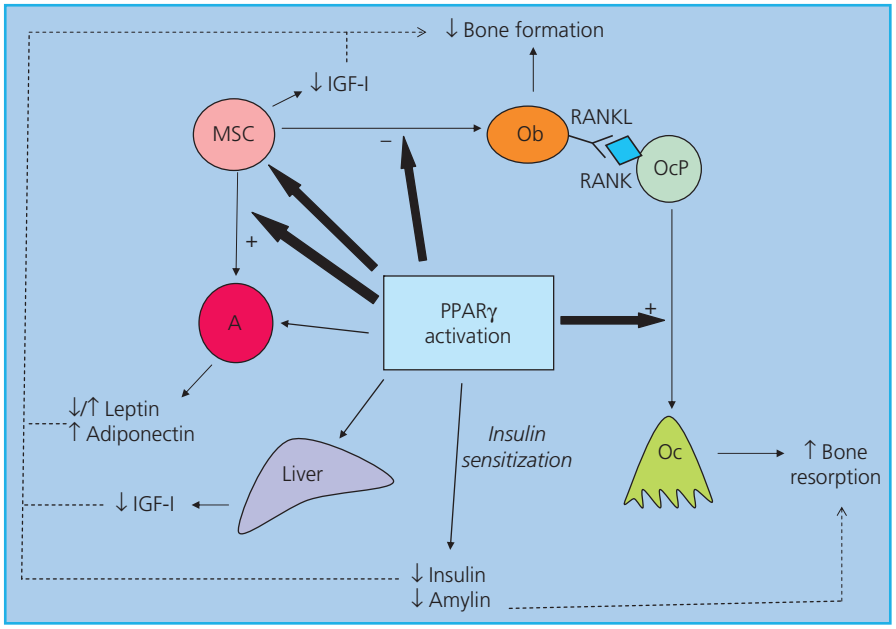

Figure 53.7 Mechanisms by which PPARγ regulates bone metabolism. Within the bone microenvironment (black arrows), activation of PPARγ signaling promotes differentiation of mesenchymal stem cells (MSC) into adipocytes (A) at the expense of osteoblasts (Ob), decreases stromal cell production of IGF-1, and promotes differentiation of osteoclast precursors (OcP) into mature bone-resorbing osteoclasts (Oc). The net effect is to decrease bone formation and increase bone resorption. Activation of PPARγ signaling at extraskeletal sites such as adipose tissue and the liver, and the ensuing effects of insulin sensitization on the β cells of the pancreas (regular arrows) may indirectly impact on the skeleton (interrupted arrows) by altering circulating levels of several hormones and cytokines, as indicated. RANKL, receptor activator of NF-κB ligand; RANK, receptor activator of NF-κB. Source: Reproduced with permission of A. Grey.

increased in T2DM, measurement of BMD in people with T2DM is still helpful in defining that person's fracture risk. Prescription of thiazolidinediones to people with T2DM who are found to be at high risk of fracture should be avoided unless there are compelling reasons to do so. Minimizing falls risk is an important component of skeletal management in diabetes; this can be achieved by targeting both macrovascular and microvascular disease complications, minimizing the risk of hypoglycemia, optimizing visual acuity, and minimizing use of other medications known to be associated with falls. Although there are no data from interventional studies on the effects of pharmacological treatments on fracture risk in diabetes, it is reasonable to assume that agents known to prevent fractures in osteoporotic populations without diabetes, such as bisphosphonates, will also be effective in diabetes [186].

Fracture healing in diabetes

Some evidence suggests that fracture healing is abnormal in diabetes. In rat models of T1DM, the mechanical and structural properties of the healing bone are inferior in the diabetic rats when compared to control animals, findings which are accompanied by evidence of both decreased callus size and collagen content [249, 250]. Interventional studies demonstrate that therapy with insulin to achieve normoglycemia is associated with fracture healing that is indistinguishable from that observed in non-diabetic animals [251, 252]. Subsequently, administration of insulin at the site of skeletal injury was also shown to promote fracture healing, without altering serum glucose, implying a role for insulin in directly mediating bone repair [253]. Few data are available from human studies, but increased rates of fracture non-union in both T1 and T2DM have been reported [254], as have higher than expected rates of serious complications in people with diabetes with open ankle fractures [255]. Diabetes is associated with a doubling of the risk of fracture-healing complications (delayed union, non-union, or malunion) [256], although long-term recovery might not be affected [257]. It is not known whether interventions specifically targeted to populations with diabetes lead to improved post-fracture outcomes. Further investigation of the influence of diabetes and its treatment on fracture repair in humans is needed.

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54 Diabetes and Cancer: Evidence for Risk, Methodology and Implications

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Key points

- Type 2 diabetes (T2DM) is associated with increased risk of several adult cancer types, independent of common risk factors such as obesity.
- The extent of the cancer risk may be overinflated in many studies due to failure to take account of several biases, including detection time bias. When these are accounted for, diabetes–cancer associations are generally very modest.
- Two hypotheses seek to explain the pathophysiological mediation between diabetes and cancer risk, namely hyperglycemia and hyperinsulinemia. There is no strong argument favoring either.
- Early studies implicated a number of glucose-lowering drug classes in either increased (insulins, TZDs, incretin-based agents) or decreased (metformin) cancer risk. In hindsight, many of these earlier analyses probably overestimated the effect sizes. Using more robust methodological approaches to reduce confounding and biases, most of the recent evidence to these questions indicates little or no effect.
- There is now a large volume of laboratory evidence supporting the plausibility of effects of glucose-lowering drug classes on tumor development. While these might not translate at an epidemiological level, there is a need to continue research on these agents to better define their efficacy.

Background

Diabetes and cancer are common chronic conditions, and they frequently coexist. Worldwide, there are 415 million people with diabetes [1]; and there are 14.1 million with new diagnoses of cancer per year [2]. In the United Kingdom (UK), it is estimated that 5 million people will have diabetes by 2025 [3], and among these, there are an estimated 730,000 people with T2DM newly diagnosed between 2007 and 2012, of whom, there will be 103,000 new cancer diagnoses in the next 10 years (personal estimates). There is recent evidence that, in T2DM populations where deaths from cardiovascular disease are declining, cancer is becoming the most common cause of death [4]. Thus, morbidity and mortality from cancer among people with T2DM is an important and common clinical problem. Estimates of co-occurrence of prevalent diabetes and cancer are age-, sex-, population, and cancer-type specific but, for example, in the Danish population, some 35% of the population will have a diagnosis of diabetes in their lifetime, 44% a diagnosis of cancer, and about 15% will have both diagnoses [5].

A link between diabetes and cancer was noted in print as early as 1914 [6], but diabetes–cancer associations were glanced over as secondary findings in papers for nearly a century and seldom were the primary outcome of interest. However, in a 1991 paper focusing specifically on this link, using population data from Sweden, Adami and colleagues [7] noted significant increases in risk of liver, endometrial, and pancreatic cancer among people with diabetes. While (in hindsight) the occurrence of pancreatic cancer was thought to be due to reverse causality (i.e. the cancer causing metabolic changes that manifest themselves as symptoms of T2DM), the other findings were higher than expected. Interest in the diabetes–cancer link peaked again in 2009, after four epidemiological studies evaluating links between diabetes therapies and cancer risk were published simultaneously in *Diabetologia*, the official journal of the European Association for the Study of Diabetes (EASD) [8]. The 2009 controversy brought together researchers from diabetes and oncology communities, and focused attentions on the methodological complexities underpinning the links between diabetes and cancer [9]. These methodological issues and their importance for clinical interpretation will be highlighted.

This chapter describes the epidemiological evidence evaluating associations between diabetes, cancer incidence and mortality, followed by a section on the interpretation of these data. The chapter will then discuss the two prevailing mechanistic hypotheses

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linking diabetes and cancer, namely hyperglycemia versus hyperinsulinemia. The central tenet of antidiabetes therapy is glucose control. From the pharmaco-epidemiological literature, there is some evidence that glucose-lowering medications might influence cancer risk, but again, discussion is required around interpretation of these data. Finally, a short section will cover the impact of diabetes in people diagnosed with cancer. Here, there are additional complexities in the interpretation of the data, beyond the scope of this chapter.

Diabetes and cancer risk: the epidemiological evidence

Cancer incidence

Over the past decade, a large volume of epidemiological evidence has accumulated of studies evaluating associations between diabetes and cancer risk, and summarized in several meta-analyses, listed in Table 54.1. In the main, the bulk of this evidence applies to populations with T2DM. These summary analyses are broadly consistent and show that diabetes is associated with an increased incident risk of the following cancer types: breast [10, 11], notably post-menopausal breast [11, 12]; colorectal [10, 13]; endometrial [14]; renal [15]; bladder [16, 17]; pancreas [18, 19]; liver [20, 21]; and non-Hodgkin lymphoma [22]. Many studies, from mainly Western populations, suggest that diabetes is inversely associated with risk of prostate cancer [23, 24], though recent analyses from studies in Asia-Pacific populations suggest the diabetes–prostate cancer relationship is the opposite, that is, a positive association [23, 25]. The reasons for these differences is an area of active research.

The above-listed relationships have been accepted by a number of international organizations, including a joint consensus statement from the American Diabetes Association, American Cancer Society, with the EASD and the European Cancer Organization [26], and a report from the American Association of Clinical Endocrinologists and American College of Endocrinology [27].

Cancer-related mortality

Findings for associations between diabetes and cancer-related mortality are broadly consistent with those for cancer incidence. There have been four major analyses (reviewed in [28]). These studies report positive associations between baseline diabetes and mortality from cancers of the colorectum (or colon), liver, pancreas, and bladder. However, associations for diabetes and mortality from prostate, breast, and endometrial cancers are less consistent than those observed for incidence of these cancers. For lung cancer (where there is no link between diabetes and cancer incidence), one large pooled analysis of 97 prospective cohorts [29], reported a significant positive association, but this was not replicated in the other analyses.

At a public health level, the mortality data are helpful as an index of disease burden. However, at a clinical level, there are limitations as mortality from cancer is conditional on the occurrence of cancer, but these studies fail to disentangle the impact of diabetes on incidence versus treatment outcome, treatment-related

Table 54.1 Summary estimates from meta-analyses of risk of incidence cancers in populations with type 2 diabetes.

Cancer type	Authors (year) (ref.)	Cohorts/case-control studies	Summary risk estimates (95% confidence intervals)
All breast cancer	Larsson et al. (2007) [11]	15/5	1.20 (1.12, 1.28)
	De Bruijin et al. (2013) [10]	unclear	1.23 (1.12, 1.34)
Post-menopausal breast cancer	Larsson et al. (2007) [11]	unclear	1.16 (1.09, 1.24)
	Boyle et al. (2012) [12]	25/15	1.27 (1.16, 1.39)
Colorectal cancer	Larsson et al. (2005) [13]	9/6	1.30 (1.20, 1.40)
	De Bruijin et al. (2013) [10]	unclear	1.26 (1.14, 1.40)
Endometrial cancer	Friberg et al. (2007) [14]	3/13	2.10 (1.93, 3.24)
Renal cancer	Larsson & Wolk (2011) [15]	9/0	1.42 (1.06, 1.91)
Bladder cancer	Larsson et al. (2006) [16]	3/7	1.24 (1.08, 1.42)
	Yang et al. (2013) [17]	15/8	1.68 (1.32, 2.13)
Pancreatic cancer	Huxley et al. (2005) [18]	19/17	1.82 (1.71, 1.94)
	Ben et al. (2011) [19]	35/0	1.94 (1.66, 2.27)
Hepatocellular carcinoma	El-Serag et al. (2006) [20]	13/13	2.50 (1.93, 3.24)
	Wang et al. (2012) [21]	32/17	2.31 (1.87, 2.84)
Non-Hodgkin lymphoma	Mitri et al. (2008) [22]	5/11	1.19 (1.04, 1.35)
Prostate cancers: Western populations	Kasper et al. (2006) [24]	12/7	0.84 (0.76, 0.93)
	Bansal et al. (2013) [23]	37*	0.81 (0.76, 0.85)
Prostate cancer: Asia-Pacific populations	Long et al. (2012) [25]	4/3	1.31 (1.12, 1.54)
	Bansal et al. (2013) [23]	8*	1.64 (1.00, 2.28)

*Unclear how many were cohort and case-control design.

morbidities and impact of T2DM on quality of life in people with cancer (see later). Furthermore, the observation that there were differences for some cancer sites between mortality and incidence suggest that some residual confounding may be present.

Type 1 diabetes and cancer

Is there a link between type 1 diabetes (T1DM) and cancer risk? This question is not always readily answered as studies often are unable to distinguish between T1DM and T2DM, and reviews on this question yield mixed results [30]. As T1DM presents in childhood, very long-term follow-up is required to detect sufficient numbers of common adulthood epithelial cancers for meaningful association analyses. Probably, for this reason, when some shorter-term studies address this question, they tend to find increases in risk of malignancies of early adulthood—such as lymphoma [31].

Large cohorts of people with T1DM are now surviving into their middle and late adulthood. A recent collaborative analysis from five countries identified 8800 cancers in populations with T1DM followed for 3.7 million person-years, and report that the pattern of increased incident cancer types mirrors that for T2DM [32]. However, overall the effects sizes are very modest and smaller than those for T2DM and cancer risk. As all these people are on long-term insulin therapy, this study concluded that they could not exclude an effect from this medication.

Interpretation of the epidemiological evidence

As a prelude to this discussion, we first define and distinguish confounding and bias, using the definitions from the STROBE (Strengthening the Reporting of Observational Studies in Epidemiology) reporting group [33]. *Confounding* literally means confusion of effects. An apparent association or lack of association is due to other factors that determine the occurrence of the disease but that are also associated with the exposure. Confounding produces relations that are factually correct, but that cannot be interpreted. *Bias* is a systematic deviation of a study's result from a true value. Typically, it is introduced during the design or implementation of a study and cannot be remedied later. Bias and confounding are not synonymous. Bias arises from flawed information or subject selection so that a wrong association is found.

Diabetes and cancer: potential confounding

A schematic representation of the causal mechanisms between diabetes and cancer risk is shown in Figure 54.1. Excess weight, commonly expressed as elevated body mass index (BMI), is a mutual risk factor for the development of T2DM and for several cancer types [34], and it is conceivable that the positive associations between T2DM and cancer incidence may simply reflect excess body weight or obesity as a confounder. There are many pathophysiological mechanisms in obesity that are common to T2DM, and may be important mediators of tumorigenesis [35]. These include alterations in sex hormone pathways, adipokines,

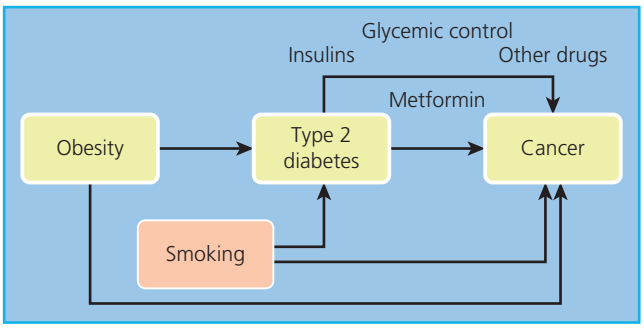


Figure 54.1 Schematic representation of the complexities of the link between obesity, diabetes, and cancer. Obesity is a mutual risk factor for type 2 diabetes and cancer, and might confound the relationship between diabetes and risk of incident cancer. Smoking is another potential mutual risk factor.

and subclinical inflammation; hyperinsulinemia and aberrations in the insulin-like growth factor (IGF) system [35].

However, it is generally held that the relationship between T2DM and cancer risk is independent of BMI [36]. There are number of justifications to support this tenet. First, whilst the list of diabetes-related cancers and obesity-related cancers overlaps, there are some exceptions. For example, there are associations between diabetes and bladder cancer, but in general, associations between obesity and bladder cancer are absent or very modest [37]. Elevated BMI is associated with increased risk of advanced prostate cancer [35], but diabetes appears to be inversely associated with prostate cancer, at least in Western populations. Second, in cohort studies where risk estimates have been specifically reported with and without adjustment for BMI, positive diabetes-cancer associations have remained for breast [38], colorectal [39], and endometrial [40] cancers.

Similarly, cigarette smoking is a mutual risk factor for the development of both diabetes and several cancer types. Although, this question is understudied, as few diabetes-related cancers are smoking-related cancers, it would seem that smoking is not a major confounder. Nonetheless, smoking status is important to consider in the interpretation of BMI-cancer associations as smokers tend to have lower mean BMI compared with non-smokers; and smoking is important in studies where mortality is the endpoint as smoking-related non-neoplastic causes of death (e.g. cardiovascular disease) might compete with neoplastic causes of death.

A note on ethnicity is pertinent. In the United States, compared with non-Hispanic whites (11%), the age-standardized prevalence of diabetes is higher among non-Hispanic blacks (22%), non-Hispanic Asians (21%), and Hispanic persons (23%) [41], but cancer incidences are generally lower in the latter three ethnic groups compared with white populations. An exception is the incidence of prostate cancer, which is higher among non-Hispanic blacks compared with white populations. Finally, cancer screening is an additional confounder—as there may be differential rates of cancer detection and diagnosis between populations with and without diabetes, if there were differential rates of cancer

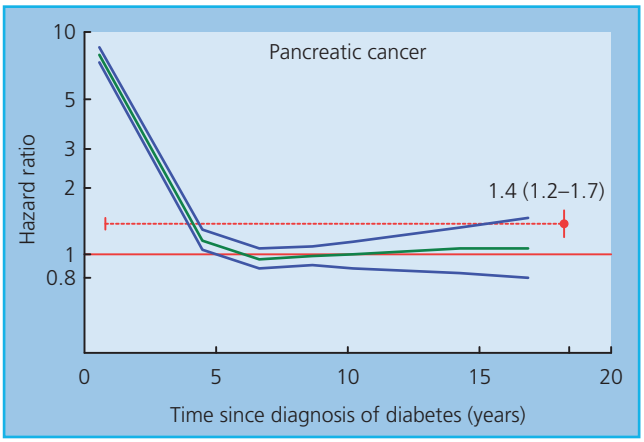
screening. Thus, with colorectal cancer as an example, there are several trial-proven effective approaches to colorectal cancer screening—including fecal occult blood testing (FOBT), once-only flexible sigmoidoscopy, and colonoscopy—but some evidence (reviewed in [28]) that people with T2DM underutilize colorectal cancer screening programs. For breast cancer screening, similarly, data indicate lower rates of attending mammographic screening among those with diabetes than those without (reviewed in [28]). As a final note to cancer screening, it is important to note that the risk estimates in Table 54.1 are relative (rather than absolute) risk. These are very modest elevated risks at an individual level and people with T1DM and T2DM do not require enhanced cancer screening.

Diabetes and cancer: potential biases

There are a number of potential biases important to the interpretation of the diabetes–cancer association. These include:

1 Detection time bias: This bias arises due to the co-diagnoses in the same time window of the disease exposure of interest (here, diabetes) and outcome of interest (here, cancer). Thus, there is a peak co-diagnosis of diabetes and cancer in the first 2 to 3 years after initial diagnosis of diabetes. However, these cancers diagnosed shortly after a new diagnosis of diabetes are generally not caused by diabetes. Inclusion of these cancers temporarily early post diagnosis of diabetes exaggerate the risk estimates for the diabetes–cancer associations (see Figure 54.2). This "co-diagnosis peak" (and potential detection bias) is common for several cancer types after a new diagnosis of diabetes [42]. Some investigators refer to this as protopathic bias [43], and argue that it is a serious cause of inflated risk estimates between diabetes and cancer incidence. Within the "co-diagnosis peak," there are at least three underlying causal relationships: (i) reverse causality, (ii) heightened clinical investigations (ascertainment bias) from diabetologists, and (iii) heightened clinical investigations from the oncology team. The simple methodological solution is to use an incident diabetes cohort and exclude cancers diagnosed in the first 2–3 years. An alternative solution is to use time-varying hazard models as shown in Figure 54.2.

2 Immortal time bias: This refers to a period of follow-up during which, by design, death or the study outcome cannot occur [44]. This bias is common and well known in the pharmaco-epidemiology literature, but not always appreciated in the general clinical epidemiology literature. In pharmaco-epidemiology studies, immortal time typically arises when the determination of an individual's treatment status involves a delay or wait period during which follow-up time is accrued. This wait period is considered immortal because individuals who end up in the treated or exposed group have to survive (be alive and event free) until the exposure definition is fulfilled—for example, at least two prescriptions of an antidiabetes therapy. If they have an event before starting treatment, they are placed in the untreated or unexposed group. Bias is introduced when this period of "immortality" is either misclassified (a misclassification bias) with regards to treatment status or excluded from the analysis (a selection bias). Immortal time bias is particularly problematic because, first, it biases the results in favor of the treatment under study by conferring a spurious survival advantage to the treated group (a misclassification bias), and second, by excluding the survival time in persons who later take up the treatment, the survival times of the narrowly defined non-treatment group is disadvantaged (selection bias) (Figure 54.3). These principles can be readily expended to diabetes as the exposure and incident cancer is the event of interest. Immortal time bias should be suspected in fixed cohort analyses where the covariate diabetes is handled as an "ever/never"



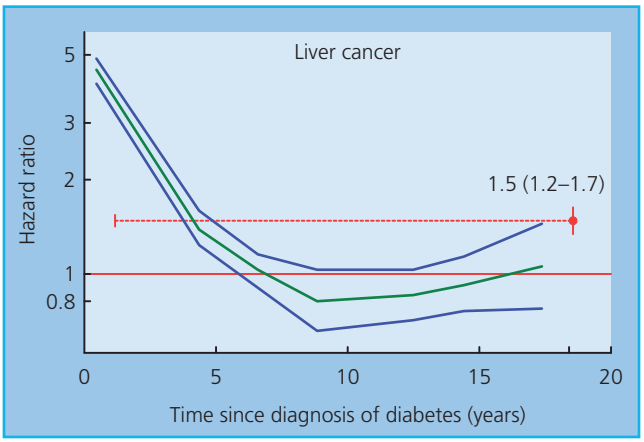


Figure 54.2 Detection time bias. This bias arises due to the co-diagnosis in time of the disease exposure of interest (here, diabetes) and outcome of interest (here, cancer). The hazard plots here are based on data from Adami et al. 1991 [7] and show how the hazard varies with time since diagnosis of diabetes, shown for pancreatic and liver cancers. There is a peak co-occurrence of the diabetes and cancer in the first 2 to 3 years. However, these cancers are not caused by diabetes. If we include these cancers in the risk association model (fixed cohort analysis: shown as a red dotted line), the net risk estimates are 1.4 and 1.5, respectively, and 95% confidence intervals (CIs) are greater than one, suggesting a significant positive association. However, in the preferred time-varying model (shown as a green line and 95% CIs as blue lines), the hazard between 5 and 15 years after diabetes diagnosis is close to one, that is, null association. It is only 15 years after diabetes diagnosis, that there is a suggestion of a positive "causal" association between diabetes and risk of pancreatic and liver cancers.

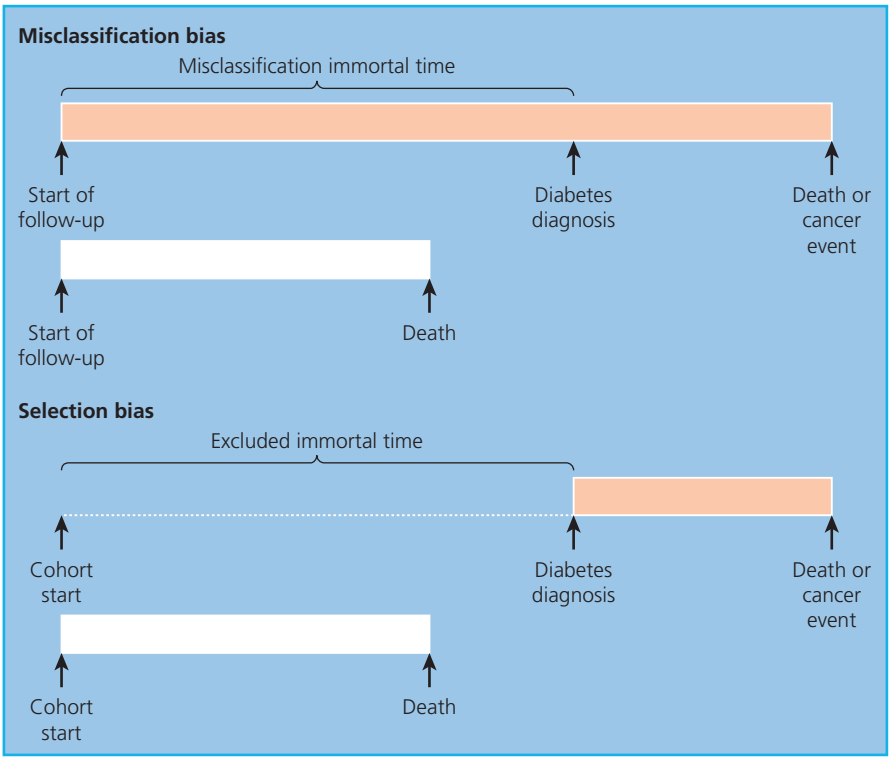


Figure 54.3 Immortal time bias is introduced in cohort studies when the period of immortal time is either incorrectly attributed to the treated group through a time-fixed analysis (top) or excluded from the analysis because the start of follow-up for the treated group is defined by the start of treatment and is, by design, later than that for the untreated group (bottom). Source: Schematic diagram adapted from [45]. Reproduced with permission of BMJ Publishing Group Ltd.

term. A methodological solution is to use time-varying models [45, 46].

3 Allocation bias: This is particularly prevalent in pharmacoepidemiological studies (discussed later) and is sometimes referred to as confounding by indication. An example might be where insulin therapy is generally prescribed late in the course of diabetes when patients are older and "sicker." Not surprisingly these biases result in an apparent increased cancer risk [47]. Methodological solutions require advanced methods such as inverse probability weighting, which is to model the data with two time-updated terms in the model [48].

4 Survival bias: This bias is due to differential survival (or differential loss to follow-up) in those undergoing the index exposure (here, diabetes or diabetes therapies) compared with that of the comparator group. In turn, this will differentially influence the number of individuals at risk of developing the index event of interest (here, subsequent incident cancer). This is sometimes referred to as susceptibility bias, and is a specific form of selection bias. The methodological solution here is to use competing risk analyses.

Hyperglycemia versus hpyerinsulinemia hypotheses

What are the drivers of cancer development in people with diabetes? There are broadly two theories: (i) hyperglycemic, and (ii) hyperinsulinemic hypotheses [49].

Excess blood glucose is the hallmark of diabetes and could be a major risk factor for cancer development [50]. Pre-diabetes is also associated with an increased risk of cancer [51]. This hypothesis suggests that hyperglycemia is a confounder in the observed increased risk of cancer outcomes associated with increasing use of "late pathway" drugs, for example, insulin therapy. When looking at evidence from *in vivo* studies, it is true that transformed cells have a high glucose requirement, in keeping with their high rates of glycolysis relative to normal cells, as first recognized by Otto Warburg, and it is still conceivable that hyperglycemic conditions would give cancer cells a relative growth advantage. However, most cancer cells have a constitutively high level of glucose uptake, and are able to fully satisfy their glucose requirements under normoglycemic conditions [52]. Experimental studies exploring dose–response relationships between glucose concentration and tumor growth generally show that increasing glucose concentration does increase proliferation, but with a plateau occurring around 5 mmol/L. There is some population-level evidence that very high or low levels of HbA_{1c}, the marker of average glucose in the blood, is related to mortality [53]. However, cancer risk does not appear associated with the duration or intensity of hyperglycemic exposure, and glucose-lowering therapy does not appear to diminish the risk of cancer in people with diabetes. For example, a meta-analysis of major trials into intensive glycemic control and cancer risk concluded that it is unlikely that hyperglycemia plays a role in cancer development [54]. Further evidence comes from data comparing antidiabetes therapies and categorizing drugs that increase insulin levels (exogenous insulin or secretagogues) and comparing these to drugs that lower insulin levels such as

metformin and thiazolidinediones. If within the drug groups one stratifies the populations by glycemic control and see no difference by HbA_{1c} status, this evidence would dispute the hyperglycemia theory [55].

T2DM is characterized, in the early stages, by insulin resistance and consequent hyperinsulinemia. The latter promotes tumor cell growth directly via insulin receptors [56], but effects may additionally be mediated indirectly via the type 1 IGF receptor [56]. In turn, many cancer cell lines express insulin and IGF receptors. Therefore high endogenous insulin levels or administration of exogenous insulin could theoretically have a promoting effect on neoplastic disease. Insulin resistance may also promote cancer risk via other mechanisms, such as decreased sex-hormone binding globulins leading to excess estrogen and stimulation of estrogen-dependent tumors or inflammation. Insulin resistance is also associated with a higher production of NEFA, interleukin-6, plasminogen activator inhibitor-1, leptin, and tumor necrosis factor α [35]. Notably, cancers are heterogeneous and insulin responsiveness is not universal. Nonetheless, the accumulation of experimental and epidemiological evidence is consistent with a hyperinsulinemia hypothesis, but overall, there is no strong argument favoring either hyperinsulinemia or hyperglycemia as the single key driver of tumorigenesis.

Pharmaco-epidemiology: glucose-lowering agents and cancer risk

Interpretation

All the confounding and biases described earlier, in relation to interpretation of epidemiological studies evaluating diabetes and cancer risk, also apply to pharmaco-epidemiology. Specific to diabetes therapies and cancer, these have been addressed in a concept paper from the Diabetes and Cancer Research Consortium (DCRC), an international group mainly focusing on pharmaco-epidemiological queries in the complex relationships between diabetes, diabetes treatment, and cancer risk [47]. In this framework document, two important methodological features were emphasized: (i) the need to account for detection time bias; and (ii) the need to set up data to account for time-varying exposures. The interpretations of many early "first-generation" reports were limited by failure to take account of these key analytical issues [46].

Allocation bias deserves specific comment. To address this bias, one solution advocated by the DCRC group is to model the data with two time-updated terms in the model: (i) a binary term for ever exposure up to that time point, and (ii) a continuous term for cumulative exposure [48]. Further methodological work from DCRC members came when Walker and colleagues [57] summarized the problems of capturing drug exposure from observational datasets and described optimal methodology to reduce this bias. For instance, they illustrated that different drugs are administered to control glucose as T2DM progresses, making direct "trial-like" comparisons between drug classes uninterpretable. In this setting, the use of ever/never drug exposure categories only should be avoided, and cumulative exposure handled statistically as a time-varying covariate—we refer to these as "second-generation" studies [46]. These points are worth remembering when reading the next sections.

Table 54.2 Anti-tumor mechanisms of action of metformin in the laboratory.

Mechanisms of action
• Activation of LKB1/AMPK pathway
• Induction of cell cycle arrest and/or apoptosis
• Inhibition of protein synthesis
• Reduction in circulating insulin levels
• Inhibition of the unfolded protein response
• Activation of the immune system

Source: Adapted from [59] with permission of Springer.

Metformin and cancer risk

For almost a decade, there have been suggestions in the epidemiological literature that, among people with T2DM, use of metformin is associated with a reduced risk of certain cancers [58]. Coupled with these observations, there are now many laboratories across the globe exploring the role of metformin in cancer, and several novel anti-cancer mechanisms have been demonstrated and validated, beyond its well-known clinical glucose-lowering effects [59] (Table 54.2). In an era when oncologists are encouraged to repurpose inexpensive licensed drugs, metformin seemed a strong candidate, and led one UK mainstream newspaper to headline "A diabetes pill that costs just 2p a day could prevent thousands dying from Britain's biggest cancer killers" [60].

However, we now understand that many of the earlier epidemiological studies on this question contained time-related biases that artificially made metformin look "protective." Most important of these was immortal time bias, described earlier. The net result of this bias is an advantage to the users of the drug of interest (here, metformin) when the analysis is simply categorized by ever/never use. This was well illustrated by Suissa and colleagues [61], who found that immortal time bias was prevalent among many studies that reported a reduced cancer risk associated with metformin use. By contrast, those studies that used methods to avoid these biases reported no effect of metformin use on cancer incidence.

Here again, treatment allocation bias is a potential pitfall to interpretation. For example, metformin is first-line treatment for diabetes, and is therefore used earlier in the disease course than other medications. Those who achieve control with metformin alone differ in disease severity from those who require additional medication. Differential allocation of drugs based on such confounding factors tends to exaggerate the "protective" benefits of metformin. Differential allocation is an inevitable bias in observational studies and has to be addressed within a randomized trial framework. Primary cancer prevention trials are currently impractically huge and thus investigators have selected to test the hypothesis that metformin is cancer protective in the

secondary cancer prevention setting. An example is an adjuvant trial in early breast cancer, NCIC MA.32, with a primary endpoint of 5-year invasive cancer-free survival [62]. The recruitment target (3582 women without diabetes) was completed in early 2013—the results of this trial are soon to be reported.

The third key appreciation in the story of metformin and cancer lies in the biology. It has become clear that many preclinical *in vivo* studies use concentrations of metformin higher than those safely obtained in the clinical setting. Most *in vitro* studies report using doses of metformin between 1 and 40 mM, which is well above the feasible therapeutic plasma levels (0.465–2.5 mg/L or 2.8–15 mM) in humans [63]. It is possible that metformin causes an energy stress in these studies that far exceeds effects seen clinically.

Insulins and cancer risk

There are hypothetical physico-chemical reasons why some insulins might be pro-tumorigenic. Specifically, molecular engineering of the insulin molecule to form some insulin analogs results in a molecule that "looks" more like IGF-I, with high affinity for the type 1 IGF receptor [64] (Figure 54.4). This receptor and its downstream pathway are important for tumor development.

In the late 2000s, several observational studies evaluated the putative link between insulin glargine and cancer risk, and were subsequently meta-analyzed in several reviews (reviewed elsewhere [65]). In general, there are many inconsistencies in the findings of these meta-analyses. In turn, these reflect important design differences in the included studies. For example, some studies evaluated any insulin use versus non-insulin therapies in people with diabetes, while others evaluated glargine versus non-glargine insulin use. As insulins are generally prescribed late in the course of diabetes, patients are older and "sicker" and not surprisingly these biases result in an apparent increased cancer risk. None of the meta-analyses directly addressed the problem of time-related biases. For similar reasons, lumping data from case-controls (where time-varying exposures generally cannot be modelled) with cohorts is problematic.

The publication of the ORIGIN trial in 2012 brought some clarity to the above inconsistencies (this debate is expanded upon elsewhere by the authors [65]). This trial randomly assigned 12,537 people with impaired glucose tolerance or T2DM to receive insulin glargine versus standard care [66]; the largest trial of its type. Although the protocol endpoints were cardiovascular non-fatal events or deaths, following the concerns emerging about cancer links in the late 2000s, the investigators additionally detailed risk per cancer type by treatment allocation. There were no differences between treatment arms for all cancer incidence or deaths, and no differences between treatment arms for specific reported cancer types. These data seem definitive, although there are some caveats. First, although median follow-up was 6.2 years in the ORIGIN trial, there is a rapid drop-off thereafter such that only 14% of recruited participants were followed to the seventh year. Many cancer epidemiologists would consider this lag period too short to assess associations between an exposure and cancer incidence. Second, there was considerable contamination of insulin use across the trial arms.

Pioglitazone and cancer risk

Pioglitazone and rosiglitazone are thiazolidinediones, which act as PPARγ agonists and are used as second-line therapies in the treatment of T2DM. However, their use has been questioned owing to safety concerns. In preclinical studies, exposure of male rats to pioglitazone was associated with an increased risk of bladder cancer. In 2005, the ProActive trial (a large European randomized controlled trial evaluating the effects of pioglitazones on cardiovascular outcomes) found a non-significant increase in the incidence of bladder cancer in the pioglitazone-treated group. Based on these animal studies and trial data, the U.S. Food and Drug Administration (FDA) commissioned the manufacturer to carry out a 10-year observational cohort study to further examine this risk. An initial mid-term analysis showed that 2 or more years of cumulative exposure to pioglitazone was associated with an increased risk of bladder cancer [67]. Around the same time, a similar increase in risk was observed in a French cohort [68], which led to the withdrawal of pioglitazone from France and Germany.

More recently, two large analyses suggest a lack of association between pioglitazone and bladder cancer. Levin and colleagues

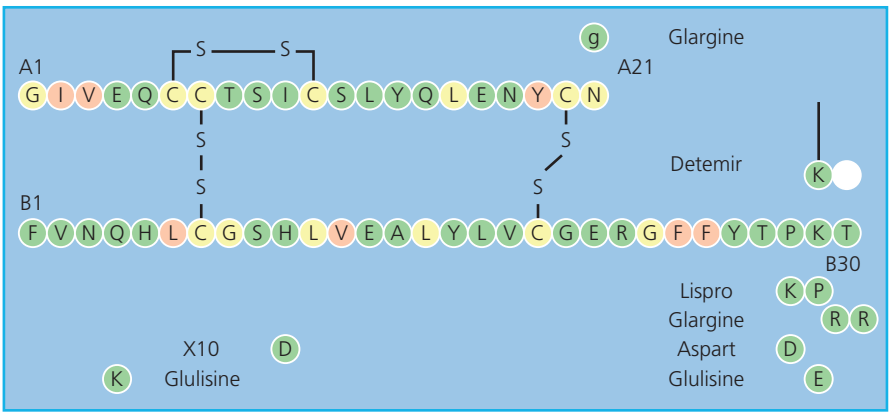


Figure 54.4 Schematic representation of molecular engineering of the insulin molecule. Most of the engineering is in the B chain, except for glargine, which also has an amino acid substitution in the A chain. These molecular changes make insulin glargine more IGF-I "like." The net results are twofold: increased affinity for the mitogenic IGF-I receptor (IGF-IR) and slower dissociation time off the IGF-IR. Source: Modified from [64].

[48], on behalf of the DCRC, performed an international (six populations) cumulative exposure analysis on 1.01 million persons with diabetes with 3248 incident bladder cancers; while Lewis et al. [69] reported a lack of association between pioglitazone use in persons with diabetes and incident bladder cancer in the 10-year follow-up of a Kaiser Permanente Northern California (KPNC) cohort (193,099 persons: 1261 bladder cancers). Both analyses found no associations between pioglitazone use and incident bladder cancer risk. An additional study from the KPNC group indicated that proteinuria testing in people with diabetes may be a confounder in studies of pioglitazone and bladder cancer [70].

Incretin-based drugs and cancer risk

Incretin-based glucose-lowering medications were introduced to the US market in 2005 and have proven to be effective glucose-lowering agents, both as glucagon-like peptide 1 receptor agonists (GLP-1RA) and as dipeptidyl peptidase 4 (DPP-4) inhibitors. From 2011, surveillance from the US FDA adverse events reporting system started to identify significantly higher risk of pancreatic cancer for GLP-1R agonists and DPP-4 inhibitors, and significantly higher risk of thyroid cancer for GLP-1R agonists. A hypothesis emerged that both drug classes promote acute pancreatitis, and then initiate histological changes suggesting subclinical chronic pancreatitis with associated pre-neoplastic lesions (e.g. ductal proliferation), and potentially, in the long run, pancreatic cancer [71]. These data initially came from pharmaco-vigilance databases and are particularly challenging to interpret for several reasons: long-term use of incretin-based glucose-lowering is limited, and there had been inadequate adjustment and modelling to take account of the biases and confounding outlined in the early paragraphs. Additionally, it is unclear whether or not pre-clinical animal model data translate directly to human cancer development.

Since these initial reports, subsequent studies have failed to demonstrate associations between incretin-based drug use and pancreatitis (reviewed in [72]), with one study pointing out that associations with pancreatitis might reflect diabetes severity rather than drug use per se [73]. For cancer, animal studies suggest a role of GLP-1R activation in the development of pancreatic cancer and thyroid cancer in rodents, but such an effect in humans seems less likely as there is relative lack of expression of GLP-1R on pancreatic ductal cells and thyroid tissues [72]. Elevated risk of pancreatic or thyroid cancers have not been replicated in human observational studies or analyses of data from clinical trials. Based on current evidence, continuous monitoring of the cancer issues related to incretin-based therapies is required.

Other medications

It is important to note that people with diabetes are commonly on several other medications, in addition to those specifically prescribed as glucose-lowering drugs. There include aspirin, statins, and antidepressants, all of which have been implicated in cancer risk reduction in other settings. The time-dependent interrelationships between the use of these drugs is clearly complex to model, and with a few exceptions [74], is currently understudied.

Impact of diabetes on outcome after cancer diagnosis

While the link between diabetes and incident cancer risk is now established, it is less clear, and indeed, more complex, to interpret whether diabetes at or after cancer diagnosis, impacts adversely on outcome. In general terms [detailed elsewhere (28)], there are two distinctive study designs: (i) inception cohort studies evaluate the effect of baseline diabetes on cancer-related mortality in general populations; whereas (ii) the oncology literature often uses cohorts of patients with a cancer diagnosis and pre-existing T2DM and evaluates the endpoints of cancer-specific survival (or mortality). Some epidemiologists refer to the latter as case fatality studies. The clinical implications of the findings from these study types differ considerably; in statistical terms, time zero is at baseline cohort entry in the former; whereas time zero is date of cancer diagnosis or cancer initial treatment in the latter.

Within the above two study types, there are multiple levels of potential confounding and biases of cancer morbidity and mortality studies. A methodological group of the DCRC has identified nine levels on the cancer pathway at which confounding may arise [28]: cancer screening use; stage at diagnosis; cancer treatment selection; cancer treatment complications and failures; peri-treatment mortality; competing risks for long-term mortality; effects of T2DM on anti-cancer therapies; effects of glucose-lowering treatments on cancer outcome; and differences in tumor biology.

In the face of the above limitations, the current evidence on the impact of diabetes on outcome after cancer diagnosis is as follows: (i) diabetes is associated with increased all-cause mortality in people with cancer, but the evidence that it influences cancer-specific mortality is inconsistent (reviewed elsewhere [28]); (ii) for some cancers, there is evidence that people with T2DM present with more advanced disease, receive suboptimal treatment, and have poorer oncological outcomes [75]; and (iii) compared with people with cancer but without diabetes, people with cancer and diabetes have a poorer quality of life and reduced physical activity [76].

Clinical implications

For day-to-day clinical practice, there are a number of key messages. First, T2DM is associated with increased risk of several adult cancer types, independent of common risk factors such as obesity. However, these elevated risks are generally very modest. While it is important that people with diabetes partake in cancer screening

programs, in common with the rest of the general population, they do not require enhanced cancer screening. This is best illustrated by colorectal cancer screening, where some commentaries have advocated high-risk screening colonoscopy for people with diabetes [77]. The British Society of Gastroenterology [78] classify risk in individuals with a family history of colorectal cancer (and without a hereditary syndrome) as moderate and subdivide this into *high-moderate* risk (lifetime risk: 1 in 6 to 10) and *low-moderate* risk (lifetime risk: 1 in 12). The recommendation in these individuals is early screening colonoscopy. The lifetime risk for colorectal cancer in people with diabetes is 1 in 20 to 40. There is therefore no need for screening colonoscopy above and beyond the general population.

Second, two hypotheses seek to explain the pathophysiological mediation between diabetes and cancer risk, namely hyperglycemia and hyperinsulinemia. There is no strong argument favoring either. In terms of general management of people with diabetes and the minimization of cancer risk, the extrapolation of recommendations applicable to the risk reduction of cardiometabolic complications seem appropriate. There is no strong case to have cancer prevention-specific recommendations among people with diabetes. Thus, shared (cardio-metabolic) recommendations including weight management, optimal glucose control, and treatment of elevated blood pressure and dyslipidemia are applicable.

Third, a number of glucose-lowering drug classes have been implicated in either increased (insulins, thiazolidinediones, incretin-based agents) or decreased (metformin) cancer risk. Most of the recent evidence to these questions has been reassuring. This information can be conveyed to people already on these medications or about to commence these as new therapies.

Finally, there is now a large volume of laboratory evidence supporting the plausibility of effects of glucose-lowering drug classes on tumor development. While these might not translate at an epidemiological level, there is a need to continue research on these agents to better define their efficacy in cancer modulation. These drugs might have an impact (either beneficial or harmful) at a clinical level in subpopulations of patients.

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Conflict of interest

AGR has received lecture honoraria and advisory board consultant fees from Novo Nordisk, manufacturer of several insulin analogs. EB has no conflict of interest.

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55 Diabetes and Infections

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Key points

- Diabetes is associated with an increased overall risk of infections.
- The presence of diabetes also modifies the course of many infections and increases morbidity and mortality.
- Multiple disturbances in innate immunity have a role in the pathogenesis of the increased prevalence of infections in people with diabetes.
- Impaired phagocytosis by neutrophils, macrophages and monocytes, impaired neutrophil chemotaxis and bactericidal activity, and impaired innate cell-mediated immunity appear to be the most important disturbances of the immune system.
- Humoral immunity appears relatively unaffected, hence plasma levels of antibodies and responsiveness to vaccination are relatively unaffected.
- In general, better regulation of the diabetes leads to an improvement in cellular immunity and function.
- Increased skin and mucosal carriage of *Staphylococcus aureus* and *Candida* species may increase risk of infection with these organisms.
- Some microorganisms become more virulent in a high glucose environment; examples include certain *Klebsiella* serotypes and *Burkholderia pseudomallei*.
- Viral infections such as hepatitis C are associated with a higher prevalence of diabetes.
- Highly active antiretroviral therapy for HIV/AIDS may also precipitate diabetes.
- Vascular disease such as microangiopathy can further impair the expression of the immune response as well as affecting the overall function of the microcirculation. It is commonly a factor in severe infections such as malignant otitis externa, emphysematous pyelonephritis, and necrotizing fasciitis.
- Diabetes increases the risk of tuberculosis approximately threefold and also increases the risk of treatment failure. Unusual or extrapulmonary sites of infection may be important and cavitatory disease is more common.
- Urinary tract infections and asymptomatic bacteriuria are more common in people with diabetes. Autonomic neuropathy is a common and important underlying factor.
- Skin and soft tissue infections are more common, with the infected diabetic foot as a prime example. Vascular disease and diabetic neuropathy are important underlying factors in the vulnerability of the foot to infection. Skin infection or infections of the external genitalia are common presenting features of diabetes. Necrotizing fasciitis is also associated with diabetes.
- Some uncommon but life-threatening infections occur almost exclusively in people with diabetes. Examples include the rhinocerebral form of mucormycosis, malignant otitis externa, Fournier gangrene and emphysematous forms of cystitis, pyelonephritis, and cholecystitis.
- Other factors that can predispose to infection include renal failure, obesity, need for hospitalization, indwelling catheters and delayed wound healing.

Introduction

People with diabetes develop infections more often than those without diabetes and the course of the infections is also more complicated. Historically, infections have been well recognized as an important cause of death in diabetes and remain a very important cause of morbidity and mortality. This is particularly true in less well-developed countries and areas, where infections are commonly the first manifestation of previously unknown diabetes. The infected diabetic foot remains a prime example of this phenomenon.

While the association between diabetes and infections is well recognized, the relationships are complex, not always clear-cut, and often controversial. Data on the true incidence of certain infections are lacking and a number of factors complicate efforts to assess risk of infections and outcomes. Studies are often retrospective and uncontrolled in nature.

Some infections, which occur predominantly in people with diabetes, are uncommon and inevitably have limited data. Examples include malignant otitis externa, mucormycosis, emphysematous forms of cholecystitis, cystitis and pyelonephritis, and Fournier gangrene.

Textbook of Diabetes, Fifth Edition. Edited by R. Holt, C. Cockram, A. Flyvbjerg and B. Goldstein.

In the case of more common infections that, while not limited to people with diabetes, have diabetes as a complicating factor, many variables make for considerable heterogeneity in the clinical course. Examples include duration of disease, presence of diabetic complications, glycemic control (both recent and longer term), access to and provision of medical services, and presence or absence of other concurrent illnesses.

A study from Utrecht has confirmed that, in general terms, people with type 1 (T1DM) and type 2 diabetes mellitus (T2DM) are at increased risk of lower (but not upper) respiratory tract infection, urinary tract infection, and skin and mucous membrane infections [1]. In this study, the well-documented increased risk of urinary infection was extended to include both risk of recurrence in both sexes and risks in men (perhaps explained by prostatitis).

A study, conducted in Ontario, Canada, compared people with diabetes with matched individuals without diabetes [2]. The investigators calculated the risk ratios, both for contracting an infection and for death from infection. Forty-six percent of people with diabetes had at least one hospitalization or outpatient visit for infections compared with 38% of those without diabetes, the relative risk ratio being 1.21. However, the risk ratios for infectious disease-related hospitalization or death were noticeably higher at 2.17 and 1.92, respectively. This may be attributable to increased severity and presence of complications. In the case of hospitalization, it could also reflect a lower threshold on the part of physicians to admit people with diabetes to hospital when they have intercurrent illnesses. A study, also from Canada (Calgary Health Region), conducted a population-based assessment of severe bloodstream infections requiring intensive care admission. Demographic and chronic conditions that were significant risk factors included diabetes, with a relative risk ratio of 5.9. The most common organisms were *Staphylococcus aureus*, *Escherichia coli*, and *Streptococcus pneumoniae* [3].

Bertoni et al. [4] also suggest that adults with diabetes are at greater risk for infection-related mortality, and that the excess risk may be mediated by cardiovascular disease (CVD). When diabetes was combined with CVD, the relative mortality risk was 3.0 (1.8–5.0), compared to 1.0 (0.5–2.2) in the absence of CVD.

Increased hospitalization rates due to bacterial infections have also been reported in adults (>14 years, $n = 4748$; RR 2.3) with T1DM and correlates with severity of any coexistent nephropathy. It was also noted that each percent unit of HbA_{1c} rise equated to a 6–10% increase in annual antibiotic purchases [5].

Further evidence that the presence of diabetes can worsen the outcome of infections comes from a number of sources. For example, T2DM is associated with an increased mortality from community-acquired pneumonia. While much of this may be explained by factors such as age and coexisting comorbid illnesses, admission hyperglycemia has been shown to be a particularly important predictor of death. Also, even in people without previously diagnosed diabetes, glucose levels in general assume importance [6].

The evidence extends also to the area of recently emerging infectious diseases. During the outbreaks of severe acute respiratory syndrome (SARS) in 2003 in Toronto, the presence of diabetes was an independent risk factor for poor outcomes (intensive care unit admission, mechanical ventilation, and death) with a threefold increase in relative risk [7]. A recent report, from Saudi Arabia, of Middle Eastern respiratory syndrome (MERS) coronavirus infection shows a 60% overall fatality rate, with underlying diabetes being present in 68% of cases, the commonest of a number of important comorbidities [8]. Increased severity of the clinical presentation of Dengue fever is also described, with increased representation of Dengue hemorrhagic fever among people with diabetes [9]. These, and other examples, emphasise the importance of diabetes both in new and emerging infectious diseases and in those that are expanding their range in response to factors such as globalization and climate change.

Both host- and organism-specific factors appear implicated in the increased susceptibility and risk. From the host perspective, defects in innate immunity are particularly important, notably decreased functions (chemotaxis, phagocytosis and killing) of neutrophils, monocytes and macrophages. Other factors include effects of diabetic complications, poor wound healing, the presence of chronic renal failure, and frequent hospitalizations, with the attendant risk of nosocomial infection.

Infections may also precipitate metabolic derangements, producing a bidirectional relationship between hyperglycemic states and infection. Some infections may also be implicated more directly in the etiology of diabetes.

Physicians working in primary care need to have high awareness of the relationships between diabetes and infection, and of the important infections that may be involved. Infections involving the foot, soft tissues, skin and nails, as well as the urinary tract, are of particular importance as they are commonly encountered in people with diabetes, may be present at diagnosis and may be the presenting feature that leads to the diagnosis of diabetes. Infections of the foot and skin will receive additional attention elsewhere in this textbook so, in order to avoid duplication, coverage in this chapter is curtailed. This should not be taken as an indication of lack of relative importance, the opposite being the case. The other chapters concerned should be taken as forming part of the overall coverage of the topic of diabetes and infections (see Chapters 17, 48 and 52).

Diabetes, the immune system and host factors

Host immune response

The increased susceptibility of people with diabetes to bacterial (and other) infections is well established. Although the mechanisms remain incompletely understood, deficiencies in the host innate immune response appear relatively more important than changes in adaptive immunity.

The presence of diabetes has multiple effects upon innate immune responses, including effects upon neutrophils, monocytes, and other components of innate immunity, which have important roles in the increased prevalence and enhanced severity of infections. The effects include reduced chemotaxis, phagocytosis and impaired bactericidal activity.

Some disturbances in the complement system and in cytokine responses have also been described in people with diabetes (e.g. low complement factor 4 and decreased cytokine responses after stimulation), but their role in the increased susceptibility to infection is less clear [10]. Consistent defects have not been demonstrated. No clear disturbances in adaptive immunity have been described. Cell-mediated immune disturbances may be minimized by good glycemic control. Humeral adaptive immunity, in particular, appears relatively unaffected as exemplified by the relatively normal antibody responses to most vaccinations and the fact that serum antibody concentrations and responses are generally normal, despite the potential for glycation of antibodies such as IgG. For example, people with diabetes respond to pneumococcal vaccine equally as well as controls without diabetes [11, 12].

The complexity of the component systems involved in the immune system makes comparison between studies difficult and it is obviously simplistic to study individual components in isolation given their interdependency.

Many studies have used i*n vitro* or animal model methodology to identify the mechanisms of immune impairment and a full review of these studies is outside the scope of this chapter. However, the following observations may serve as examples from within the range of abnormalities that have been found.

Neutrophil chemotaxis, neutrophil adherence to vascular endothelium, phagocytosis, intracellular bactericidal activity, opsonization, and other aspects of innate immunity are all depressed in hyperglycemic individuals with diabetes [13–15]. These changes lead to reduced host defense in response to infection with extracellular bacteria. Both impaired chemotaxis and phagocytosis have also been described in monocytes of people with diabetes [16].

Defects in innate immunity have been shown to predispose *db/db* mice to *S. aureus* infections. Interestingly, however, these mice show a heightened inflammatory response which occurs in association with an impaired neutrophil respiratory burst, and the recruited neutrophils fail to resolve the infection [17]. Such a heightened inflammatory response may be a factor in humans with tuberculosis. In this context also, while release of tumor necrosis factor and interleukin-1 from lipopolysaccharide-stimulated macrophages has been shown to be reduced in diabetic mice compared with control mice [18], study of monocytes from humans with diabetes indicates upregulation of the secretion of the same inflammatory mediators [19]. This further illustrates the difficulty in comparing studies conducted in different settings and species.

Some innate (e.g. cytokines, complement) immune functions are decreased while others remain unaffected. For example, while unstimulated cytokine concentrations may be higher, cytokine responses to stimuli are often reduced [20]. Interpretation of the complexity of the underlying mechanisms may also need to take into account potential underlying proinflammatory effects associated with diabetes itself.

The level of macrophage inflammatory protein 2, a mediator of lung neutrophil recruitment, is significantly decreased in diabetic mice compared to control mice [21]. The deficiency causes a delay in neutrophil recruitment in the lungs. This may be an important factor influencing the susceptibility of people with diabetes to infections of the lower respiratory tract.

Hyperglycemia impairs opsonophagocytosis by diverting nicotinic acid adenine dinucleotide phosphate (NADPH) from superoxide production into the aldose reductase-dependent polyol pathway [22], providing one further example of a mechanism by which hyperglycemia directly impairs phagocytosis.

Diabetic mice show greater than twofold induction of genes that directly or indirectly induce apoptosis [23]. By contrast, blocking of apoptosis allows for a significant improvement in wound healing and bone growth. This may influence many aspects of responses to infection, including impaired wound healing, which are important in the setting of diabetes.

These examples, while somewhat piecemeal, serve to demonstrate the range of abnormalities in the immune system that may result from hyperglycemia. Of particular importance are those spanning macrophage, monocyte and neutrophil function, and which impair adherence to endothelium, chemotaxis, phagocytosis and bactericidal activity. They also point to other abnormalities (e.g. involving apoptosis), wound healing, and cytokine responses to infection. The antioxidant systems involved in bactericidal activity may be compromised. These impairments, which are exacerbated by hyperglycemia and acidemia, may be reversed substantially, if not entirely, by normalization of pH and blood glucose levels. It needs to be emphasized, however, that the severity of effects correlates somewhat unpredictably with direct contemporaneous measures of glycemic control such as HbA_{1c}, perhaps reflecting longer term or persistent changes such as accumulation of advance glycation end products (AGEs) [24]. A role for AGEs is postulated as a component in the pathogenesis of the impaired neutrophil function. In general, a better regulation of the diabetes leads to an improvement of the cellular aspects of immune function, both innate and adaptive, despite variable correlations with HbA_{1c}.

Many questions remain as to the nature of the defects produced by diabetes, their effects upon infection risk, and their exact relationship to both long- and short-term glycemic control, very much confounded by differences in experimental methodology.

Other host-related factors

Other host-specific factors, over and above impairment and disruption of immune defenses, can further the predisposition to infection. These include vascular insufficiency (microangiopathies and macroangiopathies), sensory peripheral neuropathy, autonomic neuropathy, and skin and mucosal colonization

with pathogens such as *S. aureus* and *Candida* species. Abnormalities of the structure and function of the microcirculation can also have additional indirect adverse effects on the immune responses themselves. Thus, immunologic responses may be further compromised by microangiopathy, and additional factors related to diabetes complications specifically increase the risks of certain infections, especially those involving the foot and the urinary tract.

Obesity, which is commonly associated with diabetes, also increases the risk of certain infections. These include nosocomial infections, wound and surgical site infections, respiratory infections and infections involving the gastrointestinal tract. The presence of obesity also correlates with infected diabetic foot ulcers in people with diabetes [25].

Diabetic complications

Vascular disease is an important component in the etiology of the diabetic foot and the attendant complications of infection, ulceration, and gangrene. Micro- and macrovascular disease is very common in diabetes. Macrovascular disease may be premature, extensive, severe and present in unusual sites. Vascular insufficiency results in local tissue ischemia that can, in turn, enhance the growth of micro-aerophilic and anaerobic organisms, while simultaneously depressing the oxygen-dependent bactericidal functions of leukocytes. The antioxidant systems involved in bactericidal activity may be compromised by the combination of microvascular disease and the diabetic metabolic derangement itself. Hyperglycemia and acidemia are important predisposing factors to this latter effect and are reversed substantially by normalization of pH and blood glucose levels. Vascular disease related to diabetes may also further impair the local inflammatory response and the tissue penetration of antibiotics.

Neuropathy, both peripheral and autonomic, also contributes to the risk of foot infections and ulceration, as well as to certain other infections. Sensory peripheral neuropathy masks the recognition of trauma. Minor local trauma in people with peripheral neuropathy may result in skin ulcers, which, in turn, can become infected. Skin lesions are often either unnoticed or ignored until infection occurs. Autonomic neuropathy contributes to the etiology of foot infections by mechanisms such as decreased sweating, which predisposes to drying and fissuring of the skin, and by further exacerbating abnormalities in the control of the microcirculation. Both sensory and motor neuropathy can lead to deformity and alter the dynamics of the function of the foot. Fuller discussion of the etiologic factors related to sepsis and the diabetic foot is provided in Chapter 48.

People with diabetes-associated autonomic neuropathy may develop urinary retention and stasis in association with loss of innervation to the bladder. This predisposes them to urinary tract infections. This risk is particularly high in women. Autonomic neuropathy can also impair the function of the gastrointestinal tract, predispose to certain gastrointestinal tract infections and contribute to risk of aspiration pneumonia (in the context of gastroparesis). Renal papillary necrosis can also contribute to the risk of renal failure as well as to infection within the urinary tract.

Thus, a number of factors contribute to the vulnerability of people with diabetes to infections. Over and above the abnormalities of the immune response, vascular disease and neuropathy can greatly enhance susceptibility (e.g. in the lower limb and urinary tract). Hyperglycemia per se may specifically heighten susceptibility to certain fungal and bacterial infections, the number of which is being increasingly recognized.

Organism-specific factors

Certain organisms may show increased adherence to diabetic cells [15] and others may demonstrate increased virulence in hyperglycemic environments. Specific factors that predispose people with diabetes to infection with specific organisms include the following examples.

Candida albicans and fungi

Glucose-inducible proteins produced by *Candida albicans* are homologous to a complement receptor on phagocytes. These proteins may promote adhesion of *C. albicans* to buccal or vaginal epithelium. This adhesion, in turn, impairs phagocytosis, giving the organism an advantage over the host [15].

Ketone reductases produced by *Rhizopus* species allow these species to thrive in high glucose, acidic conditions typically present in diabetic ketoacidosis [26].

Klebsiella spp.

A bacterial genus of note in the context of diabetes is *Klebsiella*. *Klebsiella* infections are the second most common causes of Gram-negative sepsis (after *E. coli*). In a report from Taiwan, diabetes was the most commonly associated underlying condition in people presenting with community-acquired *K. pneumoniae* bacteremia [27]. The percentage of individuals with underlying diabetes was 49%, which is even higher than in earlier reports [28, 29]. Apart from the high proportion with diabetes, associations were also observed with serotype K1 (associated with impaired phagocytosis), liver abscess and other metastatic complications (endophthalmitis, meningitis, brain abscess) [27]. Primary liver abscess in other parts of Asia is also increasing in incidence, with 40% reportedly associated with diabetes [30]. Bacteremia is present in 50%, and 8–10% have metastatic complications (endophthalmitis, meningitis, brain abscess, pneumonia, skin and soft tissue infections, lung abscess, septic arthritis, renal abscess, peri-anal abscess, and prostatic abscess).

Melioidosis

A combination of organism-specific factors together with the changes in innate immunity may explain the increased susceptibility of people with diabetes to melioidosis. About 50% of cases of melioidosis occur in people with diabetes. The responsible organism, *Burkholderia pseudomallei*, has been shown to be selectively resistant to phagocytosis in the presence of diabetes.

In a study from Thailand, where melioidosis is relatively common, neutrophil responses to *B. pseudomallei*, in both people with and without diabetes showed that *B. pseudomallei* displayed reduced phagocytosis by neutrophils compared to *S. enterica typhimurium* and *E. coli*. In addition, intracellular survival of *B. pseudomallei* was detected throughout a 24-hour period, indicating intrinsic resistance of *B. pseudomallei* to killing by neutrophils. Furthermore, neutrophils from people with diabetes displayed reduced migration in response to IL-8 and an inability to delay apoptosis. Thus, *B. pseudomallei* appears to be intrinsically resistant to phagocytosis and killing by neutrophils. When added to the impaired migration and apoptosis seen in diabetes, the combination seems sufficient to explain the increased susceptibility to melioidosis [31].

Bidirectionality: the effect of infections on diabetes

Bidirectionality exists in the relationship between diabetes and infections. The effect of infections upon diabetes includes the effects of certain infections on the etiology and pathogenesis of diabetes itself, adverse effects upon hyperglycemia in established diabetes and exacerbation of diabetes complications. The importance of the potential adverse effects upon hyperglycemia in established diabetes needs to be emphasised. Infections remain an important predisposing cause of both diabetic ketoacidosis and hyperosmolar hyperglycemia syndrome.

The importance of certain viral infections in the possible etiology of diabetes has received increasing attention in recent years with respect to both T1DM and T2DM.

Viral infections have been implicated in the etiology of T1DM for many years. Although this complicated topic is beyond the general scope of this chapter and is considered in detail in Chapters 3 and 10, it is noteworthy that type 1a (autoimmune) diabetes is increasing in prevalence globally, providing strong evidence that environmental factors are involved in the clinical expression of the disease. Viruses have long been included in the list of putative environmental triggers. Enteroviruses (especially Coxsackie B viruses, B4 in particular), rubella, mumps, rotavirus, parvovirus, and cytomegalovirus have all been implicated and continue to be reported [32, 33]. Although correlations between the presentation of diabetes and the occurrence of a preceding viral infection have been recognized, a direct causal relationship, with fulfillment of Koch postulates, remains difficult to prove, possibly because other inflammatory factors are also required. In this context, it is interesting to note that the process may be associated with a dominant CD4 T-helper type 1 immune response, whereas the dominance of a T-helper type 2 response, as seen in the face of certain infectious and parasitic agents, may protect against T1DM and other autoimmune diseases. Thus, the increasing freedom from such infections, especially in more developed areas of the world, may allow increased expression of an underlying genetic predisposition. Infection by certain viruses, such as the Coxsackie B viruses, may then be associated with the appearance of (and persistence of) β-cell antigens, mediated by mechanisms such as molecular mimicry and activation of Toll-like receptors. Lack of exposure to infection and infestation in early childhood appears to dilute the ability of the innate immune system to withstand autoimmune responses and challenges. T1DM is not alone in this respect and the general concept has become known as the "hygiene hypothesis" [34]. The potential role of alterations in the gut microbiome is also receiving increasing attention and is dicscussed further in chapter 17.

The high prevalence of T2DM in association with hepatitis C infection and the progression of certain diabetes complications (e.g. diabetic nephropathy) in association with hepatitis B are other noteworthy examples. The treatment of HIV/AIDS with protease inhibitors predisposes to diabetes, metabolic syndrome, and increased cardiovascular risk. The public health implications of these issues are considerable given the concordance of the diabetes epidemic with these other highly prevalent diseases.

All infections, especially if severe, have the potential to exacerbate hyperglycemia by a number of mechanisms (e.g. worsening of insulin resistance by production of "stress" or counter-regulatory hormones and production of cytokines such as IL-1 and tumor necrosis factor) [35]. Infection remains a major factor in the pathogenesis of diabetic ketoacidosis or hyperosmolar hyperglycemia. Infections can also precipitate hypoglycemia if symptoms, such as anorexia, nausea and vomiting, lead to reduced food intake. Malaria and its treatment with quinine can also induce hypoglycemia.

Hepatitis C

A number of reports from North America, Europe, and the Middle East consistently demonstrate an increased prevalence of diabetes (ranging from 24% to 62%) among people with chronic hepatitis C virus (HCV) infection compared both with persons with other forms of liver disease and with other control groups. Among HCV-infected individuals reported prevalence of diabetes (21–50%) is much higher when compared with other forms of chronic liver disease (2–12%) or those without liver disease (2–6%) [36–41].

In the USA, T2DM occurs more often in persons with HCV infection who are above 40 years of age, particularly those aged between 40–49 years where the relative risk ratio is 3.8. Apart from age, the prevalence of diabetes is greatest in people who are non-white, have a high body mass index, are below the poverty level, and have a family history of diabetes. The prevalence of T1DM appears to be unaffected [42].

The suggestion that HCV infection predisposes to T2DM as a result of progressive liver damage is supported by the observations that the association is most marked in the older age groups (>40 years), and that there is higher risk among those with advanced HCV cirrhosis. The presence of diabetes is also associated with more severe hepatic fibrosis. The higher prevalence of diabetes in comparison with that seen in other liver diseases suggests an additional mechanism specific to hepatitis C. Tumor necrosis factor has been suggested as one possible candidate [43].

HCV infection is also strongly associated with diabetes among intravenous drug users and this is independent of HIV infection or use of highly active antiretroviral therapy (HAART) [44]. Thus,

it is important to monitor people with chronic HCV infection for development of diabetes. Bidirectionality again applies with weight loss and good glycemic control improving hepatitis outcomes.

HIV/AIDS

Although HIV/AIDS has not in itself been reported to increase the risk of diabetes, the treatment of HIV/AIDS with antiretroviral therapy (ART) predisposes to T2DM, other metabolic risks, and premature cardiovascular disease. In the Multicenter AIDS Cohort Study, HIV-infected men had a greater odds of insulin resistance than HIV-negative men, regardless of ART exposure, and diabetes mellitus incidence was four times higher among HIV-infected men on ART compared with uninfected men [45, 46]. The incidence of diabetes increases with cumulative exposure to ART [47].

This has become a major problem in the management of this already very complicated disease. The effects occur via disturbances in lipid homeostasis and fat partitioning (lipodystrophy), insulin resistance, insulin secretion, and mitochondrial dysfunction. Insulin resistance is more important than impaired insulin secretion. ART for HIV-1 infection is frequently complicated by lipodystrophy (peripheral fat loss and relative visceral obesity), dyslipidemia and insulin resistance, especially with zidovudine, stavudine, and didanosine. HIV-infected adults receiving ART also have an increased incidence of hypertension, as well as cardiovascular morbidity.

Whether ART-naïve individuals have altered risk of subsequent CVD or T2DM remains unclear, although insulin resistance has been reported among protease inhibitor (PI)-naïve persons with HIV infection, in association with fat redistribution. Exposure to antiretroviral therapy for more than 1 year is associated with increasing risk of T2DM. Although the risk is greatest among individuals treated with PI, attributed to a direct inhibitory effect on cellular glucose transport by PI medications [44], an increased prevalence of diabetes among those receiving a PI-sparing regimen has also been found. Nucleoside analog-induced mitochondrial toxicity is probably of importance. Cessation of PI appears to have little beneficial effect in reversing lipodystrophy, although it may improve the metabolic control in diabetes. Alteration of thymidine analog nucleoside reverse transcriptase inhibitors may, however, confer benefit on lipodystrophy [48, 49]. Another study in HIV-infected persons initiating ART reported that higher levels of the inflammatory markers high-sensitivity C-reactive protein, sTNFR1 and sTNFR2 were associated with an increased risk for diabetes mellitus despite suppressive ART. These data suggest that the inflammatory milieu of HIV infection may also contribute to the development of insulin resistance [50].

In a study of almost 900 people with HIV-infection, initiation of ART was evaluated for prevalence and incidence of metabolic syndrome and subsequent diagnosis of CVD and T2DM over a 3-year period. The prevalence of baseline metabolic syndrome was 8.5% and 7.8% (ATP-III and IDF criteria, respectively). Substantial progression to metabolic syndrome occurred within 3 years following initiation of ART. The presence of metabolic syndrome at baseline was significantly associated with an increased risk of T2DM while metabolic syndrome occurring during the 3-year period was associated with an increased risk of both CVD and diabetes [51, 52].

In another study [53], 123 of 6513 people with HIV-infection developed diabetes during almost 28,000 person-years of follow-up, an incidence of 4.4 cases per 1000 person-years. An increased incidence rate ratio was found for men, older age, obesity and African American, or Asian ethnicity. Strong associations were observed with treatment using nucleoside reverse-transcriptase inhibitors (NRTI), NRTI + PI, and NRTI + PI + non-nucleoside reverse-transcriptase inhibitors (NNRTI), but not with an NRTI + NNRTI regimen.

Lipodystrophy is a crucial aspect of the association of ART with insulin resistance, leading to relative preponderance of visceral fat, hepatic steatosis, and fat deposition at other "ectopic" sites. HIV-infected persons with lipodystrophy, compared with those without lipodystrophy, have a reduction in plasma adiponectin and adipose tissue adiponectin mRNA levels of approximately 50%, correlating with insulin resistance and increased cytokine levels [52].

Because baseline and incident metabolic syndrome identifies individuals at risk for both CVD and T2DM, evaluation in all people commencing ART is warranted. A fasting plasma glucose concentration should be checked before initiation of therapy and monitored every 3–6 months, especially in those receiving changes in treatment or who have significant risk factors for insulin resistance. An oral glucose tolerance test may be required, particularly in the presence of risk factors or equivocal glucose concentrations. Dietary guidelines established for the general population remain relevant for the management of glucose disorders in the context of HIV infection. Weight loss through increased activity and caloric restriction should be recommended for overweight individuals with HIV-infection.

Metformin improves insulin sensitivity in people with HIV lipodystrophy and is an effective antidiabetes medication; however, it should be used with caution in those receiving an NRTI (in particular zidovudine, didanosine, and stavudine), and in persons with impaired renal function because of the possibility of lactic acidosis. The newer integrase strand transfer inhibitor, dolutegravir, will increase the level of metformin by decreasing renal clearance. Close monitoring is warranted and dosage adjustment of metformin may be needed. Thiazolidinediones (pioglitazone) may also improve insulin sensitivity in people with HIV lipoatrophy. Insulin therapy should be used according to standard recommendations. Substitution of an NNRTI for a PI has been observed to improve insulin resistance but this needs to be balanced against any risk to virus control. Careful discussion with the HIV physician is therefore essential and it may be deemed safer to increase the antihypoglycemic treatment rather than changing the components of the ART regimen [54–56].

Hepatitis B

Although, in contrast to hepatitis C, hepatitis B virus (HBV) has been less consistently associated with an increased prevalence of

diabetes, the presence of hepatitis B markers may nevertheless influence the natural history of diabetes and its complications and the relationship may be bidirectional as the presence of diabetes is associated with more severe fibrosis and cirrhosis. However, there is uncertainty as to cause and effect given the general association of diabetes with liver cirrhosis [57].

Chinese people with HBV-infection and T2DM have been shown to be more likely to develop end-stage renal disease than non-HBV infected people with T2DM (8.7 vs. 6.4%) with a hazard ratio of 4.5. The association of chronic HBV infection with increased risk of end-stage renal disease was independent of other potential confounding factors. People with HBV-infection also reported earlier onset of diabetes and had a higher frequency of diabetic retinopathy than those without HBV-infection (28% compared to 22%). Cardiovascular complications appeared unaffected [58].

Specific infections either strongly associated with diabetes or in which the presence of diabetes is important

Infections involving the head and neck

Two head and neck infections that are associated with high rates of morbidity and mortality, malignant otitis externa and rhinocerebral mucormycosis, are particularly noteworthy in people with diabetes.

Malignant otitis externa

Malignant otitis externa is an invasive infection of the external auditory canal and skull base that typically arises in elderly people with diabetes. An early series was described in 1968 [59]. Most cases (86–90%) have been reported in people with diabetes. *Pseudomonas aeruginosa* is nearly always the causal organism (>98% of cases) although *Aspergillus* species or other fungi, are occasionally responsible. Microangiopathy in the ear canal has been suggested as a predisposing factor.

Presenting features include severe intractable headache and otalgia, otorrhea, and deafness, often over a period of weeks to months. Intense cellulitis is combined with edema of the ear canal. Focal neurologic signs and cranial nerve palsies may occur. The pain may involve the temporomandibular joint and be aggravated by chewing. Osteomyelitis of the skull base and temporomandibular joint is a potentially life-threatening complication and the mortality in the pre-antibiotic era exceeded 50%. On otoscopy, granulation tissue may be seen in the floor of the ear canal, often in association with edema and intense cellulitis. The tympanic membrane is usually intact. Computed tomography (CT) and magnetic resonance imaging (MRI) studies are essential for defining the extent of bone and soft tissue involvement, together with the bony destruction of the skull base that may be seen in advanced cases.

Systemic antipseudomonal antibiotics are the primary therapy. Early referral to an otorhinolaryngologist is essential and allows diagnostic confirmation by surgical biopsy. Debridement of necrotic tissue can also be carried out if necessary, although the introduction of effective antibiotic therapy has reduced the requirement for surgery. With the introduction of quinolones, the cure rate has increased to 90%, with few adverse effects reported and oral therapy rendered possible. Prolonged treatment for 6–8 weeks is recommended, as for osteomyelitis [60]. Thus, treatment consists of prolonged administration (6–8 weeks) of an antipseudomonal agent (typically, an orally administered quinolone). The emergence of ciprofloxacin resistance is a potential problem. It is recommended that systemic quinolone use be reserved for treatment of invasive ear infections caused by susceptible pathogens. For otitis externa caused by *Aspergillus* species, treatment would include surgical debridement; treatment with voriconazole, posaconazole, or amphotericin B. An example of invasive aspergillosis involving the skull base is shown in Figure 55.1.

Mucormycosis (zygomycosis)

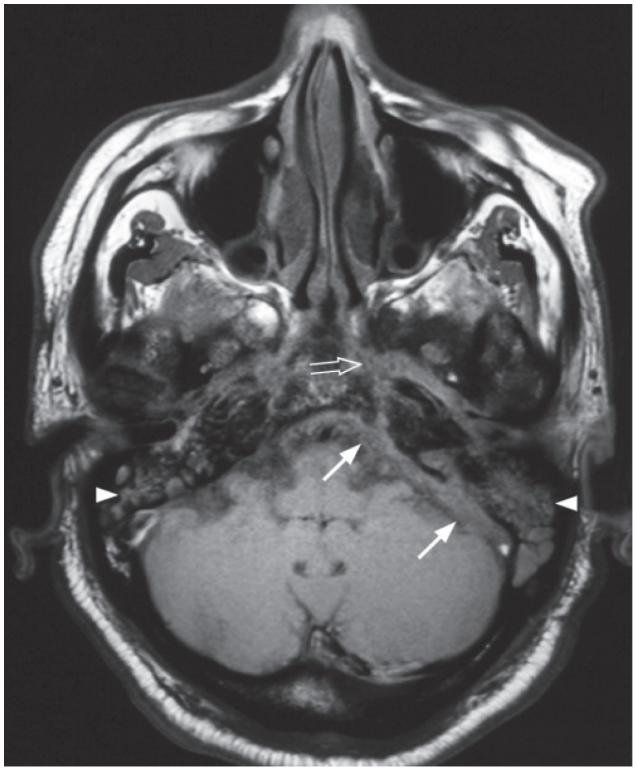
The term mucormycosis is used to describe a variety of infections caused by fungi of the *Rhizopus* and *Mucor* species which belong to the order Mucorales (class Zygomycetes). These fungi are ubiquitous saprophytes and infections produced by them are essentially confined to immunocompromised individuals. The fungi have a predilection to invade blood vessels. Ketone reductases produced by *Rhizopus* spp. allow them to thrive in high glucose, acidic conditions as are typically present in diabetic ketoacidosis [26]. Rhinocerebral, pulmonary, gastrointestinal, cutaneous and disseminated forms of the infection are described. The rhinocerebral manifestation (and with sinus involvement) has the highest frequency and is potentially the most lethal in the context of people with diabetes.

The close connection with diabetes is becoming increasingly diluted as other causes of an immunocompromised state become increasingly common or survivable (notably hematologic cancer and bone marrow transplant recipients). Nevertheless, diabetes remains the most common underlying factor in most reports. In a review of 49 cases of pulmonary mucormycosis, diabetes was the underlying cause of the immunocompromised state in 9 (25%) [61]. In another study, the prevalence and mortality in people with diabetes were 36% and 44%, respectively [62]. It typically, although not exclusively, occurs in association with ketoacidosis, severe hyperglycemia and/or a debilitated state.

Rhinocerebral mucormycosis is a life-threatening fungal infection. Untreated it is universally fatal; if recognized early there is a 20% survival rate. Presenting features include facial or ocular pain and nasal stuffiness. Generalized malaise and fever may also be present. Intranasal black eschars or necrotic turbinates may be found and, if present, provide sites that can be biopsied. Treatment consists of surgical debridement of the involved sinuses and prolonged intravenous therapy with amphotericin B or alternative antifungal agents such as some newer azoles.

Acute invasive fungal sinusitis can also result from aspergillosis, as can malignant otitis externa. Biopsy confirmation of the microbiologic diagnosis is therefore useful [63].

(a)



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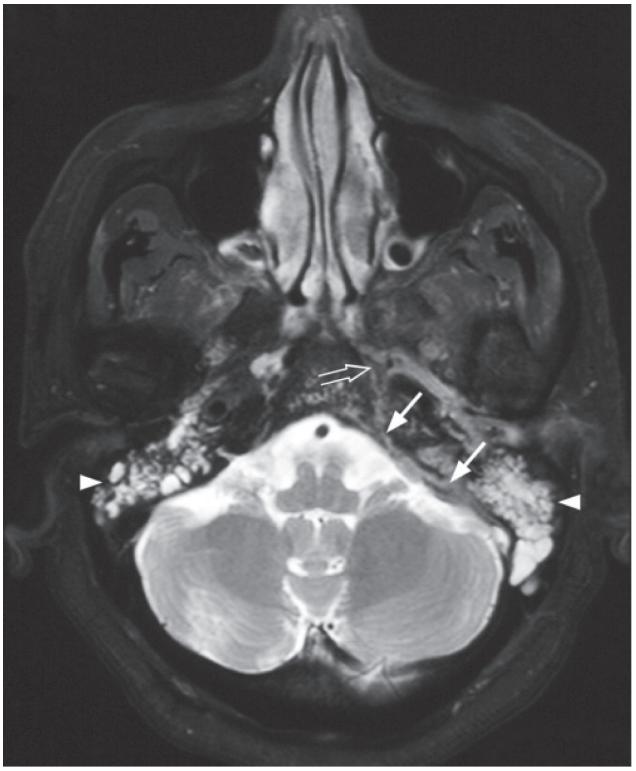


Figure 55.1 Magnetic resonance imaging (MRI) scan of skull base in a 59-year-old man with a 20-year history of diabetes (with nephropathy), treated with insulin who developed severe extensive invasive aspergillosis. He presented with headache and vertigo followed by left sixth and seventh nerve palsies. He subsequently developed bilateral sensorineural hearing impairment and blindness secondary to extensive skull base infiltration by the invasive aspergillosis. MRI demonstrated enhancing soft tissue closely related to the left posterolateral wall of the nasopharynx with parapharyngeal, skull base, perineural and dural infiltration. Biopsy showed inflamed fibrous tissue with degenerated fungal filaments. Culture confirmed *Aspergillus flavus*. He is receiving lifelong therapy with voriconazole. He remains blind. MRI of skull base in the axial plane with: (a) T1-weighted; and (b) post-gadolinium T1-weighted sequences. These show marked dural thickening (arrows) with enhancement in the left posterior cranial fossa. An abnormal signal with enhancement is also noted in the adjacent left petrous apex (open arrow). Note also the presence of inflammatory fluid within both mastoid air cells (arrow-heads). Source: Acknowledgments to Dr. K.T. Wong, Consultant Radiologist, for preparation and reporting of the figures, and to Professor A. Ahuja for permission to use the figures. Both are placed at the Department of Diagnostic Radiology and Organ Imaging, Prince of Wales Hospital, Chinese University of Hong Kong, Hong Kong.

Endophthalmitis

Secondary endophthalmitis may occur as a rare but devastating metastatic complication of septicemia and in this setting is almost entirely confined to people with diabetes. *E. coli* and *Klebsiella* are the more likely pathogens and urinary tract infection is reported as the most common underlying source of infection [64].

People with diabetes are also more prone to postoperative infections following eye surgery or infections secondary to eye trauma. Overall, the most common cause of endophthalmitis is as a postoperative complication of cataract surgery [65], a procedure commonly carried out in people with diabetes.

Periodontal disease

People with diabetes are very prone to periodontal disease compared to the general population, with a two- to fourfold relative increase in prevalence and a particular predilection for those whose diabetes is poorly controlled.

The associated periodontitis, if left untreated, can result in loss of attachment of ligament fibers and supporting alveolar bone which in turn can increase the mobility of teeth and necessitate extraction. Tooth abscesses and episodes of bacteremia also become more likely. Diabetes may complicate the pathogenesis of periodontitis by causing abnormalities in the vasculature of the gingival tissues, in addition to the effects upon immune responses described earlier. Aggressive and difficult to treat forms of periodontitis are also more common in adults with diabetes. Periodontal health is influenced by glycemic control to the extent that the prevalence of periodontal diseases among people with well-controlled diabetes is not increased [66].

A bidirectional relationship has also been suggested whereby the presence of periodontal disease adds to the overall burden of chronic inflammation, thereby adversely affecting glycemic control as well as overall risk of CVD and diabetic nephropathy.

Respiratory tract infections and tuberculosis

The increased risk of mortality and morbidity from community-acquired pneumonia has been described earlier and includes pneumonia either directly resulting from, or secondary to, common infections such as influenza and *S. pneumoniae* and also includes *Legionella* infections [67]. The risk of bacteremia following pneumococcal infection is increased [68]. Viral shedding may be more prolonged following influenza infections in people with comorbidities including diabetes, which may influence decisions regarding initiation and duration of antiviral therapy [69].

Lower respiratory tract infections, resulting from *S. aureus* and Gram-negative organisms such as *K. pneumoniae*, are more common in people with diabetes. Melioidosis has also been discussed earlier as an example of organism-specific factors that interact with diabetes to increase risk of infection. People with diabetes are also thought to be at increased risk for *S. aureus* pneumonia and this may result from higher rates of nasal carriage of *S. aureus* in people with diabetes (up to 30%) compared to healthy individuals (11%) [70].

Any respiratory infection in people with diabetes is associated with increased mortality. In the USA, people with diabetes are reportedly four times more likely to die from pneumonia or influenza than are people without diabetes [71].

The importance of diabetes as the most common underlying predisposing factor for thoracic empyema has also long been recognized. *Klebsiella* spp are again notable as the most common pathogens, while other important pathogens include streptococci, *S. aureus* and anaerobes [72].

Diabetes and tuberculosis

An association between diabetes and tuberculosis has been widely accepted in the past, and solid epidemiological evidence has emerged in the last decade to establish firmly a close link. Systemic reviews have confirmed that people with diabetes are approximately three times more likely to develop active tuberculosis than are people without diabetes, albeit with varying estimates of overall risk (ranging from two- to 11-fold) [3–5, 73, 74].

The importance of the association is often neglected in the larger arena of public health, for example when compared with the risk of tuberculosis associated with HIV/AIDS. The increase in risk appears consistent across geographical regions, and regardless of both study design and background incidence of tuberculosis. It appears greatest among younger people in areas of high tuberculosis incidence and in non-North American populations [73]. The public health impact may be particularly high in low-income or middle-income countries or areas that are at the forefront of the diabetes epidemic and where tuberculosis remains endemic [74–76] and may therefore be particularly high in countries such as China and India.

The impact of the diabetes epidemic on tuberculosis incidence in India has been modeled by Stevenson et al. [77]. They suggest that diabetes accounts for 14.8% (range 7.1–23.8%) of pulmonary tuberculosis and 20.2% (8.3–41.9%) of smear-positive tuberculosis, with an excess risk of the latter in urban areas. This can be compared to an overall estimate of 3.4% for the proportion of adult tuberculosis incidence ascribed to HIV/AIDS in India [78].

The association of tuberculosis with diabetes reflects impaired innate immunity as well as a reduced adaptive T-helper type 1 response with reduced secretion of T-helper type 1-related cytokines, thereby increasing the risk of progression from tuberculosis infection to active disease as well as increasing the risk of latent tuberculosis following initial primary infection. Regarding the clinical presentation, extrapulmonary or unusual manifestations of tuberculosis are more common in the context of diabetes. People with tuberculosis and diabetes are more likely to develop opacities over the lower lung fields, extensive parenchymal lesions, any cavity, multiple cavities and large cavities compared to those without DM and these radiological abnormalities are more common in the presence of poorer glycemic control [79, 80].

In addition to the increased risk, there is evidence that people with diabetes are at increased risk of worse outcomes, including treatment failure, relapse, and mortality [81]. People with diabetes are more likely to remain smear positive after 2–3 months of treatment as shown in six of nine studies evaluating sputum conversion [81]. A study from Indonesia indicated a doubling of the risk of remaining smear positive at the end of treatment [82]. The same group has also shown that the presence of T2DM may adversely affect the bioavailability of rifampicin and lead to an increase in dose requirement [83]. A study from Brazil found that those with tuberculosis and diabetes had poorer treatment outcomes even after adjusting for confounding factors [84].

One of the options to improve treatment outcomes might be to extend the period of treatment. In Hong Kong, an area with much pioneering experience of tuberculosis treatment since the 1950s, the Centre for Health Protection recognizes the risk of a worse outcome, and its guidelines recommend a more prolonged period of treatment for people with diabetes compared to those without. For example, when treating pulmonary tuberculosis using a standard regimen of four drugs for the first 2 months followed by two drugs, a total treatment duration of 9 months, rather than 6 months, is recommended.

Two examples of individuals with tuberculosis in association with diabetes are shown in Figure 55.2. It is perhaps noteworthy that neither was receiving regular follow-up care for the diabetes.

Bidirectionality again needs to be remembered because the presence of tuberculosis is very likely to have a negative impact upon hyperglycemia. Tuberculosis, as with other infectious diseases, can lead to deterioration of glycemic control and complicate the management of diabetes. Unpredictable effects upon glycemic control may result from alterations in inflammatory processes, changes in appetite and body weight and, importantly, through drug–drug interactions. Rifampicin, the most important drug, increases the hepatic metabolism of sulfonylurea drugs, although with great inter-individual variation. It may also lead to an enhanced glucose-lowering effect of metformin [85].

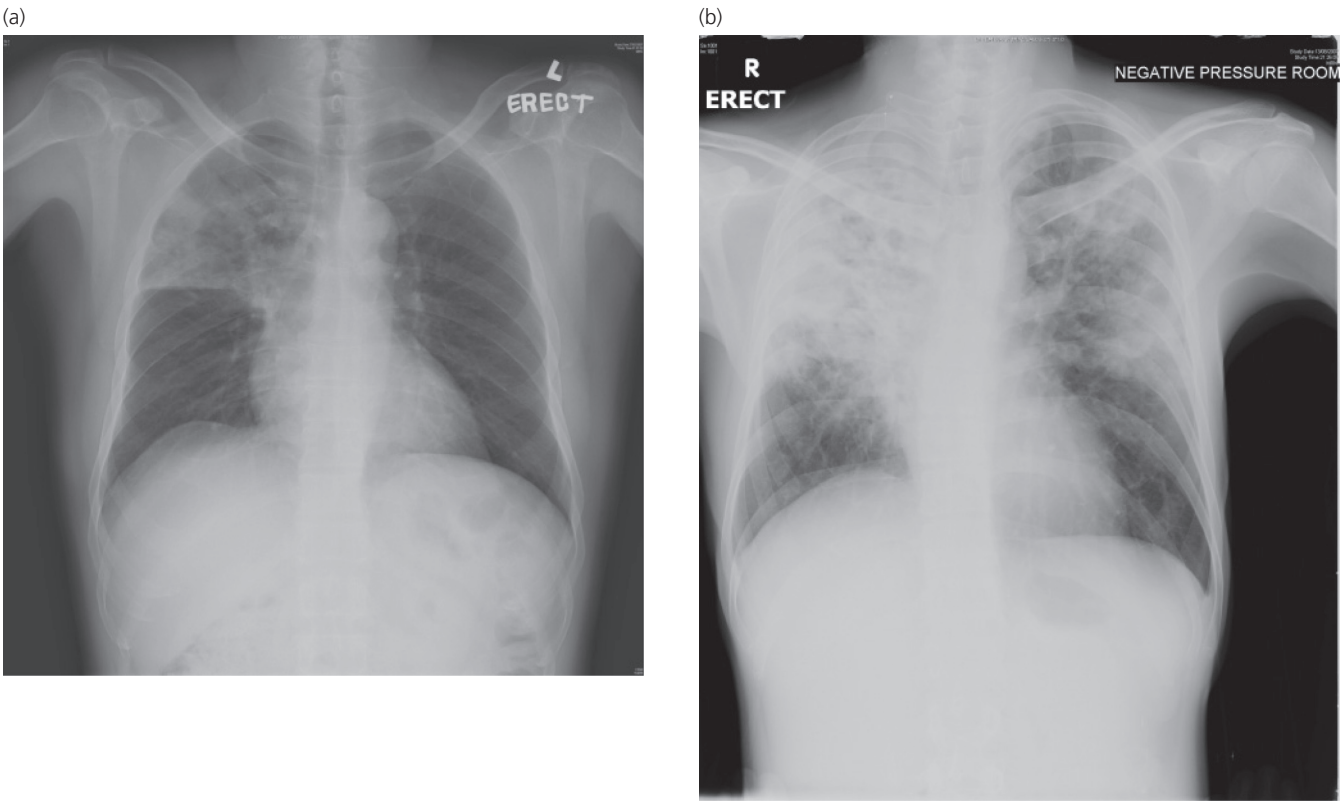


Figure 55.2 (a) A 49-year-old man with diabetes and obesity, not receiving regular follow-up, and presenting with hemoptysis, sputum smear positive for tuberculosis. Chest X-ray shows extensive right upper lobe pneumonic changes. (b) A 30-year-old man with diabetes but no regular follow-up, presents with a cough for 4 months with weight loss, sputum smear positive for tuberculosis. Chest X-ray shows extensive bilateral and cavitatory disease.

Some national treatment guidelines (e.g. Indonesia) strongly recommend the use of insulin therapy since insulin has no direct pharmacokinetic interactions with rifampicin or other anti-tuberculous agents. Thus people with concurrent diabetes and tuberculosis may have specific needs during treatment, including close monitoring of glycemic control, renal and hepatic function, as well as counselling and education. There is therefore a strong case to be made for integrated care together with service and policy development [85]. The issue of screening is pertinent, both for diabetes in people with tuberculosis and for tuberculosis in people with diabetes.

Infections of the urinary tract

Epidemiology and risk factors

Urinary tract infection (UTI) is frequently encountered in people with diabetes. Asymptomatic bacteriuria also occurs with a higher frequency. One study has demonstrated a prevalence rate for asymptomatic bacteriuria of 26% in women with diabetes, compared to 6% in women without diabetes [86, 87].

A randomized controlled trial of antibiotic treatment for asymptomatic bacteriuria revealed no differences in the development of symptomatic UTI, time to onset of symptoms, risk of pyelonephritis or need for hospitalization [86]. On this basis, diabetes does not appear to warrant either screening for, or treating, asymptomatic bacteriuria. However, this remains a controversial issue and, from the practical standpoint, ascertaining "asymptomatic status" with confidence, particularly in older women with diabetes, can be difficult or impossible.

A number of studies confirm the increased risk of symptomatic UTI in association with diabetes. In one study of more than 600 women [88], those with T2DM had an overall risk of 20%. A recent study has extended the risk to include recurrence rates as well as risk to men [1].

Diabetes is a risk factor for cystitis in postmenopausal women, leading to a two- to threefold increase in risk [89]. An increased prevalence of asymptomatic vaginal *E. coli* colonization has also been reported in postmenopausal women who are receiving insulin treatment. This vaginal colonization may be mediated by greater adherence of type 1 fimbriated *E. coli* to uroepithelial cells in women with diabetes, may be related to impaired cytokine secretion, or may reflect a reduced polymorphonuclear inflammatory response [86, 90].

Diabetes also increases the risk of complications of UTI, serious or unusual forms of infection, and need for prolonged hospitalization [91]. It is a risk factor for acute pyelonephritis in women (odds ratio 4.1), and is the strongest of the various risk factors

examined. Among hospitalized patients, 16.7% reported having diabetes compared with 5.8% of non-hospitalized patients [86]. A three- to fivefold increase in risk also exists in people with diabetes aged less than 44 years [88].

Diabetic autonomic neuropathy is an important predisposing factor to UTI. This affects the sympathetic and parasympathetic afferent fibers to the bladder and causes decreased reflex detrusor activity. Impaired bladder sensation results in bladder distension, increased residual urine volume, vesicoureteric reflux and recurrent upper UTI [92, 93]. Some cases are related to urinary catheterization or instrumentation [86, 92, 93]. Additional factors predisposing to UTI include: glycosuria, sexual intercourse, history of previous UTI, obstruction, longer duration of diabetes, poor glycemic control, decreased urinary cytokine excretion, increased *E. coli* adhesion, macroalbuminuria, and neutrophil dysfunction [92, 93]. Renal papillary necrosis and chronic renal failure also contribute to the complex array of risk to the urinary tract.

Microbiology

E. coli is the most commonly reported organism. *Klebsiella* is also a problem, especially among individuals with uncommon severe forms of UTI, such as emphysematous pyelonephritis. Other organisms include *Acinetobacter* species, group B streptococci, and *P. aeruginosa* [86]. The latter should be suspected particularly if there is a history of recent instrumentation or hospitalization.

C. albicans in the urine can be associated with incomplete bladder emptying and high glucose concentrations in the urine. Diabetes has been shown to be present in 39% of hospitalized patients with funguria [86]. Candiduria may signify contamination of the urine specimen, benign saprophytic colonization (± catheter), or may be indicative of true invasive infection of the upper and/or lower urinary tract [94]. Diabetes is also a risk factor for multidrug-resistant UTI, perhaps related to recurrent or increased exposure to antibiotics [95].

Clinical features of urinary tract infection in diabetes

Uncomplicated UTIs may be asymptomatic. Symptoms, when present, are generally similar to those experienced by the non-diabetic population. Infection of the lower urinary tract usually presents as dysuria, frequency or urgency. Fever, flank pain, chills and rigors, vomiting and costovertebral angle tenderness raise the suspicion of upper tract infection with renal involvement. Bilateral renal involvement is also more frequent and bilateral pyelonephritis is twice as common in people with diabetes. Bacteremia may be present.

A poor response to appropriate antibiotic therapy should raise the suspicion of the presence of complications. These may include renal papillary necrosis and perinephric abscess. The symptoms of renal papillary necrosis include flank and abdominal pain (which mimic both pyelonephritis and ureteric colic), together with fever. Renal functional impairment is commonly found. Features such as a persisting high fever despite antibiotic treatment, hypotension or septicemic shock, and a palpable tender renal mass may point to the presence of a perinephric abscess. In one series of patients with perinephric abscess, 36% had diabetes [96].

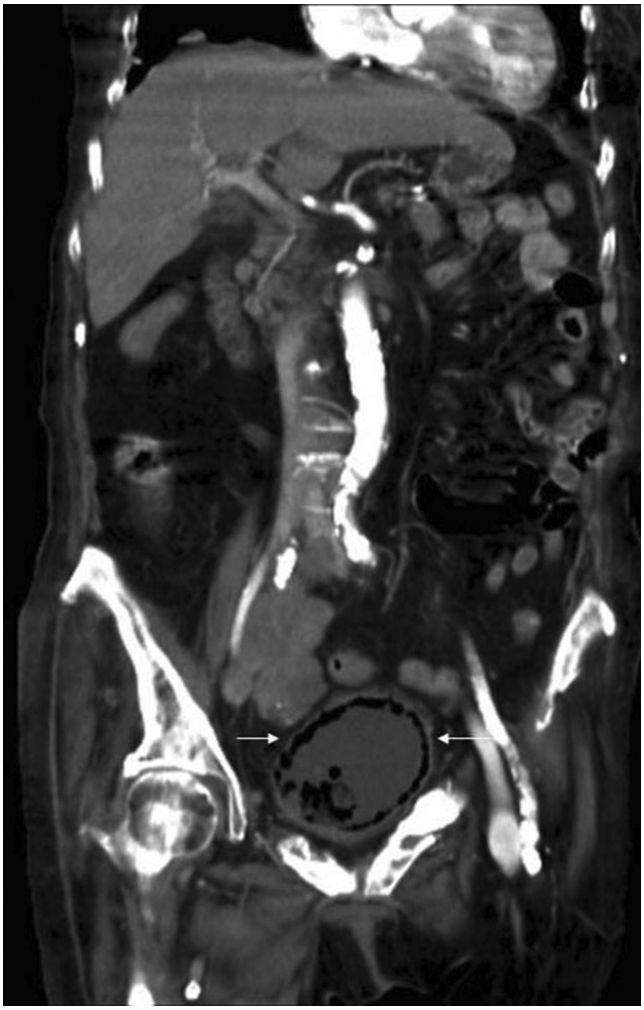


Figure 55.3 Example of emphysematous cystitis in a 67-year-old woman with diabetes and end-stage renal disease requiring hemodialysis. She developed septic shock with lower abdominal tenderness. Blood and urine cultures showed *E. coli*. Computed tomography (CT) scan shows air pockets inside the urinary bladder (arrows). Source: Sun JT, et al. Life-threatening urinary tract infection. *Q J Med* 2009; **102**:223. Reproduced with permission of Oxford University Press.

Emphysematous cystitis and emphysematous pyelonephritis

Although uncommon, the severity of these infections warrants their special consideration. Emphysematous cystitis is an uncommon complication of lower UTI characterized by the presence of gas in the bladder wall (Figure 55.3). It presents with hematuria, pneumaturia, and abdominal pain. Plain abdominal radiography or CT scan are indicated to detect the presence of gas. Surgical intervention may be required in up to 20% of cases and mortality is reportedly up to 10%. Emphysematous cystitis requires aggressive treatment in hospital and intravenous antibiotic therapy [97].

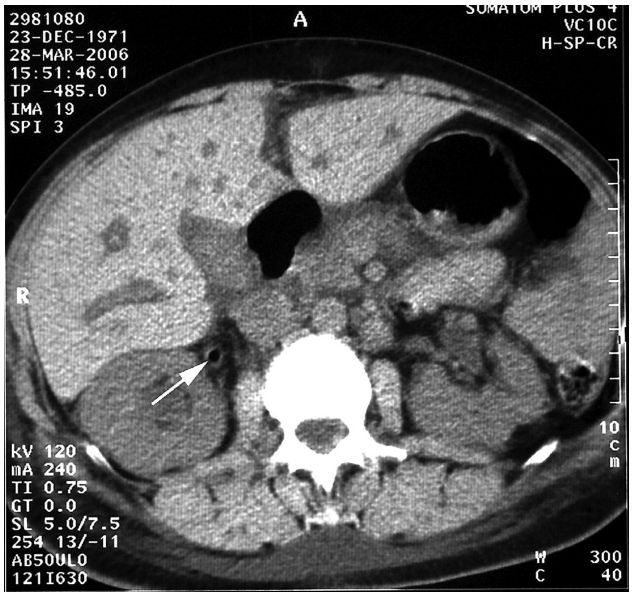


Figure 55.4 Emphysematous pyelonephritis: computed tomography tomography (CT) scan demonstrating gas in the right ureter (indicated by arrow) and a moderate hydronephrosis in a 34-year-old woman with type 1 diabetes. The responsible was organism was *E. coli*. She responded to antibiotics and drainage by nephrostomy, followed by ureteroscopy during which obstructing necrotic slough was removed. Source: Clark T, et al. A case of emphysematous pyelonephritis. *J R Soc Med* 2009; **102**:75–77. Copyright © 2009 SAGE Publications.

Emphysematous pyelonephritis is an infection that is almost exclusively limited to people with diabetes, who account for 90% of cases (Figure 55.4). It predominantly occurs in women and carries a grave prognosis [98]. It is a necrotizing infection of the renal parenchyma and surrounding areas which can be focal or diffuse and may spread to the collecting system or perinephric tissues. The formation and presence of gas in the renal parenchyma, collecting system or perinephric area may be contributed to by fermentation of glucose when present at high concentrations, by the presence of gas-forming organisms and by impaired renal perfusion. Mixed acid fermentation of glucose by Enterobacteriaceae has been suggested as a major pathway of gas formation [99].

A lengthy list of pathogens has been reported; however, as with other UTIs in the context of diabetes, the most common pathogens are *E. coli* (in 70%) and *Klebsiella* (in 30%). Vasculopathy of the renal circulation is believed to be a major factor in the pathogenesis, once again emphasizing the importance of vascular disease in the clinical manifestation of the more severe forms of infection related to diabetes.

Presenting features include fever, abdominal pain, nausea and vomiting, and drowsiness or stupor. As a result of these nonspecific symptoms the diagnosis is often delayed. The presence of features such as renal angle tenderness, pyuria or pneumaturia should lead to a high index of suspicion. A flank mass may be detected, often accompanied by crepitus. Disseminated intravascular coagulation, septicemic shock, and acute renal failure are all associated with a poor prognosis.

The diagnosis is established by radiologic identification of gas in renal tissue. This is best demonstrated by CT. The plain abdominal X-ray sensitivity is lower. Ultrasonography can also be used, but CT should be regarded as the investigation of choice. In a report of 46 cases in Taiwan, 96% had diabetes with HbA_{1c} higher than 8% (>64 mmol/mol), and 22% also had features of obstruction [100]. Mortality can exceed 50% in patients treated with antibiotics alone. Medical therapy alone is therefore not recommended. Patients may require percutaneous drainage (for localized cases with abscess formation or obstruction) or nephrectomy (in extensive cases). The advent of CT has allowed a more rational approach to the use of these surgical interventions, by allowing more accurate delineation of factors such as gas distribution, obstruction and abscess formation [101].

Diagnosis of urinary tract infection

A high index of suspicion is required, with particular attention in the presence of diabetic neuropathy, renal dysfunction, or renal papillary necrosis. Microscopic examination of the urine may reveal leukocytosis and pyuria. Urine culture and sensitivity should always be carried out. In febrile patients or in suspected upper tract infection, blood culture is essential to detect bacteremia or Gram-negative septicemia.

Plain abdominal radiography is useful to help rule out obstructive uropathy, stones and emphysematous infection. Ultrasonography is a sensitive, safe, and inexpensive technique for initial screening. Ultrasound or CT can confirm the diagnosis of renal abscess, mass, presence of air in the urinary tract and the extent of perinephric spread of infection. The diagnosis of renal papillary necrosis may require ultimate confirmation by retrograde pyelography.

Treatment of urinary tract infection

Treatment should be tailored to take account of local antibiotic resistance patterns (if known), as well as previous history of UTI, previous antibiotic exposure (and possible allergies) together with other risk factors such as recent instrumentation or catheterization. Uncomplicated UTI may be treated with co-trimoxazole (if the local resistance rate is <15–20%), fluoroquinolones, nitrofurantoin, ampicillin, amoxicillin +/– clavulanate, or sulbactam. Increasing resistance to fluoroquinolones has been noted recently. Co-trimoxazole may potentiate the hypoglycemic effect of some oral antidiabetes agents and should be used with caution.

Complicated infections require hospitalization and parenteral antibiotics. Intravenous therapy is continued until fever resolves, following which oral antibiotics can be substituted to complete at least 2 weeks of treatment. Second- or third-generation cephalosporins, β-lactam/β-lactamase inhibitor combinations, or fluoroquinolones may need to be considered in individuals with risk factors, and the possibility of infection with *Pseudomonas* may influence this choice, particularly in the setting of nosocomial exposure or recent instrumentation.

Upper urinary tract involvement with UTI may be up to five times more frequent in people with diabetes compared with

people without diabetes and may be unsuspected or asymptomatic. More prolonged courses of antibiotics (7–14 days) may be considered wise even in the context of apparently uncomplicated UTI [84]. This may also reduce the risk of subsequent relapse. Repeated urine culture to document bacteriologic cure 2–4 weeks post-treatment is advisable given high rates of relapse or treatment failure.

Distinguishing *Candida* infection from colonization is difficult. Removal of an indwelling catheter, if present, is recommended as an initial intervention. Antifungal agents such as fluconazole may be considered in patients with invasive disease.

Intra-abdominal infections other than those within the urinary tract

The potential for interaction between diabetes and various infections of the gastrointestinal tract is considerable. A few examples may be considered. In this context, although the presence of increased risk of *Helicobacter pylori* infection in people with diabetes remains controversial, the presence of diabetes may, in turn, reduce the effectiveness of antibiotic regimens aimed at eradicating the infection. The presence of gastritis may also influence the endocrine functions of the gut, and may also influence the absorption and handling of oral glucose-lowering drugs such as metformin.

Emphysematous cholecystitis

Cholecystitis is probably no more common in people with diabetes than in the general population; however, severe fulminating infection, especially with gas-forming organisms (enteric Gram-negative rods and anaerobes) is more common.

Emphysematous cholecystitis is a rare variant of acute cholecystitis caused by ischemia of the gallbladder wall and infection with gas-producing organisms. It is strongly associated with diabetes (35–55% of cases have underlying diabetes) [102].

Gangrene and perforation of the gallbladder are more frequent, and the overall mortality is substantially higher (at least 15% compared to less than 4%) when compared with acute cholecystitis. *Clostridium perfringens*, *E. coli*, and *Bacillus fragilis* are the most frequently encountered pathogens. Emphysematous cholecystitis is thought to result from acalculous cystic duct obstruction, associated with inflammatory edema, which can eventually lead to cystic artery occlusion. Colonization by gas-forming organisms contributes to necrosis of the mucosa, venous congestion, gangrene and, eventually, gallbladder perforation. Gallstones are present in only about half of patients.

The early clinical manifestations may be indistinguishable from those of acute cholecystitis. Right hypochondrial pain and fever are present in all cases, and other important features include nausea and vomiting, septic shock, jaundice, and peritonitis. Toxicity is marked, and jaundice may develop in the later stages from biliary obstruction. The gallbladder may be palpable in 25–50% of patients. It should be remembered that Murphy's sign (pain and inspiratory arrest on palpation of the right upper quadrant) might be absent in patients with underlying diabetic neuropathy. Crepitus on palpation is an ominous sign. Additional complications include pericholecystic abscess, gallbladder necrosis, generalized or biliary peritonitis, and localized perforation sealed by the omentum.

Plain abdominal X-ray or ultrasound can lead to diagnosis in 95% of cases. In a plain radiograph, gas may be visible in the gallbladder lumen or within the gallbladder wall as a gaseous ring. CT is the most sensitive modality for the detection of intraluminal or intramural gallbladder gas and also demonstrates local complications such as pericholecystic inflammatory changes, abscess formation or perforation. Initiation of appropriate antibiotics and early cholecystectomy is crucial. Emergency surgery is needed because of the high incidence of gangrene and perforation [103, 104].

Liver and other intra-abdominal abscesses

Although liver abscesses may occur in many situations not involving diabetes, the issue is of sufficient importance to justify inclusion in this section.

In keeping with the susceptibility to *Klebsiella* infections described earlier, associations between diabetes and *K. pneumoniae* liver abscess have been reported, notably from Taiwan and Korea [105–107]. Examples from Hong Kong are shown in Figure 55.5.

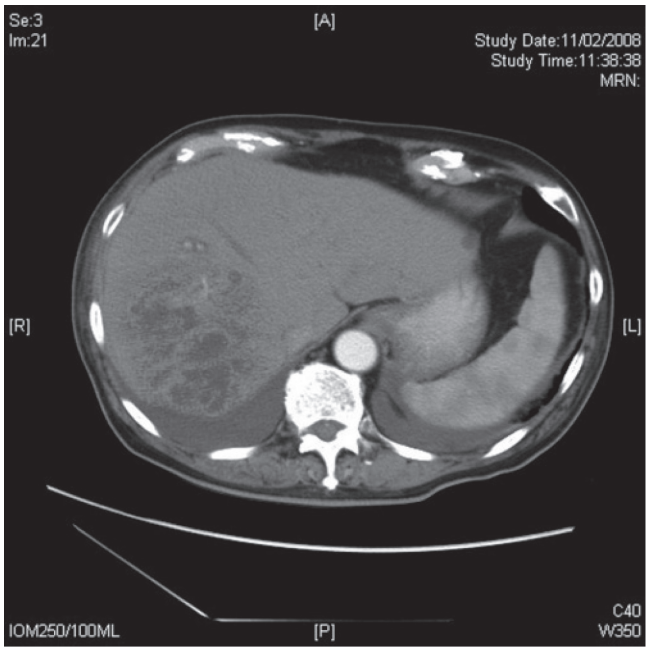
In Korea, invasive liver abscess is particularly associated both with *K. pneumoniae* (78% of the total, 40% of whom have diabetes) and with the K1 serotype (60%) [30].

Diabetes is the most common underlying risk factor specifically for the virulent K1 serotype, but not for non-*Klebsiella* abscesses [108]. In a population-based series of pyogenic liver abscess reported from Taiwan and including 29,703 participants [109], diabetes was a risk factor in 33% leading to an odds ratio of 9 and was associated with an increasing incidence. Liver abscess in people with diabetes was not, however, associated with increased mortality, particularly if therapeutic percutaneous drainage procedures are performed. Eighty percent were associated with *K. pneumoniae* and not as a mixed infection with other organisms. Primary liver abscess in other parts of Asia is also increasing in incidence [30], with 40% reportedly associated with diabetes. Bacteremia is present in 50%, and 8–10% of these cases have metastatic complications (e.g. endophthalmitis, meningitis, brain abscess, pneumonia, skin and soft tissue lesions).

In a series from Europe ($n = 1448$), the presence of diabetes was associated with a 3.6-fold increase in risk for pyogenic liver abscess, and also with a higher 30-day post-discharge mortality rate compared with people who did not have diabetes [110].

In the context of the K1 serotype of *Klebsiella* species, a pathogenic role for the magA gene in the serotype-specific region of the K1 capsule gene cluster, together with a K1 capsular polysaccharide per se, is considered as one of the virulence determinants essential for the development of invasive liver abscess. MagA, an outer membrane protein contributing to capsular polysaccharide

(a)



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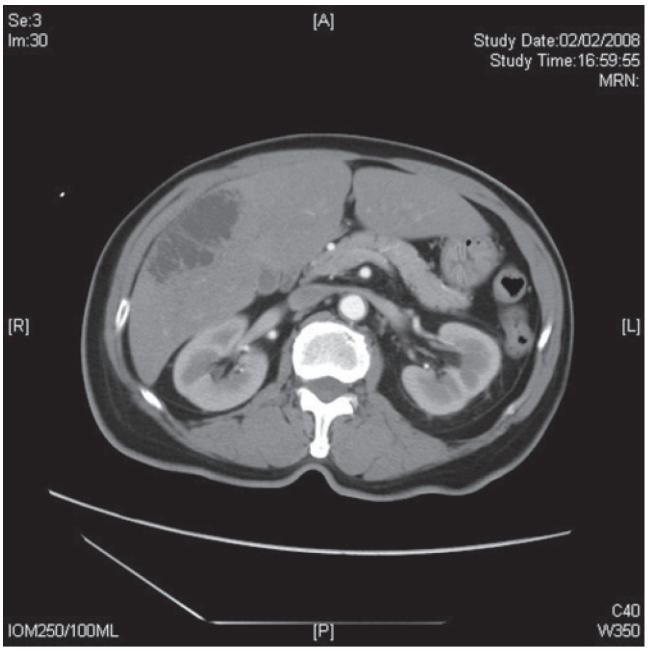

Figure 55.5 (a) CT-scan of an 82-year-old man with fever and newly diagnosed diabetes. Blood culture grew *Klebsiella pneumoniae*. The scan shows an 8 × 8.2 cm heterogeneous lesion in the right lobe of the liver composed of multiple rim-enhancing lesions, with septation and hypodense cystic components. A further three smaller similar lesions (1–2.5 cm) were also seen inferiorly. Overall features are suggestive of liver abscesses. He recovered with drainage and antibiotics. (b) CT-scan of a 77-year-old woman with underlying diabetes, fever and right upper quadrant pain. Both blood culture and pus (from the liver abscess) grew *K. pneumoniae*. The CT scan shows an irregular ovoid lesion with multiple locules and thin intervening septations in the periphery of liver segment V and measuring 7.3 × 3.2 × 6.1 cm. The features suggest liver abscess with signs of early liquefaction. The woman recovered with drainage and antibiotics. Source: The authors acknowledge the Department of Diagnostic Radiology and Organ Imaging, Prince of Wales Hospital, Chinese University of Hong Kong for kindly supplying the images and permitting their use.

formation, coexists with serotype K1 and has been identified as the major virulence factor of *K. pneumoniae* [109]. Poor glycemic control also has a role by impairing neutrophil phagocytosis of K1/K2 type *K. pneumoniae*, whereas it does not significantly affect the phagocytosis of non-K1/K2 *K. pneumoniae*. An rmpA-associated hypermucoviscosity phenotype has also been reported in invasive purulent diseases caused by *K. pneumoniae*.

Most isolates are susceptible to cephalosporins (especially third-generation agents) and fluoroquinolones; however, therapeutic drainage is also needed and also assists with obtaining specimens for culture and susceptibility testing.

Metastatic abscesses may occur elsewhere in the abdomen, either singly or in combination with other sites, as well as within the urinary tract. A notorious, although uncommon, example is psoas abscess where responsible organisms are likely to be *S. aureus*, *Mycobacterium tuberculosis*, *E. coli*, or *Klebsiella*.

Skin and superficial soft tissue infections

Skin and subcutaneous tissues

Infections involving the skin, nails, and subcutaneous tissues are very common, and the skin and subcutaneous tissues are frequent targets of infection in diabetes, particularly in association with poor glycemic control. Candidal infections, bacterial infections such as furunculosis, dermatophycoses, and onychophycoses are all commonly seen and may be the reason for diabetes being identified. Cutaneous forms of mucormycosis or other fungal infections may occur and be diagnosed following skin biopsy. More detailed consideration is given to these disorders in Chapter 52 and is not repeated here.

Sensory neuropathy, atherosclerotic vascular disease, and hyperglycemia predispose people with diabetes to skin and soft tissue infections. Additional risk factors for the development of cellulitis include a past history of cellulitis, edema, peripheral vascular disease, tinea infection, and dryness of the skin. The predominant organisms involved are group A streptococcus and *S. aureus*. Cellulitis can also occur in less usual settings. For example with *S. pneumoniae* (pneumococcal) infections, cellulitis may occur in association with extracutaneous foci of disease, the suggestion being that, in this setting, the cellulitis results from hematogenous spread rather than local infection [111].

People with diabetes, particularly those who inject insulin, often have asymptomatic nasal, mucosal and skin colonization with potential pathogens such as *S. aureus*. Nasal colonization may also contribute to increased risk of staphylococcal pneumonia, for example in association with influenza.

According to data from the National Health and Nutrition Examination Survey (NHANES), people with diabetes who are colonized with *S. aureus* are also more likely to have a methicillin- resistant *S. aureus* isolate than a susceptible one (odds ratio 2.6; 95% CI: 1.1–6.1) [112]. A recent increase in community-associated methicillin-resistant *S. aureus* (CA-MRSA) gives additional cause for concern. A recent report evaluating CA-MRSA in three communities found that 77% of skin or soft tissue infections were methicillin-resistant [113]. The underlying conditions identified included smoking (35%), previous skin infection (21%), and diabetes (19%).

Mucosal and skin colonization with *C. albicans* is also common and may involve numerous sites including the genitalia of both sexes as well as the mouth, skin, and nails [114]. Balanitis and vulval candidiasis are common presenting features of diabetes.

Colonization may predispose to cutaneous or incisional staphylococcal (or other bacterial) infections as well as transient bacteremia. Entry sites may also include areas of fungal skin infection (e.g. intertrigo). Infection at distant sites with abscess formation or septicemia may then ensue. In two relatively early studies (each from the 1960s) older people with diabetes were shown both to be at greater risk of staphylococcal septicemia and also to suffer a substantially higher mortality (69% in those with diabetes compared to 42% overall) [115, 116].

Deeper soft tissue infections

Deeper soft tissue infections also occur with increased frequency in people with diabetes. Examples include pyomyositis, necrotizing fasciitis, and Fournier gangrene. Pyomyositis, usually associated with infection by *S. aureus*, occurs in muscles that have undergone trauma, especially when associated with hematoma formation.

Necrotizing fasciitis

Necrotizing fasciitis is a deep-seated life-threatening infection of subcutaneous tissue. Progressive destruction of fascia, fat, and muscle ensues. Although relatively uncommon, necrotizing fasciitis is a life-threatening condition. Necrotizing fasciitis and Fournier gangrene (a form of necrotizing fasciitis involving the perineum), as well as other necrotizing soft tissue infections resulting from a variety of organisms, all have reported associations with diabetes. Diabetes is the most common of a number of conditions predisposing to necrotizing fasciitis, all of which are associated with compromise to the immune system.

As its name indicates, necrotizing fasciitis spreads initially along fascial planes; however, as infection and inflammation progress, necrosis of muscle, subcutaneous tissues and overlying skin occurs. Necrotizing fasciitis usually follows identifiable episodes of trauma such as burns, insect bites or abrasions, or can result from exposure of non-intact skin to a source of infection. The most common sites are the limbs, abdominal wall, and perineum. Involvement of the vulva in women with diabetes may begin as a Bartholin gland ductal abscess, usually associated with obesity [117].

Polymicrobial infection is most commonly observed, with streptococci and *Enterobacteriaceae* being the most common isolates. The great majority of cases result from infection with anaerobes together with one or more facultative aerobes, whereas about 10% are associated with group A streptococcus, with or without *S. aureus*. Thus, group A streptococcus is the most common cause of infection by a single organism and can also occur in combination with staphylococci, including CA-MRSA. A recent article describing necrotizing fasciitis caused by CA-MRSA showed that although current or past intravenous drug abuse underlay 43% of patients, 21% occurred in people with diabetes [118].

Vibrio, *Aeromonas*, *Haemophilus*, and *Salmonella* infections have also been reported. An interesting example is infection by halophilic marine *Vibrios* either following exposure of non-intact skin to seawater [119] or following bites by marine organisms, such as crabs, and this should be considered when a history of appropriate exposure is present.

Necrotizing fasciitis carries a high mortality, particularly when affecting the lower extremities or perineum, and is rapidly fatal unless diagnosed promptly and treated aggressively. It may be initially misdiagnosed as a benign soft tissue infection and a high index of suspicion is therefore required. Skin changes may be minimal in the early phase of infection.

Early disease may be characterized by severe local pain, which is either disproportionate to or precedes other clinical features such as local inflammation and cellulitis, fever and systemic toxicity. Cellulitis may spread rapidly, unseen in deeper fascial planes. Crepitus is present in about half of cases. Violaceous discoloration of the skin may be noticed and may progress into blistering and bullae. Thrombosis and vasculitis each contribute to necrosis of the superficial fascia and suppuration from liquefactive necrosis. Gangrene and ulceration can result. Anesthesia of overlying skin may indicate destruction of subcutaneous nerves.

Plain radiographs, ultrasound, CT and MRI scan can each assist in both diagnosis and management by identifying the presence of gas in the tissues and by delineating the extent of the disease. Aerobic and anaerobic cultures should be taken from within the lesion, as should blood cultures.

Surgical debridement and fasciotomy are the mainstays of therapy. The single most important issue influencing mortality is time to surgical debridement. Thus, timely diagnosis, empirical broad-spectrum antibiotic therapy (including anaerobic cover) and aggressive surgical debridement of affected tissue are crucial components of management. The antibiotic cover can subsequently be tailored according to culture and sensitivity results. Additional supportive therapy in an intensive care environment should be provided where possible and as necessary.

Fournier gangrene

Fournier gangrene is a specific form of necrotizing fasciitis involving the perineum, scrotum, and penis. Overall mortality is very high. As with other forms of necrotizing fasciitis, diabetes is the most common of a number of potential predisposing conditions with a reported presence ranging 32–60% of cases [120, 121].

Infection is usually polymicrobial with a lengthy list of potential pathogens which is similar to that seen in other forms of necrotizing fasciitis (*E. coli*, *Bacteroides* spp, staphylococci, streptococci, *Proteus* spp, *Pseudomonas* spp, enterococci). *C. perfringens* is present in the great majority (>90%) of cases in which myonecrosis is present.

Initial malaise and scrotal discomfort or pain is followed by systemic toxicity. Blistering ulceration and necrosis of the skin occur and in the later stages progress to scrotal swelling and a foul purulent discharge. Crepitus may be present. Sources of infection include abnormalities of the urogenital system (most notably urethral trauma, instrumentation or a chronic indwelling catheter, scrotal abscess or injury, insect bite) and local gastrointestinal abnormalities (e.g. ischiorectal or perianal abscess, incarcerated inguinal hernia).

Diagnosis is predominantly clinical. Radiologic imaging techniques may reveal subcutaneous gas and delineate the extent of involvement, as with other forms of necrotizing fasciitis.

Fournier gangrene is a surgical emergency, and extensive debridement is required. Urinary or fecal diversion may be required, as may laparotomy. Broad-spectrum antibiotic therapies with anaerobic cover, as well as general supportive measures are indicated as with other forms of necrotizing fasciitis. The results of microbiologic investigation may allow subsequent tailoring of antibiotics.

Infected diabetic foot

Foot infection is the most common soft tissue infection associated with diabetes and therefore is a topic of the utmost importance to all who deal with people with diabetes. However, a specific chapter (chapter 48) is devoted entirely to this topic. Thus, in order to avoid duplication, the topic receives only brief discussion in this chapter.

Disease-related peripheral neuropathy and peripheral vascular disease are both important in the etiology of foot infections, although the clinical presentations of the "predominantly ischemic" and the "predominantly neuropathic" foot differ. Serious complications include osteomyelitis, amputation, or even death. Infection often begins after minor trauma, which may be unnoticed, especially in the presence of sensory neuropathy. Cellulitis, soft tissue necrosis and extension into bone, leading to osteomyelitis, may then follow. Involved organisms most commonly include group A streptococcus and *S. aureus*, as well as aerobic Gram-positive cocci, Gram-negative rods and anaerobes.

The mainstays of management include exploration and debridement of the necrotic tissue and administration of appropriate antibiotics. In moderate to severe cellulitis or in the presence of osteomyelitis that places the limb at risk, the patient should be hospitalized for broad-spectrum antibiotic therapy and surgical intervention.

As in most diabetes-related infections, poor glycemic control plays an important part, and foot infections remain a common presenting feature of newly diagnosed diabetes, particularly in less developed parts of the world. Prevention of foot ulcers involves a multidisciplinary team approach. Foot care is an essential component of all diabetes education programs and should include proper foot care habits, protective footwear, and pressure reduction.

Bone and joint infections

Bone and joint infections remain a significant problem for people with diabetes and can be very difficult to treat. Diabetes is a risk factor for both osteomyelitis and septic arthritis.

The different types of osteomyelitis require differing medical and surgical therapeutic strategies. The three main types, classified according to etiology, include osteomyelitis secondary to a contiguous focus of infection (e.g. after trauma, surgery or insertion of a joint prosthesis); osteomyelitis secondary to vascular insufficiency (e.g. diabetic foot infections); or osteomyelitis secondary to hematogenous spread of infection. The most common reason for septic arthritis is following insertion of joint prostheses. All are more common in people with diabetes, with osteomyelitis of the foot at the forefront. Taking, as an example, osteomyelitis of the spine, then a recurring theme occurs with a combination of both increased risk of hematogenous vertebral osteomyelitis (two- to sixfold) and predisposition to infection involving unusual organisms [122]. Acute osteomyelitis can respond to antibiotics alone but prolonged courses are required for bone and joint infections given the physiologic and anatomical characteristics of the tissues involved. Early diagnosis, together with bone sampling for microbiologic and pathologic examination to allow targeted and long-lasting antimicrobial therapy, allows the best outcomes. As with the diabetic foot, a multidisciplinary approach is required for success, including expertise in orthopedic surgery and infectious diseases, together with vascular surgery. Surgical intervention should be considered if medical treatment fails, for diagnostic confirmation, or in the presence of complications.

Chronic osteomyelitis may be associated with avascular necrosis of bone and formation of sequestrum (dead bone), and surgical debridement is then necessary for cure in addition to antibiotic therapy. It is important to remember the possibility of infection by *M. tuberculosis* [123].

Iatrogenic and surgical site infections

Insulin injections

Infections at the site of insulin injections are very uncommon and remain so even when traditional hygienic practices are not applied. Although not advised, administration of insulin through clothing is also not associated with increased risk of infection. Abscesses at needle sites are occasionally seen in individuals receiving subcutaneous insulin infusions [124]. Likewise, pulp infection over the distal phalanges in association with self-blood glucose monitoring is exceedingly unusual.

Surgical site infections

An association between diabetes and an increased risk of surgical site infections has been known to exist for many years.

Studies addressing this question have frequently focused on the risk of postoperative infection following coronary artery bypass grafting. The association has been generally assumed to be causally related to the deleterious effect of hyperglycemia on immune function [125].

Three studies support an increased risk of postoperative infection associated with postoperative hyperglycemia among those with diabetes undergoing bypass grafting [126–128]; however, whether or not hyperglycemia imposes an independent risk for infection remains controversial. In none of the studies was mortality increased and, in one, postoperative hyperglycemia was correlated with a higher risk of infection while an elevated HbA_{1c} was not. The studies demonstrate, however, that improved glucose control during the operative and perioperative period can reduce the risk of postoperative infections in people with diabetes undergoing cardiac surgery. One retrospective study of 1574 patients undergoing coronary artery bypass grafting at a single institution found no increase in mortality or rates of infection among those with higher postoperative glucose levels and 34.6% of patients in this series had a diagnosis of diabetes. Nevertheless, increased glucose concentrations were associated with increased hospital charges and a longer postoperative stay.

Both allograft rejection and risk for infection appear to be higher in transplant recipients with diabetes. In one study, the risk of serious infection was higher in heart transplant recipients with diabetes in the early postoperative period [129]. In another study, renal transplant recipients had a greater risk of both acute allograft rejection and infection when perioperative glycemic control was poor [130].

Dialysis

Ambulatory peritoneal dialysis is a common form of treatment for end-stage renal disease in people with diabetes. For those receiving continuous ambulatory peritoneal dialysis, episodes of catheter-related peritonitis are common, although variable from individual to individual, with some developing multiple episodes. Overall, however, the rate of infection does not appear to be greater in people with diabetes than those without diabetes, perhaps reflecting impairment of immunity associated with end-stage renal disease per se.

The issue of peritonitis in people receiving continuous ambulatory peritoneal dialysis is an important one given the large number of people with diabetes receiving this treatment. It is well recognized that peritonitis, despite significant reductions in the last two decades, remains the most important complication of continuous ambulatory peritoneal dialysis with an overall mortality of about 3.5%, irrespective of both the underlying cause of the infection and the renal failure [131]. The degree to which the presence of diabetes adds to the already considerable infection risk remains uncertain. People with diabetes may, however, be generally more unwell and have additional factors and complications such as macrovascular disease, need for hospitalization and predilection to certain infections, such as candidiasis. All of these may, in principle, contribute to the already very considerable risk.

Principles of treatment, prevention, and general care

General principles

A high level of awareness is required in people with diabetes and in all healthcare providers, both to allow prevention and early, prompt recognition and diagnosis. Education, good glycemic control and general steps to maintain health and nutrition are all important measures aimed at minimizing risk. Careful attention to foot care is particularly emphasized. Vigilant measures should be instituted to prevent infection. When infections do occur, evolving antibiotic resistance patterns and other local factors must be considered, with CA-MRSA and tuberculosis both providing obvious examples of the importance of this.

The choice of antibiotic therapy follows the same general principles as for any other individual. Use of empirical broad-spectrum antibiotics is generally recommended until microbiologic results can guide treatment. Due caution should be applied in the presence of diabetic complications. For example, the use of potentially nephrotoxic agents in the context of diabetic nephropathy may aggravate renal dysfunction, and in turn impaired renal function requires caution with doses and monitoring of blood levels. The presence of gastroparesis or autonomic neuropathy may hinder, or render unreliable, the absorption of oral drugs. People who are blind or partially sighted as a result of eye complications may also be at increased risk, for example when exposed to drugs that impair hearing or balance. Longer courses of antibiotic therapy may be appropriate, for instance in treating UTI.

Antiviral agents are recommended in the setting of influenza, and a more aggressive treatment approach may be appropriate even when presentation is relatively late [69]. Responses to treatment should also be carefully monitored (e.g. in the case of tuberculosis) [82]. The importance of appropriate referral to surgical or other specialist colleagues has been stressed repeatedly. Examples include surgical debridement in the case of necrotizing fasciitis, and incision and drainage of abscesses.

People with diabetes generally have a normal response to vaccines and should receive immunizations according to established guidelines. None of the vaccines currently available are contraindicated on the basis of diabetes alone. Because of increased susceptibility to complications, routine immunization against pneumococcus and influenza is recommended, particularly for older people with diabetes or for those with additional comorbidity such as chronic respiratory disease. Influenza vaccination has been shown to reduce hospital admissions significantly during influenza outbreaks [132]. Hepatitis B vaccination is also important although some populations may require additional or booster doses over and above standard recommended regimens.

Glycemic control

All physicians need to be aware of the importance of careful monitoring of diabetic control in the presence of infection and should

be on guard against destabilization of control or development of complications. Interestingly, in people without diabetes following hospitalization, even mild degrees of hyperglycemia are associated with increased mortality in association with severe illness. Although depressed immune function correlates somewhat variably with traditional measures of glycemic control, there is sufficient evidence to indicate an inverse relationship between the two which is potentially reversible. Previously undiagnosed diabetes may also be first detected following hospitalization and then needs to be distinguished from hospital-related hyperglycemia which later reverts to normal.

People with T1DM or others receiving insulin need to be aware of the probability of changing insulin requirements in response to infection and to the risk of severe consequences such as diabetic ketoacidosis. Many people with T2DM, who are not on insulin, need to be transferred temporarily to insulin therapy as the stress of illness frequently adversely affects glycemic control. Hospital admission is mandatory if severe destabilization of glycemic control occurs, or if symptoms such as nausea and vomiting interfere significantly with oral food intake. In this situation, intravenous insulin-glucose regimens are recommended. While good glycemic control is important, it is also important to avoid hypoglycemia. Interaction between the diabetes care team and other involved specialists should be initiated as early as possible.

The importance of perioperative glycemic control in people with diabetes undergoing surgery also needs to be emphasized in order to minimize negative impacts upon postoperative infection rates and wound healing (see Chapter 34).

Attention to other risk factors (e.g. neurologic and vascular complications) is also important in order to minimize the risk of infections and infection-related complications. The importance of the presence of microangiopathy and neuropathy in the risk of the more severe forms of infection is again emphasized.

For more detailed description of these aspects of care, readers are referred to clinical practice recommendations, for example those of the American Diabetes Association or to other national or international guidelines, as well as to other relevant chapters in this textbook.

Awareness among physicians needs to be high, especially with regard to the unusual and severe forms of infection that may occur. The general approach to antibiotic treatment is the same as for people without diabetes, but details may differ (e.g. doses and duration of therapy). Responses to vaccination are generally normal, and influenza and pneumococcal vaccination is recommended. Careful attention to glycemic control and to other underlying factors is essential.

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10 Psychosocial Aspects of Diabetes

56 Psychological Factors and Diabetes Mellitus

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Key points

- People who report chronic stress, low stress resilience, sleeping problems, or depression are at increased risk of developing type 2 diabetes mellitus (T2DM). Recent evidence suggests that chronic stress is also a risk factor for the development of type 1 diabetes mellitus (T1DM). The mechanisms remain poorly understood.
- Both T1DM and T2DM can affect the psychological and neuropsychological status of children and adults. In most instances, these effects are modest in magnitude and are most likely to be associated with certain adverse events that occur during the course of diabetes or its management.
- Children show remarkable psychological resilience to the diagnosis of T1DM. About one-third report some psychological distress shortly after diagnosis but this generally subsides within 6 months. Problematic adjustment is characterized by increased depressive symptomatology, more anxiety, social withdrawal and sleep disturbances. A similar adjustment reaction is often seen in parents, particularly mothers, of children with newly diagnosed T1DM. Diagnoses of post-traumatic stress disorder are also more common in parents, occurring at rates comparable with that reported in children diagnosed with cancer.
- During the first 5–10 years of their diabetes, most children and adolescents show adequate psychological functioning; however, after 10 years of diabetes, their rates of anxiety, depression, or eating disorders are markedly increased, with as many as one-third of adolescents with diabetes meeting criteria for one or more psychiatric disorders.
- Macrovascular disease, chronic foot ulceration, and proliferative retinopathy increase the risk of psychopathology, an understandable reaction to serious complications; however, lifetime psychiatric disorders such as depression may also increase the risk of later development of complications such as retinopathy. Recurrent diabetic ketoacidosis, particularly in young women, is also predicted by poor psychological functioning, and by high rates of family dysfunction.
- Diabetes-specific distress and fear of hypoglycemia are both relatively common. The latter may lead to premature treatment as blood glucose levels begin to fall, resulting in persistent hyperglycemia.
- Generic health-related quality of life and health status for those with diabetes does not differ from people with other chronic conditions, such as arthritis. Lower health-related quality of life is associated with diabetes complications, being female, physical inactivity, low income, and recurrently hypoglycemia.
- Diabetes-specific quality of life can be impaired by intensive diabetes management or improved with flexible approaches to intensification of treatment.
- Interventions such as individual or group therapy or counseling based on the principles of cognitive behavioral therapy (CBT) or mindfulness-based therapies are effective in improving mental well-being. Web-based CBT is also effective.
- Diabetes management and health outcomes are influenced by reciprocal relationships between glycemic control and psychological variables. The latter include enduring psychological traits such as locus of control, coping style, temperament, and transitory psychological states (stress, anxiety, depression). Diabetes is also strongly related to family functioning, especially in children and adolescents: low family conflict, good communication, cohesion, and marital satisfaction relate to better diabetes control.
- Self-care behaviors (medication-taking, self-monitoring of blood glucose, healthy eating, physical activity) are only weakly related to glycemic control, but this may reflect the inaccuracy of self-reported behaviors, the crudeness of the self-report measures or the discrepancy between "typical" recent behaviors (e.g. past 2 weeks) and HbA_{1c} (the average blood glucose over the past 8–12 weeks).
- Effective interventions to improve psychological well-being, self-care, and health outcomes include empowerment-based approaches, structured training/education, as well as psychotherapy and family therapy. The components of effective programs include (with various emphasis) goal-setting, problem-solving, coping, managing stress, self-motivation, and self-management skills.
- Cognitive dysfunction in diabetes is generally mild, but when diabetes is diagnosed in the first 5–7 years of life, children have an elevated risk of

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manifesting clinically significant impairments in all cognitive domains. Those with a later onset of diabetes show modest effects, most evident on measures of intelligence, academic achievement, and psychomotor efficiency. Deficits appear early in the course of the disease, and are evident within 2–3 years after diagnosis. Hypoglycemia was long considered to be the major cause of this neurocognitive dysfunction but more recent research suggests that adverse effects on cognition usually occurs only when hypoglycemia extends over a prolonged period of time. Although the etiology of neurocognitive changes in children remains poorly understood, a growing body of evidence implicates chronic hyperglycemia and, in particular, the development of microvascular and macrovascular complications.

- In adults with T1DM, neurocognitive deficits are quite modest and are most apparent on measures of intelligence, psychomotor speed, and executive function. Older adults with T2DM manifest marked reductions in memory function and, in both groups, the strongest predictor of cognitive dysfunction is chronic hyperglycemia and the presence of biomedical complications, particularly retinopathy and peripheral neuropathy.
- Structural damage to the brain is also common in both children and adults with either T1DM or T2DM. Not only is there a reduction in cortical gray matter density, but white matter structures may be disrupted. Cerebral atrophy is often present, neural slowing is evident on electroencephalography and regional cerebral blood flow is altered.

Introduction

Diabetes and psychology have long been linked. Areteus of Cappadocia (1st or 2nd century) described life with diabetes as "disgusting and painful." In the 17th century, Thomas Willis mentioned long grief and melancholia as potential causes of diabetes. More than three centuries later, a meta-analysis of modern longitudinal epidemiological studies confirmed that Willis was right. This chapter examines four major points of intersection: (1) psychological risk factors for diabetes, (2) psychological impact of diabetes and its complications, (3) psychological factors that influence, or are influenced by, the everyday management of diabetes, and (4) the neuropsychological or cognitive consequences of diabetes.

Psychological risk factors for the development of diabetes

Longitudinal epidemiological studies have shown that not only depression and anxiety, but also general emotional stress, sleeping problems, anger, and hostility, are associated with increased risk of developing type 2 diabetes (T2DM) [1–3]. Using data from the British Household Panel Survey ($n > 9000$), Mommesteeg et al. [4] found that, compared to adults reporting a low level of psychological distress, those with higher levels were at 33% increased risk of developing T2DM during the 18-year follow-up. Additional analyses showed that this association might be mediated by a low energy level and impaired health status. Both sleep quality and quantity (too much and too little) predict the onset of T2DM. In a systematic review of 10 longitudinal studies, involving >107,000 men and women without diabetes at baseline [5], short sleep duration (≤5–6 hours per night) increased diabetes risk by 28%, while long duration (>8–9 hours/night) increased risk by 48%; difficulty in initiating and maintaining sleep increased diabetes risk by 57% and 84%, respectively [5]. For other psychological factors (such as childhood neglect, a large number of adverse life events, and elevated work stress), there are conflicting findings [2].

Only one prospective study so far has investigated stress as a risk factor for type 1 diabetes (T1DM). In an updated analysis of the All Babies In southeast Sweden (ABIS) study, 58 children from the 10,495 participants developed T1DM, with childhood experience of a serious life event being associated with a higher risk (HR 3.0; 95% CI: 1.6–5.6) [6, 7]. Chapter 57 will describe how depression is an important risk factor for the development of T2DM.

The majority of studies have focused on emotional problems or psychological factors as transient states, such as current depression or stress levels. However, if psychological factors do indeed have an impact on the development of T2DM, this is most likely a process over several years. Therefore, personality factors or traits may also play an important role. The role of stress resilience in the onset of T2DM was investigated prospectively in a national cohort study of 1.5 million male military conscripts in Sweden (from 1969 to 1997) with follow-up over 25 years (from 1987–2012) [8]. Stress resilience was assessed using a "gold standard" interview by psychologists (with high inter-rater reliability). Controlling for family history of T2DM and baseline BMI, those with low stress resilience were 51% more likely to be diagnosed with T2DM than those with greater innate ability to cope with stress [8]. Chronic stress was associated with a number of unhealthy behaviors (e.g. physical inactivity, unhealthy diet, sleep problems, smoking) as well as activating the innate immune system (i.e. increased interleukin 6 and other cytokine mediators of stress response, which are also involved in mediating insulin resistance). A recent systematic review of 10 longitudinal and 13 cross-sectional studies investigated whether various personality characteristics are associated with having, or the risk of developing, metabolic syndrome but there is conflicting evidence for high hostility, neuroticism, or Type D (distressed and socially inhibited) personality as risk factors, possibly reflecting publication bias [9]. Consequently, we need new epidemiological cohort studies with a prospectively published study protocol to further our knowledge about the role of chronic emotional stress, depression/anxiety, and personality traits as risk factors for the development of T2DM. One example is the Maastricht Study [10], which will investigate not only depression and anxiety, but also various personality factors in relation to T2DM. Future research also needs to focus on

identifying behavioral and physiological mechanisms linking various forms of stress and incident T2DM.

The psychological impact of diabetes and its complications

Psychological distress shortly after diagnosis

People with diabetes ought to manifest significant psychological distress, or so goes conventional clinical wisdom. The term psychological distress refers not only to depressive and anxiety symptoms, but also to diabetes-specific distress. Depression and anxiety are both common general mental health disorders, while diabetes-specific distress reflects a person's negative emotional response to the burden of living with diabetes, not the presence of a psychiatric condition [11]. Depression, anxiety, and diabetes-specific distress partly overlap, but are not interchangeable constructs. People with diabetes live with a condition that shortens their life expectancy, can lead to debilitating biomedical complications (e.g. blindness or neuropathy), and requires them to take daily responsibility for managing their health (e.g. with medications or insulin injections, and careful monitoring of diet, physical activity, and blood glucose levels) for the remainder of their lives. Interestingly, however, in the Hoorn Study, a diagnosis of screening-detected T2DM was not associated with significant psychological distress [12].

Children and their parents

In contrast to many expectations, children and adults show remarkable psychological resilience to a diagnosis of diabetes. In what may be the most comprehensive prospective psychological study of children with T1DM and their families, Kovacs et al. [13] assessed 95 children, 8–13 years of age, shortly after discharge from their initial hospitalization, and followed them for 6–10 years. Within 3 months of diagnosis, 36% of the children experienced sufficient psychological distress to meet criteria for a diagnosable psychiatric disorder [14]. Most had "adjustment disorder," defined as a transient reaction that exceeds the normal and expected response to a stressor, which develops within 3 months of onset of the stressor and lasts no more than 6 months. The occurrence of such a disorder signals that the child is beginning to come to terms with the diabetes, and can be considered a component of the "mourning process" that often accompanies the development of any chronic illness [15]. As expected, recovery was rapid, with 93% showing complete remission of psychiatric symptoms within 9 months.

Greatly elevated rates of post-traumatic stress disorder (PTSD) have also been reported in a prospective study of parents evaluated at 6 weeks, and 6 and 12 months after their child's diagnosis. Depending on the time point, 16–22% of mothers and 8–14% of fathers met DSM-IV criteria for a PTSD diagnosis [16]. These rates were significantly higher than symptoms in the general population but are comparable with those seen in mothers of children diagnosed with cancer. The best predictor of PTSD severity at 12 months was PTSD severity at 6 months; episodes of hypoglycemia were also associated with an increased severity of PTSD.

In a systematic review of eight cross-sectional studies that focused on fear of hypoglycemia in parents of children under the age of 12 with T1DM, fear of hypoglycemia was common, especially among mothers [17]. Moreover, fear was related more to hypoglycemia severity than frequency, particularly if the child had experienced a hypoglycemic convulsion [17].

Adults

The onset of diabetes during adulthood ought to produce similar adjustment disorders within several months of diagnosis in both the individual and partners or close family members. A German study used structured interviews that provided diagnoses according to DSM-IV in a sample of adults (aged 17–40 years) with newly diagnosed T1DM and compared them with a large reference group, comprising a representative population sample of 2046 persons of a similar age. Persons with T1DM had a rate of major depressive episodes twice that of the reference group (5.8% vs. 2.7%) [18]. A more careful analysis showed that these differences were statistically significant only for women with T1DM (9.3% vs. 3.2% in the reference group), with no differences in men (3.6% vs. 2.2%), nor for other psychiatric disorders [18]. Studies of adults with T2DM report mixed findings regarding psychological morbidity in the first year following diagnosis. A meta-analysis has demonstrated the prevalence of depression to be higher in adults with diagnosed T2DM compared to those with undiagnosed T2DM, impaired glucose metabolism or normal glucose metabolism [19]. The recent LifeLines study was a large epidemiological study of 90,686 participants who underwent diagnostic psychiatric interviews and had fasting glucose levels taken [20]. In contrast with the earlier meta-analysis [19], LifeLines shows that depression is independently associated with T2DM, both diagnosed (odds ratio [OR] = 1.4:1.1–1.8; $p = 0.006$) and undiagnosed (OR = 1.8:1.3–2.6; $p = 0.001$), while anxiety is independently associated with diagnosed T2DM (OR = 1.4:1.2–1.7; $p < 0.001$) but not undiagnosed T2DM [18]. A smaller clinical study of 71 participants reported that more than 50% expressed no emotional reaction to the diagnosis and felt that they could cope [21]. In a prospective study of 116 adults with newly diagnosed T2DM identified by a targeted population-screening program, the diagnosis had no substantial impact on psychological well-being, shortly after, and 6 and 12 months after diagnosis [12].

Psychological reactions emerging in the course of diabetes

Living with and managing diabetes is a complex endeavor. People with T1DM or insulin-treated T2DM must take responsibility for administering insulin doses and checking blood glucose levels (often several times per day), carefully monitoring food intake and physical activity, and then readjusting insulin, food and/or exercise in response to high or low blood glucose values or during acute illness. For those with T2DM not using insulin, the treatment regimen can be less onerous but adopting and sustaining

healthy lifestyle behaviors can also be burdensome, and not understanding how to adjust diet and physical activity to improve outcomes can be frustrating and demoralizing. In either instance, people with diabetes and their families assume primary responsibility for these self-care behaviors, all of which are directed at achieving or maintaining optimal glycemic control and quality of life.

Depression, anxiety, and diabetes-specific distress in children and adolescents

As duration of T1DM increases, it appears that many children and adolescents function well psychologically, although small increases may be evident in depressive and anxiety symptomatology and internalizing behaviors, such as somatic complaints, social withdrawal, and sleep disturbance. In school-aged children [22], this is evident after 2–3 years of T1DM, yet the magnitude of these changes does not reach clinically significant psychopathology. Somewhat higher rates of externalizing, or aggressive, behaviors have also been reported, with this phenomenon especially pronounced in boys [22], and strongly associated with persistent hyperglycemia [23].

Children who report more difficulties in managing their T1DM also show more symptoms of psychological distress. Level of psychological distress shortly after T1DM onset is often a good predictor of psychological problems later [24]. This suggests that it is helpful to assess psychological well-being shortly after diabetes onset and to monitor this routinely thereafter. De Wit et al. reported a randomized controlled trial that confirmed the utility of monitoring psychological well-being in adolescents with diabetes, for example with the MY-Q questionnaire [25, 26]. The frequency of assessments can be adjusted to the needs of the young person with diabetes, and intensified where indicated to guide further clinical actions and initiate stepped care [27].

When a structured psychiatric interview is used to assess for clinically significant psychopathology, marked elevations are found in rates of psychiatric disorder. Not only are girls more often affected than boys [28, 29], but their risk for recurrence of depression is also greater. In a cohort of Australian children with newly diagnosed T1DM assessed over a 10-year period, 37% had at least one DSM-IV diagnosis [28]; of those, 60% met criteria for two or more disorders and 55% met criteria for three or more disorders [28]. Mood, anxiety, and eating disorders were each present in 17% of the sample and nearly 20% manifested a behavioral disorder. Those adolescents who met criteria for a DSM-IV psychiatric disorder were also more likely to have manifested significant externalizing problems shortly after diagnosis, which were likely to have preceded diagnosis. Other investigators have identified maternal psychopathology as a potent predictor of subsequent psychiatric disorder and increased depressive symptomatology in children and adults with T1DM [30].

Elevated rates of suicidal ideation have been reported for adolescents with T1DM, with lifetime prevalence rates of ~26%, compared to 9–12% for adolescents without diabetes [31]. Although the rate of actual suicide attempts is low among youth with diabetes (4%), suicidal ideation was associated with greatly increased rates of disengagement from medical treatment.

Relatively little is known about diabetes-specific distress in children and adolescents. Largely, this is due to the dearth of appropriate measures for this age group and lack of recognition, until recently, of the potentially important role of diabetes-specific distress. A recent systematic review [32] highlights that only three measures have been developed specifically for adolescents and prevalence of clinically relevant diabetes-specific distress is estimated to affect around one-third of adolescents. Diabetes distress appears to be associated with HbA_{1c} (particularly when age-appropriate measures of diabetes distress are used), although associations with self-care behaviors were mixed [32]. While parental emotional support appears to be associated with lower rates of diabetes-specific distress, neither age nor gender appear predictive of diabetes-specific distress [32]. Importantly, diabetes-specific distress was strongly associated with depressive symptoms [32], suggesting that these constructs are inter-related and perhaps that interventions to reduce diabetes-specific distress may improve general well-being of adolescents with diabetes.

Depression, anxiety, and diabetes-specific distress in adults

The process of psychological adaptation to the diagnosis of diabetes in adulthood remains incompletely understood, largely because few longitudinal studies have been conducted with adults [33]. The Diabetes Control and Complications Trial (DCCT) Research Group [34], which is the largest follow-up study of adults with T1DM, found no change in self-reported psychological symptomatology over a follow-up period of 6–9 years, and found no relationship between type of treatment (conventional or intensive insulin therapy) and levels of psychological distress [35]. In an early systematic review, rates of clinically significant depression were higher in both treatment groups (25%) compared with rates of depressive symptoms (measured by self-report questionnaire) in the general population (14%) [36].

Cross-sectional studies of adults with either T1DM or T2DM have demonstrated repeatedly that rates of psychological distress, particularly depressive symptoms and anxiety, tend to be higher than the general population, but are usually comparable to those reported in individuals with other chronic conditions [37–39]. Using self-report measures of psychological symptoms, Peyrot and Rubin [40] found greatly elevated rates of both depressive (41%) and anxiety symptomatology (49%), with 38% of their entire sample showing elevations in both domains; however, repeated reassessment of these individuals over a 6-month period indicated that these effects are quite unstable. Across all three assessments, only 13% of the sample was persistently disturbed. The strongest predictors of ongoing distress included being female, having less than a high school education, being middle-aged, and having more than two diabetes-related biomedical complications [41]. Nefs et al. clearly showed that the best predictor of future depressive symptoms is a history of depression [33].

The concept of diabetes-specific distress emerged in the adult diabetes literature around two decades ago, with the publication of the Problem Areas in Diabetes scale [42]. There was no significant difference in distress scores among those with T1DM or insulin-treated T2DM, and scores were only weakly associated with age and diabetes duration [42]. Sixty percent of study participants reported at least one diabetes-related problem as "serious," with the top five most frequently endorsed "serious" problems being:

- worries about the future and the possibility of serious complications;
- feeling guilty or anxious when you get off track with your diabetes management;
- feeling scared when you think about living with diabetes;
- feeling discouraged with your diabetes regimen; and
- feeling depressed with you think about living with diabetes.

This seminal study also found that diabetes-specific distress was associated negatively with self-care (after adjustment for age, diabetes duration, and general emotional distress) and correlated positively with HbA_{1c}. Various international and more recent studies corroborate these findings [43–45]. A recent review found that elevated diabetes-specific distress is experienced by 20–30% of adults with T1DM, and more likely in women and in those with longer T1DM duration, severe hypoglycemia and younger age [46]. While many of the key emotional problems may not discriminate by diabetes type [42], studies have noted that the distress experienced by adults with T1DM tends to relate to "worries about low blood sugar reactions" and "feeling burned out by the constant effort to manage diabetes," while that experienced by adults with T2DM relates more to "not having clear and concrete goals for your diabetes care" and "feeling constantly concerned about food and eating" [46].

Psychological reactions to acute biomedical complications

Acute complications of diabetes include diabetic ketoacidosis (DKA; Chapter 36) and severe hypoglycemia (Chapter 35), both of which may be rare or recurrent events for an individual, and be influenced by an individual's personal and treatment characteristics.

The frequency of DKA peaks in adolescence, and recurrent DKA remains an issue among only a minority of adults with T1DM, largely predicted by intentional insulin omission. In the only narrative review of this topic, Skinner notes that this is because of feelings of depression, resentment, denial, and rebellion against diabetes [47]. Many interventions have potential depending on the person's circumstances: changing insulin regimens (including nurse-led injections, insulin pump), cognitive behavioral therapy, and family therapy are all options. He described that an important step in resolving recurrent DKA is a multidisciplinary approach, with knowledge of the person with diabetes from a psychosocial perspective and, most importantly, not losing contact with the person experiencing recurrent DKA.

Acute hypoglycemic episodes are often uncomfortable and unpredictable. They are accompanied by autonomic arousal characterized by aversive symptoms such as trembling, sweating, light-headedness, pounding heart, nervousness, feelings of agitation and worries that this episode could lead to a seizure, coma or death if not treated promptly. Thus, the development of fear of hypoglycemia, and the corresponding effort to avoid any situation that may lead to a recurrence of a hypoglycemic event, is unsurprising and an adaptive psychological reaction. In the DAWN2 study, conducted in 17 countries, 56% of participants with diabetes reported being worried about hypoglycemic events [48]. Fear of hypoglycemia is, indeed, indiscriminate, occurring in children [49] and adults with diabetes [50, 51], but especially in parents [49] and spouses [52], who can be more fearful than the individual, as they are often more acutely aware of its impact, while the person is unconscious with little recall of the event. In the DAWN2 study, for example, 61% of family members of people with diabetes reported to be worried about hypoglycemia [53].

Adults with T1DM, who experience recurrent hypoglycemia, or even a single episode of severe hypoglycemia when accompanied by seizure or coma, have greater fear of hypoglycemia [54]. This can be accompanied by broader diabetes-specific distress and impaired generic emotional well-being [55]. This is likely to be a consequence of several factors, including pre-existing personality traits, particularly neuroticism or trait anxiety, and current level of psychological distress [56]. Recent work has begun to explore the relationship between fear of hypoglycemia, and risk of severe hypoglycemia, identifying four subgroups (e.g. low fear/low risk; high fear/high risk; low fear/high risk; high fear/low risk), demonstrating the complexity of such fear and the importance of understanding the nature of the fear for determining suitable clinical interventions [57].

Less is known about the impact of hypoglycemia on adults with T2DM, but a narrative review concluded that (recurrent) hypoglycemia has a negative impact on quality of life [58]. Hypoglycemia is associated with more depressive and anxiety symptoms, and also with impairments of the ability to drive, work, and function in ways that are important for quality of life [58].

In addition to being associated with higher levels of generalized psychological distress, fear of hypoglycemia may lead people with diabetes, and parents of children with diabetes, to avoid hypoglycemia by treating falling blood glucose prematurely and hence maintaining blood glucose at higher than optimal levels [59]. Other, much rarer, diabetes-specific fears include fear of injecting or self-testing [56, 60, 61]; the prevalence of a phobia to needles or blood and injury remains controversial but is likely between 1–10% [56, 60, 61].

Psychological reactions to long-term biomedical complications

Several international studies have now demonstrated that worries about the future and the possibility of serious complications are the foremost "problem areas" for people with diabetes [42–45]. This is unsurprising given that long-term complications (such as retinopathy, neuropathy, nephropathy) can have a devastating impact upon the individual's health [62]. Due to the emphasis

placed on the importance of managing diabetes optimally to prevent complications, their development may also be viewed by people with diabetes, their families, healthcare providers, and others as a sign that they have "failed" to self-manage the condition adequately. Thus, it is reasonable to consider that the onset of complications leads to psychological distress, due to the emotional impact and significance of a new health status but also to a change in self-perception or identity and to self-blame and guilt. This conjecture has not been tested empirically and it is unknown how adults react psychologically immediately after a complication appears. However, as a group, adults with complications usually have greater levels of depression [63, 64]. A prospective cohort study reported that 24% of adults with diabetes presenting with their first diabetic foot ulcer had clinically significant major depression, and this was associated with a threefold risk of death during an 18-month follow-up period [65]. Other studies have also demonstrated marked increases in depressive symptomatology with peripheral neuropathy, and have attributed this psychological distress to the physical distress associated with reduced feeling in the feet and unsteadiness, as well as its unpredictability [66, 67].

People who develop retinopathy, and with it varying degrees of vision loss, experience a range of adverse social impacts (including social isolation, increasing dependence on others, disruption to family functioning) as well as an array of emotional impact (including loss of confidence, fear, vulnerability, anger, stress, depression) [68]. However, the degree of psychological distress secondary to visual loss may not be unique to people with diabetes; at least one study of older adults has reported no significant difference in psychological adjustment between those with and without diabetes, either at the onset of visual loss or when re-evaluated 12 months later [69].

Quality of life

Psychological distress has so far been the primary focus of this discussion, but the extent to which diabetes affects the individual's perceived quality of life is also important. Defining and measuring quality of life remains controversial, although it is generally agreed that it is multidimensional (including physical, psychological, and social domains), subjective (domains will vary in importance and relevance for each individual), and dynamic (changing over time) [70]. A useful way to gain insight about this is to ask a person with diabetes "what aspects of life are important for your quality of life?" and, then "how does your diabetes affect these?"

Generic, health-related quality of life

Most attempts to assess quality of life actually assess health status, or what is commonly (and perhaps confusingly) referred to as "health-related quality of life," with the two most frequently used measures being the SF-36 and EQ-5D [70]. In people with diabetes, such measures are typically more sensitive to differences between those with and without macrovascular complications or other non-diabetes-related comorbidities [71], or following major procedures such as pancreas transplant [72], than to differences between those with and without microvascular complications or using intensive versus conventional treatment regimens [73]. Large-scale studies comparing the health-related quality of life of people with various chronic conditions have typically found little evidence that it is differentially disrupted in adults with diabetes. For example, when health-related quality of life was assessed in a large cohort of adults with diabetes using the Medical Outcome Study (MOS-36) questionnaire, people with diabetes reported more problems in physical and social functioning than those without chronic conditions, but tended to function better than people with cardiovascular, pulmonary, or gastrointestinal disorders [74]. For individuals with T1DM, poorer health-related quality of life is associated with being older, having biomedical complications, being female, being less physically active, and having a lower income [75]. Similarly, among individuals with T2DM, impaired health-related quality of life was associated with being female, the presence of diabetes-related complications, other non-diabetes-related comorbidities, and duration of diabetes [76].

Nieuwesteeg et al. [77] reviewed 17 studies that compared generic quality of life of children and adolescents with T1DM with that of their healthy peers. The authors concluded that the weighted effect sizes across all studies indicated no substantial differences in quality of life domains between children and adolescents with T1DM and healthy controls. On the other hand, disease-specific problems were certainly present.

Most recently, the DAWN2 study has shed light on the quality of life of 1368 adults with T1DM and 7228 adults with T2DM from 17 countries [48]. Overall, the impact of diabetes on various dimensions of quality of life was negative, with only 28% reporting a positive impact on at least one of the six life dimensions. A negative impact of diabetes on physical health was reported by 62% of respondents, followed by emotional well-being (by 46%), financial situation (by 44%), leisure activities (by 38%), work or studies (by 35%), and on relationships with family and friends by 21%. Approximately 40% of respondents (range: 19–65%) reported that their medication routine interferes with their ability to live a normal life.

Diabetes-specific quality of life

Diabetes-specific quality of life instruments do not enable comparisons between conditions but they are more likely to be sensitive in measuring the impact of diabetes and are also more responsive in assessing the consequences of treatment changes than generic or health-related measures [70]. This is because they include domains that are particularly relevant to diabetes, for example dietary freedom, and exclude other domains of less relevance, such as mobility.

The Diabetes Quality of Life (DQOL) measure was the first questionnaire to be developed specifically to assess the impact of diabetes upon quality of life [78]. It was designed for use in the DCCT to examine explicitly factors such as satisfaction, impact of diabetes, social and vocational worry and diabetes-related worry. The DCCT findings suggested that quality of life is unimpaired by type of treatment (conventional or intensive insulin

therapy) [79]. The apparently benign experience of being in the intensive-treatment arm of the DCCT (despite more injections, more blood glucose monitoring, and a threefold increase in severe hypoglycemia) may be a consequence of the greater level of psychological and medical support provided in such clinical trials. Alternately, it may reflect the relative insensitivity of the DQOL measure, which is capable of detecting the impact of major treatments (e.g. pancreatic transplantation) but is less sensitive to the more subtle differences between types of insulin regimen [70].

Another widely used tool to assess diabetes-specific quality of life is the ADDQoL [80]. While healthy adults with T1DM or T2DM typically report a good overall present quality of life, on average, they also indicate that the impact of diabetes on their quality of life is negative [80, 81]. In particular, the aspect of life most negatively impaired by diabetes is the freedom to eat as I wish, an item that captures eating what, when, how much or how little the person prefers and, importantly, not having to eat when he or she does not wish to do so [81, 82]. Diabetes-specific quality of life is typically more negatively impaired for those using insulin compared with other medications, and for those living with one or more long-term complications [80]. However, several randomized trials demonstrate that more flexible and convenient treatment regimens (even when insulin is required) improve diabetes-specific quality of life compared with treatment regimens that impose more rigidity in terms of timing of medications and meals [82, 83].

De Wit et al. have reviewed the instruments used to assess quality of life in young people with diabetes, identifying five diabetes-specific instruments, each with limited evidence regarding psychometric properties and various issues limiting their application in clinical practice [84]. They concluded that the PedsQL and the KINDL-R appear to be the most suitable instruments, but also that further research is needed to seek standardization of measurement in adolescents and to establish cross-cultural validity. In a review by Nieuwesteeg [77], boys with T1DM reported better diabetes-specific quality of life than the girls with T1DM. More recent studies evaluating changes in quality of life associated with the use of continuous subcutaneous insulin infusion have been mixed, with some indicating no benefit, while others suggested modest benefit [85], particularly amongst children and their parents [86]. Optimal metabolic control has sometimes [87], but not invariably [88], been found to be associated with better diabetes-specific quality of life in adolescents.

Age at onset of diabetes may also affect certain aspects of life quality. An early survey found that adults diagnosed with T1DM before 9 years of age were more satisfied with their marriage, and were more likely to have children than those diagnosed later [89]. The authors suggest that individuals diagnosed earlier in development may be more adept at integrating the condition as part of their lifestyle and, thus, find less disruption from diabetes later in life. More recent work also suggests that the linkages between marital satisfaction, higher levels of diabetes-related satisfaction and better glycemic control may reflect better psychosocial adaptation to a variety of illness-related and marital role stresses and strains [90]. Among older adults (mean age 81 years), the aspects of life most negatively impaired by diabetes are independence and dietary freedom [91].

The impact of psychological factors on diabetes management

The relentlessness of self-care, lack of immediate reward, unpredictability of blood glucose levels, and the feelings of guilt, anxiety, and failure that a person can experience when blood glucose levels are suboptimal (or unexplainable) can cause diabetes-specific distress, and may adversely affect general mood and emotional well-being. Conversely, certain personality traits or coping styles that are intrinsic to an individual's psychological make-up may modulate the person's ability to manage diabetes self-care activities, as may environmental and psychosocial factors, such as peer pressure to engage in certain "forbidden" activities, disruptive interpersonal conflicts, and the normal stresses and strains of everyday life. Overall, an individual's "psychology" may influence, and be influenced by, the process of diabetes management.

According to a systems model of health, there is no simple direct relationship between any single psychological variable and glycemic control [92]. Rather, health outcomes are determined by a system of reciprocal relationships amongst multiple psychological, behavioral, and physiologic variables. Figure 56.1 shows one such model of this process. Psychological *traits* are relatively enduring characteristics that include personality, temperament, and coping style. These may have an indirect impact on glycemic control, via their impact on self-care behaviors and emotional state. Psychological *states*, such as stress, are more transitory, reflecting emotions at a given point in time. These may influence glycemic control directly via the autonomic nervous system or, indirectly, by affecting the individual's self-care behaviors. Both family interactions and self-care behaviors may affect, and be affected by, the individual's mood or level of stress. Family functioning, including conflicts and degree of family cohesiveness, can

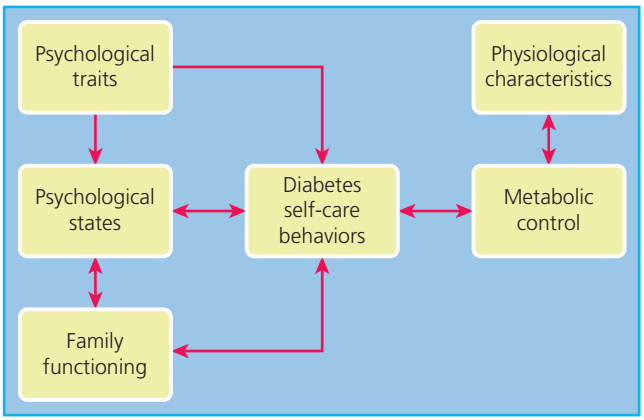

Figure 56.1 A systems model of the relationships between psychological, social, behavioral, and glycemic factors.

affect psychological state (and vice versa), but can also influence self-care behaviors. Self-care behaviors include medication use, diet, exercise and monitoring, and these behaviors serve as the primary final common pathway to glycemic control.

Psychological traits and glycemia

Early psychological research in diabetes focused on the influence of personality traits, and found that glycemic control is more likely to be optimal in individuals with certain personality characteristics such as a strong need for achievement and a high level of responsivity to social demands [93]. By contrast, glycemic control tends to be worse in those who are opportunistic and alienated [94], or who have poor impulse control, a propensity for self-destructive behaviors, and difficulty maintaining interpersonal relationships [95]. Recent work demonstrates that, in adults with T2DM, higher neuroticism levels are associated with better glycemic control, suggesting that moderate levels of worry may be needed to motivate these older adults to manage their diabetes [96]. Furthermore, adults with T2DM and type D personality—defined as high negative affect coupled with high social inhibition—report more barriers to medication use and are less likely to eat healthily or to consult health professionals when problems with diabetes management occur [97].

Locus of control is another psychological trait that may affect glycemic state. Individuals who have an "internal" locus of control believe that they are responsible for their health, whereas those who have an "external" locus believe that their outcomes are due more to chance, or some other outside force (e.g. significant others or health professionals) [98]. One of the most important studies in this area was an early study of insulin pump therapy in the 1980s [99]. Those choosing insulin pumps rather than insulin injections reported higher levels of "medical" control, that is, they believed that their health professionals and treatment regimen were responsible for their diabetes outcomes. Furthermore, among those using pumps at the end of the study, those with worse glycemic control (and those who experienced DKA) held highest beliefs in "medical" control, indicating that they placed undue faith in the newly developed technology to manage their diabetes. This and other studies (e.g. [100]) indicate that individuals with an internal locus generally have better glycemic control, although that is not invariably the case [101], and few studies demonstrate a strong link between locus of control and self-care [100].

Reconciliation of these discrepancies may require a reconceptualization of the locus of control construct. Multidimensional measures that examine different aspects of sense of control as well as different modes of and motivation for control may ultimately provide investigators with deeper insights into the complex interrelationships between perception of control and optimal diabetes management [102]. The complexity of these interactions has been underscored in a study that measured locus of control, self-efficacy and outcome expectancy, and used this information to predict HbA_{1c} among people with T2DM from a predominantly disadvantaged background [103]. Those with an internal locus of control who reported low self-efficacy and low outcome expectancy tended to have better glycemic control, whereas those with an internal locus of control who also expressed low self-efficacy and high outcome expectancy tended to have suboptimal glycemic control [104]. Having an internal locus of control may be particularly beneficial to those with little confidence in their ability to follow their physicians' recommendations (i.e. low self-efficacy), as well as little confidence that following those recommendations will actually improve their health (low outcome expectancies).

Coping styles, broadly categorized as emotion-focused and problem-focused [105], serve to modulate the individual's response to stressful situations. Emotion-focused or cognitive coping attempts to reduce threats from the environment by reinterpreting or reappraising the situation ("Stay calm, it really can't hurt you"). Problem-focused coping, in contrast, seeks to change the environment and thereby eliminate the threat. Within each of these categories, specific behavioral strategies may be differentially effective. Some may actually exacerbate stress (e.g. emotion-arousing strategies that include anger, impatience, or anxiety), while others (e.g. stoicism) may reduce or "buffer" the effects of stress [104]. In adolescents with T1DM, an emotion-focused coping style (e.g. behavioral and mental disengagement; aggressive coping) is associated with suboptimal glycemic control and reduced diabetes-specific quality of life, whereas active coping strategies (directed at approaching and making a direct effort to change the situation causing psychological distress) are linked to better glycemic control [106]. A meta-analysis of 21 studies has shown that the use of approach coping is associated with both better overall psychological adjustment and with somewhat better glycemic control [107].

If traits truly reflect enduring personality characteristics, they ought to predict long-term self-care behaviors, as shown in a longitudinal study of children and adolescents [101]. Coping style assessed soon after diabetes onset predicted adherence behaviors 4 years later. Those children who used more mature defense mechanisms and showed greater adaptive capacity, such as higher stress tolerance or greater persistence shortly after diagnosis, were most likely to manage their diabetes satisfactorily in the long term. Two recent reviews indicate that positive psychological characteristics (e.g. optimism, self-efficacy, and resilience) from childhood through to adulthood are consistently associated with optimal glycemic control, fewer diabetes-related complications, and reduced mortality rates [108, 109]. The mechanisms mediating these associations may include behavioral factors (e.g. medication-taking, healthy eating) as well as reduced inflammation, and improved neuroendocrine and autonomic functioning.

Psychological states and glycemia

Another psychological state worthy of consideration is emotional stress. Stress stimulates the release of several stress hormones to mobilize energy to enable the "fight or flight" response. However, in people with little or no endogenous insulin production, stress-induced increases in blood glucose cannot be metabolized properly. Thus, environmental stress and the individual's emotional reaction impact the management of glycemic levels. An

early review [110] demonstrated that the relationship between stress and glycemia is complex and idiosyncratic, causing hyperglycemia, hypoglycemia, or having no effect at all on glucose levels, and often dependent on the initial glycemic state.

The complexities of demonstrating the relationship between stress and glycemia are exacerbated by the many variables that influence the generalizability of findings [111, 112]. Studies have been conducted in children, adolescents and adults with T1DM or T2DM. Stressful experiences have been documented in self-report studies using simple checklists, validated questionnaires, in-depth interviews, or in experimental studies with exposure to an array of stressors (mathematical problems, video games). The duration of exposure may be influential and the major limitation of such studies is that they do not necessarily reflect real-life stressors. Real-world stress can be caused by trauma, threat, major life events (e.g. bereavement or losing a job), chronic stressors (e.g. long-term unemployment or carer responsibilities), or other day-to-day "hassles" (e.g. work, finances, relationships, exams, noise, illness/surgery). Furthermore, individuals perceive stressors in different ways, either as negative (e.g. death, financial problems) or positive (e.g. birth of a child, marriage). Exactly how stress affects glycemia remains controversial and few empirical studies have been conducted in recent years [111, 112]. A relatively recent 5-year prospective study of 132 adolescents, using longitudinal growth curve modelling, found that stressful life events (reported annually) predicted greater psychological distress, and suboptimal self-care and glycemic control [113]. The effect was stronger in older adolescents and that the effect of stress on glycemic control was likely mediated by self-care behaviors.

Family characteristics, interactions, and glycemia

Diabetes can dramatically disrupt the entire family, particularly when the individual with diabetes is a child or adolescent [114]. Children, especially younger ones, are more likely to have optimal glycemic control when their parents take an active role in managing their diabetes, whereas for adolescents, shared management responsibilities with parents typically results in more favorable outcomes [115–117]. Within the family, low levels of conflict are associated with better control [118], as is a higher level of social support from family and friends [119]. Conversely, suboptimal glycemic control in children and adolescents is predicted by higher maternal trait anxiety levels [120], lower parental intelligence [121], greater levels of family stress, more family conflict and less family cohesion [122], and sociodemographic variables (e.g. single-parent households) [123]. In adults with diabetes, better marital satisfaction is associated with better diabetes-related quality of life [90, 124], less diabetes-specific distress [90], and a non-significant trend towards better glycemic control [90].

The relationship between family characteristics and glycemic control in children is most likely mediated via a behavioral pathway whereby family conflicts disrupt planning and performance of diabetes management activities; this pattern has been supported by a large prospective study [122]. New, web-based interventions that aim to decrease parenting stress in parents with a child who has diabetes are currently being tested [125].

The impact of behavioral factors ("adherence") on diabetes management

Historically, the terms "concordance," "adherence," and "compliance" have been used interchangeably to refer to the extent to which an individual simply follows their diabetes management regimen or plan, so-called "doctor's orders." This model is now referred to as the "acute care model." In recent years, there has been a shift from the acute care model to chronic care models [126], and in terminology, from "adherence" to "engagement" in self-care. Chronic care models acknowledge that:

- Most of the diabetes care activities are self-care activities by the person with diabetes.
- Diabetes self-care management is behaviorally complex.
  - It can be helpful to consider diabetes management (e.g. taking medications, self-monitoring of blood glucose (SMBG), eating healthily, counting carbohydrates (if relevant), and physical activity) as a series of balls that need to be juggled, while balancing on a beam (that represents life and all its competing demands (e.g. work, family, social life).
  - If, from time to time, one or more balls are dropped, it is not something to be criticized or viewed as a character flaw but rather it is because juggling all day every day is challenging, tedious and, ultimately, exhausting.
- Clinicians can offer advice but optimal outcomes are less likely to be achieved unless the person is fully engaged in adopting and sustaining the self-care behaviors and only the person themselves is in a position to know what self-care activities are appropriate, possible, and sustainable in their unique living situation [127].
- The degree, to which one *follows* a diabetes regimen, cannot be determined easily because there is no standard against which the person's actual behavior can be compared. For example:
  - Few clinicians provide a written management plan that specifies all aspects of diabetes care.
  - Recommendations often differ between clinicians, and the extent to which the clinician has communicated clearly in the consultation or the extent to which the person agrees with the regimen discussed is often unclear.
  - As it is the person with diabetes, and not the healthcare professional, who is responsible for nearly all diabetes care, increasingly, these outdated terms and gross over-simplifications of the realities of managing diabetes are being replaced with the question of the extent to which a person with diabetes *engages* in various self-care behaviors [128, 129].
- Not all self-care activities are equal in value in terms of their relative effectiveness for optimizing glycemic control. Furthermore, certain self-care behaviors are far more likely to be maintained than others.
  - The international DAWN2 study demonstrated that taking medications as recommended and having a healthy diet are

more common than self-monitoring of blood glucose (SMBG) and physical activity, and that engagement in these activities varies across countries [48].

- Specific self-care behaviors are sometimes [130], but not invariably [131], related to glycemic control.

Behavioral factors: the example of self-monitoring of blood glucose (SMBG)

Self-monitoring of blood glucose ought to be a particularly salient self-care activity. A large medical registry study of 24,312 adults with diabetes found that those with T1DM who self-monitored three or more times daily subsequently had HbA_{1c} values that were 1% (11 mmol/mol) lower than those who monitored less frequently. For adults with T2DM using oral medication or insulin, monitoring at least daily also resulted in a statistically and clinically significant reduction in HbA_{1c} (0.6%, 7 mmol/mol). For adults with T2DM not using medications (for whom there was no clear recommendation regarding SMBG frequency), there was a statistically significant HbA_{1c} reduction (0.4%, 4 mmol/mol) compared with those not using SMBG at all [132]. Other studies have provided less positive results. For example, a clinical trial comparing continuous glucose monitoring (CGM) with SMBG found a small different in HbA_{1c} (0.5%, 6 mmol/mol) at 26 weeks favoring CGM in adults aged 25 years or older but no difference among those aged 15–24 years or 8–14 years [133]. Use of CGM averaging six or more days per week was 83% in the adult group, 30% in the young adult group, and 50% in the pediatric group. These data indicate that active use of the CGM device is crucial in achieving improved glycemic control and that further work is needed to determine barriers to effective use.

In adults with T2DM not using insulin, the value of SMBG is more controversial. In recent years, a systematic review and a meta-analysis concluded there is little clinical benefit from SMBG in this group [134, 135]. However, these reviews combined studies with considerable variation in trial design and implementation of SMBG (education, frequency, and follow-up action) and it is unsurprising that little benefit was found "on average" [134–137]. These data suggest that simply monitoring blood glucose values, and not using that information to adjust insulin or oral medications frequently and systematically, has little meaningful impact on long-term glycemic control; however, they also suggest that there is considerable benefit to be derived by individuals who are motivated to monitor [136, 137].

It is noteworthy that SMBG has no dose-response and is not an active agent (i.e. the mere act of checking blood glucose levels cannot reduce HbA_{1c}). Indeed, while SMBG is often considered as a single self-care activity among many others, it is actually just one aspect of a complex intervention with multiple facets including:

- agreement on glucose targets between the person and their health professional;
- timing and frequency of SMBG;
- a supportive health professional trained in interpretation of SMBG patterns;
- appropriate training and feedback for the person with T2DM;
- collaborative review of SMBG patterns to identify areas for improvement and what may have contributed to the readings;
- a plan for how to change diet, physical activity levels, or medication;
- behavioral change (i.e. modifying diet, increasing physical activity, or changing medication regimen).

A more recent clinical trial demonstrated that a structured approach to monitoring (incorporating these steps) indicates SMBG offers both clinical benefits (i.e. reduced HbA_{1c}, particularly in those following the protocol as intended) [138], as well as improved emotional well-being and confidence in diabetes self-care [138, 139].

Methodological issues in self-care assessment

The generally weak relationship between self-care behaviors and glycemic control remains problematic for any model purporting to predict successful diabetes management. This could reflect the possibility that HbA_{1c} is not the most appropriate measure of glycemic control but it is more likely that the unexplained variance in glycemic control reflects unspecified physiologic or situational characteristics, as well as difficulties inherent in measuring various self-care behaviors [140]. A review of 23 studies found that greater medication adherence was associated with better HbA_{1c} and this was a stronger relationship when adherence was characterized in terms of prescription refills (78%; 7 of 9 studies) than when self-report (subjective) measures were used [141]. As self-care is typically assessed by asking people to describe their behavior, rather than by direct observation, it is possible that self-reports may exaggerate or otherwise misrepresent the extent to which person with diabetes performed a particular self-care behavior [140]. Furthermore, self-care questionnaires typically ask the person to report on their average behavior over the past week (or few weeks), whereas HbA_{1c} reflected average blood glucose over the past 8–12 weeks. Thus, "average" behaviors may be too crude and the two time periods are likely incompatible with a strong relationship. Finally, other factors such as stress, dietary behaviors, physical activity levels, hormonal changes, and other medications can affect blood glucose such that they may have an (unmeasured) influence on HbA_{1c}.

Interventions to reduce psychological distress and improve quality of life, self-care, and glycemic control

Reducing depression and diabetes distress

The treatment of depression among people with diabetes is both necessary and effective. A systematic review and meta-analysis of 14 randomized controlled trials (involving 1724 adults with T1DM or T2DM) demonstrated that treatment (psychotherapy, pharmacotherapy, or collaborative care) is effective in reducing depressive symptoms [142]; of the various treatment options available, the effect was greatest for psychotherapeutic interventions (Cohen's $d = -0.58$). Cognitive-behavioral therapy (CBT) appears

to be particularly promising in reducing the severity of depressive symptomatology. CBT trains individuals to use problem-solving strategies to reduce stressful situations and trains them to use cognitive techniques to "think away" their distorted beliefs, and replace them with more accurate and adaptive thoughts. Van Bastelaar et al. tested a web-based, diabetes-specific treatment of depression that was based on the principles of CBT, showing that this intervention reduced both depression and diabetes-specific distress [143].

Another effective treatment approach is mindfulness-based cognitive therapy (MBCT). MBCT is an 8-week protocolized therapy program that can be delivered in groups or individually. MBCT combines meditation exercises with elements of cognitive therapy. The main goal of this intervention is the cultivation of mindfulness, which is the self-regulation of one's attention focusing on direct experience, while adopting an open, curious, and accepting attitude toward these experiences, especially one's psychological processes, such as thoughts and feelings. Mindfulness-based interventions appear to be effective in people with diabetes who report elevated levels of depression and/or anxiety [144, 145]. Few studies have focused specifically on reducing diabetes-specific distress, though many intervention trials have included diabetes distress as a secondary outcome [143]. Recently, a systematic review of 41 such trials (involving 6650 adults with T1DM or T2DM) demonstrated no overall effect of intervention on diabetes distress [146]. Where diabetes distress was reduced, this was most likely to occur when the intervention was psychoeducational in nature, involving at least six sessions, over at least 3 months' duration, and delivered by a generalist rather than a mental health professional [146]. Further intervention studies focused specifically on the reduction of diabetes-specific distress are needed.

Empowerment-based approaches to improve outcomes

The "empowerment" approach encourages clinicians to understand what living with diabetes is like from the individual's perspective and to enable people with diabetes to take personal responsibility for their health, making self-selected choices about self-management [127, 147]. Embracing empowerment requires a paradigm shift on the part of clinicians to a position where they acknowledge that the person with diabetes is in control of, responsible for, and ultimately lives with the consequences of, their own diabetes care. Knowledge is the cornerstone of empowerment. Empowerment programs also aim to improve the persons' ability to identify and set realistic goals, apply problem-solving strategies to overcome barriers to those goals, develop more effective coping strategies in general, manage stress more effectively, increase social support and improve self-motivation. Empowerment occurs when the health professional's objective is to enable the person with diabetes to make autonomous, informed decisions, and when the person with diabetes is doing so [147].

The theoretical argument is compelling and a review of qualitative studies describes positive experiences in using the empowerment approach [148]. However, surprisingly few trials have been conducted. Results from an early randomized controlled trial demonstrated that following a 6-week empowerment program, adults with diabetes showed a significant decline in HbA_{1c} as well as increased ability to set goals, manage stress, obtain external support and make decisions about diabetes management [149]. The limitations of this study include the short-term follow-up (6 weeks post intervention) and small sample ($n = 64$), which was highly educated (77% college education, 84% diabetes education). Other trials of person-centered consultation approaches have had less positive outcomes overall. For example, in a randomized trial involving 250 adults with newly-diagnosed T2DM, in which clinicians in the intervention arm received 1.5 days theoretical and practical training in person-centered consulting skills, the intervention group reported significantly better communication with the doctor, greater treatment satisfaction and better psychological well-being than the control group [150]. However, there was no impact on glycemic control and cardiovascular risk increased, prompting the authors to urge caution: "Professionals committed to achieving the benefits of patient-centered consulting should take care not to lose focus on disease while paying attention to the unique experience of illness of each patient" [150: 1208].

Structured training/education to improve outcomes

The education of people with diabetes has evolved from didactic information-giving ("obedience training to follow dietary prescriptions" [151:1724]) one-to-one or in large groups, to theoretically driven, evidence-based structured training in small groups, in which people with diabetes are able to talk with diabetes educators (nurses/dieticians) and their peers about their diabetes, and problems with self-care, and learn the knowledge and skills they need for a life with diabetes (Chapter 24). In modern times, this approach began in Germany in the 1980s, with the structured diabetes teaching and treatment program developed by Michael Berger and Ingrid Mühlhauser, where several trials demonstrated the effectiveness of flexible, intensive insulin therapy for improving glycemic control in people with T1DM without increasing severe hypoglycemia [151] (unlike the intensive treatment approach adopted in the DCCT [34]). In the UK, this approach was adopted as the "Dose Adjustment For Normal Eating" (DAFNE) program, where an RCT demonstrated, for the first time, the unique combination of benefits for both biomedical and psychological outcomes [82]. Several studies have demonstrated sustainability of outcomes over the long term [152], and successful implementation in the real-world [153, 154], while qualitative research has highlighted where the program can be improved [155], and this is now the focus of further research (DAFNE*plus*) in the UK. The DESMOND program offers a range of structured training sessions for people with newly diagnosed or ongoing T2DM, with RCT findings demonstrating greater improvements in weight loss, smoking cessation, and beliefs about illness, although no benefit for glycemic control up to 12 months after diagnosis [156]. Three years later, HbA_{1c} had improved in both groups, but no differences were observed between those receiving DESMOND or control intervention in any biomedical or psychological outcomes [157]. Importantly, improvements in four out of

five health beliefs were sustained [157], and these were found to be predictive of psychological distress at 3 years, indicating the importance of early formative experiences around diagnosis, and in terms of education provision and health provider support [158].

Programs have also been developed that teach those using insulin to recognize and anticipate blood glucose fluctuations to enable them to prevent extreme high and low levels, and reduce their fear of hypoglycemia. A review demonstrated that the benefits of the face-to-face "Blood Glucose Awareness Training" (BGAT) program, developed in the USA, can be substantial. There was a 57–92% reduction in severe hypoglycemic events, 65–86% reduction in driving mishaps, 10–51% improvement in hypoglycemia awareness, and a 6–21% reduction in fear of hypoglycemia [159]. Several studies have been limited by small sample sizes, and by a focus on skills acquisition (estimation of blood glucose) rather than clinically important outcomes, such as severe hypoglycemia. The German, face-to-face program "HyPOS" has also demonstrated improved awareness of hypoglycemia and reduced frequency of severe hypoglycemia in a fully powered RCT [160].

Technological approaches to improve outcomes

Advanced technologies for insulin delivery (e.g. predictive low glucose suspend pumps) and real-time continuous glucose monitoring (RT-CGM) have improved dramatically in recent years, and have the potential to reduce HbA_{1c} and fear of hypoglycemia, and to improve quality of life [161]. In the first large-scale trial of sensor-augmented pump therapy in 485 adults and children with T1DM, over a 12-month follow-up, sensor-augmented pump therapy offered significant advantages in terms of reducing fear of hypoglycemia in adults and parents of children, as well as improving treatment satisfaction in adults, children and parents [162]. However, such devices are expensive and require uninterrupted use (which many users find too burdensome). A 12-month observational study of sensor-augmented pump therapy in 15 countries in Europe and Israel found that improvement in HbA_{1c} was associated with more frequent sensor use [163]; average sensor use over 12 months was 30% (range: 0–94%) and sensor use decreased with time (37% over first 3 months, 27% over final 3 months). For those with recurrent severe hypoglycemia and its debilitating impact on quality of life, the adoption of technology into everyday management seems an obvious option. However, a recent trial demonstrated that insulin pumps and RT-CGM offered no added benefit over multiple daily injections and standard finger-prick SMBG for reducing severe hypoglycemia, time spent in hypoglycemia, or fear of hypoglycemia—with the insulin pumps offering an advantage in terms of greater treatment satisfaction [164].

Most recently, the personal impact of "closed loop" (artificial pancreas) technology has been investigated overnight in the home setting. Semi-structured interviews with 15 adolescents with T1DM using the technology and 13 parents have demonstrated several perceived benefits (e.g. reassurance/peace of mind, confidence, "time off" from diabetes demands, safety, and improved glycemic control) as well as disadvantages (e.g. difficulties with calibration, alarms, and size of the devices, and mixed effects were found on fear of hypoglycemia) [165]. Semi-structured interviews with 24 adults using the technology have demonstrated similar positive and negative themes [166].

Cognitive-behavioral approaches to improve outcomes

Individual or group psychotherapy or supportive counselling is effective in children or adults with diabetes [167]. Many recommendations have been made for such interventions, while several recent meta-analyses have generally found them to have modest effects in reducing psychological distress and improving glycemic control [168–170]. Traditional individualized and group therapy provides emotional support for both children and adults with diabetes, and may be particularly beneficial for those who are confronting the development of complications. When a time-limited problem-oriented individualized treatment was compared with standard insulin treatment counselling in adults with T1DM, those receiving psychotherapy showed greater reductions in both problem severity and HbA_{1c} [171].

Coping skills training programs are effective in improving the diabetes management skills of adolescents treated with intensive insulin therapy [172]. Based on a cognitive–behavioral skills-building model, coping skills training presents participants with a series of social situations that are particularly problematic for adolescents, and asks them to demonstrate how they would resolve that situation (e.g. manage food choices with friends). As implemented by Grey et al. [172], groups of two to three adolescents role-play each scenario with a highly trained group leader who provides correction and models appropriate coping behavior. Six weekly sessions lasting 60–90 minutes followed by monthly visits are typical for a training program. Over a 12-month follow-up period, adolescents randomized to coping skills training plus intensive diabetes management had significantly lower HbA_{1c} (7.5% vs. 8.5%; 58 vs. 69 mmol/mol) and reported better self-efficacy as well as less difficulty in coping with diabetes and less depression when compared with adolescents who received intensive diabetes management alone [116].

Peyrot and Rubin [173] discuss the utility of including both problem-focused and emotion-focused interventions as part of an integrated behavior change support program. According to their model, interventions must occur in a particular sequence of five steps:

1 Specify the person's problem;
2 Translate the person's intentions to change into concrete, attainable goals;
3 Collaborate with the person to identify barriers to reach those goals and formulate effective strategies;
4 Establish a "contract" with the person to meet, or approach, those goals; and
5 Provide continuing support.

This framework makes much sense from a clinical perspective. The extent to which such an approach is successful in initiating lasting clinically significant changes in mood, behavior, and glycemic control is likely to be dependent on the problem, the

person, and the relationship with health professionals, but it is certainly an approach worth evaluating in formal clinical trials. Arguably, this was the basis of the HypoCOMPaSS study, which demonstrated prevention of severe hypoglycemia and reduced fear of hypoglycemia in a 6-month RCT [164] as well as in an, as yet, unpublished 2-year follow-up study. The new DAFNE*plus* program will incorporate concrete goal-setting into the structured training and provide ongoing proactive health professional support, both of which will then be evaluated in a RCT.

More traditional psychotherapeutic approaches

Several behavioral and psychological interventions have been developed to improve engagement in self-care among people with diabetes [173, 174]. These differ from more traditional group therapy programs in so far as they use several sessions to target one or more self-care behaviors and the psychological factors that may interfere with optimal self-care. A typical self-management program may meet once or twice monthly for seven or more sessions, discuss specific self-care strategies (e.g. SMBG, physical activity), role-play appropriate behaviors, use homework assignments to practice what has been learned and resolve problems or barriers encountered during diabetes management. Variations on this basic theme include the use of 6 or 12 monthly "booster" sessions after the end of the program, which are designed to review and reinforce previously learned material. Interventions developed initially for people without diabetes with high levels of psychological distress are increasingly being applied to persons with diabetes, and both CBT and "motivational interviewing" [175, 176] or "motivational enhancement therapy" [154] programs have led to modest improvements in HbA_{1c} and in self-reported quality of life.

Family-focused behavioral interventions are particularly successful in improving diabetes management in children. In one of the largest studies of its kind, Wysocki et al. [177] randomized 119 families of adolescents to either 10 sessions of behavioral family systems group therapy, 10 sessions of an education and support group, or standard diabetes therapy (with minimal psychological support). Behavioral family systems therapy included four modules:

- problem-solving training, which focused on conflict resolution;
- communication skills training;
- cognitive restructuring to identify and change those attitudes and beliefs that impede effective communication;
- specialized family therapy interventions.

In the 12 months following treatment, adolescents who participated in behavioral family systems therapy showed long-term improvement in relationships with their parents compared with adolescents in the other two treatment groups, and also manifested improved adherence to their diabetes management regimen, although these behavioral and psychological changes were not associated with improvements in metabolic control [178]. Similar interventional approaches have also been applied to older adults with T2DM and, as is the case with children and adults with T1DM, there are reductions in psychological distress and occasionally, but not invariably, small improvements in long-term glycemic control [179].

Neuropsychological and cognitive consequences of diabetes

Diabetes affects cognition as well as emotion, leading to disruption of mental efficiency and neuropsychological dysfunction. The magnitude of these effects is relatively modest in most individuals, and few people with diabetes manifest "clinically significant" cognitive changes unless they developed diabetes early in life. Until recently, when cognitive dysfunction was found in people with diabetes it was invariably attributed to the adverse effects of severe and recurrent hypoglycemia on the CNS. New research suggests that chronic hyperglycemia, and the metabolic and vascular complications that are associated with it, underlie the development of most structural and functional changes to the CNS, particularly in adults [180]. Although hypoglycemia can never be considered to be entirely benign, it may have a relatively small role in the etiology of neurocognitive changes in younger adults with diabetes [181, 182].

CNS sequelae of diabetes in children and adolescents

Cognitive manifestations

The nature and extent of cognitive dysfunction in children and adolescents differs depending on age of diagnosis. Those diagnosed in the first 5–7 years of life appear to have an elevated risk of manifesting a moderately severe cognitive impairment, which is evident across a range of cognitive domains, including measures of attention, mental flexibility, psychomotor efficiency, learning, memory, problem-solving, and overall intelligence [183–187]. In contrast, those diagnosed after that early "critical period" show very mild cognitive dysfunction that is limited primarily to measures of overall intelligence and to performance on speeded tasks, particularly those having a visuo-perceptual component [184]. Learning, memory and problem-solving skills are largely intact in this "later onset" population, or are inconsistently affected [188, 189]. In some studies, children with diabetes tend to achieve lower scores than their peers without diabetes on measures of academic achievement, regardless of age at diagnosis [190], with this especially pronounced in children with a very early onset of diabetes [191]. In a large and a more recent study [192], 2500 individuals with T1DM selected from the Swedish Childhood Diabetes Register were coupled to national population registers including the Swedish Education Register and were found to be similar to four controls from the general population, matched for year of birth and residence at the time of diagnosis [192]. T1DM had negative effects on mean final grades in compulsory school and theoretical programs in upper secondary school. Children with early-onset diabetes (before age of 4 years) suffered a greater disadvantage in compulsory school. It is unclear whether school performance of young people with T1DM differs between countries

[193]. A recent Australian study, for example, used data on four educational outcome domains from 666 children with T1DM and 3260 school and school-year matched children without diabetes. There were no significant differences between those with T1DM and their peers, across any of the tested domains and school years analyzed [194]. Furthermore, there was no decline over time or following diagnosis. However, children with T1DM had lower school attendance, with 3% fewer days attended per year. Less optimal glycemic control was associated with a lower test score and with poorer attendance. In the same Australian study, a history of severe hypoglycemia, diabetic ketoacidosis, and the age of onset of diabetes were not associated with school test scores. However, a longitudinal study from the DKA Brain Injury group compared young people (aged 6–18 years) with T1DM, who presented at diagnosis with or without DKA [195]. These two groups were compared at four time points: <48 hours, 5 days, 28 days, and 6 months after diagnosis, using data from magnetic resonance imaging (MRI) and spectroscopy with cognitive assessment at each time point. Those with DKA at diagnosis had reductions in white matter volume over 6 months in the frontal, temporal, and parietal lobes. Age at time of presentation and pH level were predictors of the neuroimaging and functional outcomes.

Overall, the magnitude of the cognitive dysfunction seen in children with diabetes is modest, as demonstrated by a formal meta-analysis of 19 pediatric studies encompassing 1393 children with diabetes and 731 healthy comparators [184]. For studies comparing children with later-onset T1DM with children without diabetes, Cohen's *d* values were ≤0.20, indicating small to negligible effects. In contrast, effect sizes were more than twice as large when comparing those with early-onset diabetes and their peers without diabetes [184]. Using clinical rather than statistical criteria, there are similarly marked differences between children with an early, as compared with a later, onset of diabetes. One large study found that 24% of children with early-onset diabetes met criteria for clinically significant impairment, compared with only 6% of children with a later onset of diabetes, and 6% of a comparison group without diabetes [196].

This "age at onset" phenomenon continues in adults diagnosed with diabetes early in life. Young adults who developed diabetes before 7 years of age performed more poorly on measures of information processing speed, and earned lower performance IQ scores than their peers with diabetes diagnosed at or after age 7 [197]. Abnormalities in brain structure are also evident. Magnetic resonance imaging (MRI) scans showed higher rates of mild to moderate ventricular atrophy (61% vs. 20%), as well as somewhat higher rates of small punctate white matter lesions within the hippocampus (14% vs. 2%). Smaller brain volumes were also correlated with poorer cognitive test performance, supporting the view that cognition dysfunction is necessarily linked to changes in CNS morphology.

Neurocognitive abnormalities appear relatively early in the course of diabetes (within 2–3 years of diagnosis). In an older, prospective pediatric study, a representative sample of 90 newly diagnosed youngsters with diabetes and 84 healthy children drawn from the community have been followed over a 12-year period. No between-group differences were evident at study entry [188] but, 2 years later, those children diagnosed before age 4 manifested developmental delays as their scores on both the Wechsler Vocabulary and Block Design subtests improved less over time, relative to either children with a later diabetes onset or to community control children [189]. After 6 years of follow-up, children with diabetes—regardless of age at diagnosis—performed worse than their peers without diabetes on measures of intelligence, attention, processing speed, long-term memory, and executive skills. Children with an early age at onset were particularly affected, and performed significantly worse on measures of attention and executive function than those with a later onset of diabetes [185]. After 12 years of follow-up, these children with diabetes—now young adults—continued to earn lower verbal and full-scale IQ scores, demonstrating that these effects are not a developmental delay, but reflect a true, albeit modest, loss in cognitive efficiency, relative to those without diabetes [198]. Studies have also noted gradual decline in IQ scores as diabetes duration increases [198, 199].

Effects of hypoglycemic episodes on brain function

As young children with diabetes (aged <6 years) are often unable to recognize, describe, and/or manage their hypoglycemic symptoms, special attention needs to be given to hypoglycemia risk in this group. Hypoglycemia may also present more often in children with T1DM because of variable eating patterns and erratic activities. At the same time, use of new therapeutic options, such as new long-acting insulin analogs and continuous glucose monitors and low glucose suspend insulin pumps, may lower the incidence of severe hypoglycemia. Older studies suggest that severe hypoglycemia causes neuropsychological deficits, particularly in children whose diabetes is diagnosed below the age of 6 years [196, 200]. More recent data have confirmed this notion, but effect sizes appear to be small [201, 202]. For example, a meta-analysis based on data from 441 children with recurrent severe hypoglycemia and 560 children without recurrent severe hypoglycemia [201] found that the children with recurrent severe hypoglycemia only had slightly lower performance. This was evident for the cognitive domains: intelligence, verbal fluency/language and particularly in memory and learning, while no impairment was found for motor speed [201]. A working group of the American Diabetes Association and The Endocrine Society reviewed the evidence about the impact of hypoglycemia, concluding that 4–10% of deaths of people with T1DM were caused by hypoglycemia [202]. In the DCCT, participants with and without a history of severe hypoglycemia performed the same on a comprehensive battery of neurocognitive tests at 18 years follow-up [203].

The potential impact of hypoglycemia on brain functioning has also been studied in T2DM. In a population-based study, older adults with T2DM with hypoglycemic episodes that required emergency medical care had a doubled risk of incident dementia [204]. However, it is noteworthy that the study did not use detailed tests of cognitive function at baseline. The ACCORD MIND study also assessed cognitive function in people with T2DM randomly

assigned to the intensive versus the standard therapy arms. No differences in cognitive function were observed between groups at 20-month or 40-month follow-up, despite the fact that the intensive therapy group experienced three times as much hypoglycemia [205].

Brain structure and function in adults with type 1 diabetes

Neurocognitive manifestations

A highly circumscribed pattern of mild cognitive dysfunction characteristic of adults with T1DM has been identified from a systematic meta-analysis of data from 31 studies published in English between 1980 and 2004 that compared the performance of those with and without diabetes on multiple cognitive domains [206]. People with T1DM, aged 18–50 years and in relatively good health, performed significantly worse on measures of intelligence, attention, psychomotor speed, cognitive flexibility, and visual perception, whereas no between-group differences were found on measures of language, learning, and memory. Even when differences were detected, they were modest at best, with effect sizes ranging from 0.3 to 0.8 standard deviation units. Not all cognitive domains were affected; learning and memory skills, which are generally considered to be sensitive to early brain damage [207], were well preserved in this diverse population, despite an average of ≥20 years of T1DM. Moreover, with only one exception ("crystallized intelligence"), virtually all of the cognitive tasks on which people with diabetes performed worse were those that also required a rapid response. Thus, mental slowing appears to be the fundamental deficit associated with T1DM in adulthood [208]. A similar pattern of results was found in older adults (≥60 years) with T1DM [209]. Remarkably, the magnitude of the cognitive differences found in these older adults was similar ($d = 0.3$–0.5) to that reported in their younger counterparts, despite their longer duration of diabetes.

Similarly to children, adults with diabetes also manifest slowed neural processing on measures of brainstem auditory evoked potentials [210], visual evoked potentials [211], and EEG recordings [212]. The magnitude of these effects is greatest in those individuals who have clinically significant microvascular complications [213, 214]. Multiple studies have demonstrated that cerebral blood flow patterns are abnormal in adults with diabetes, with these effects greatest in frontal and frontotemporal brain regions [215]. Changes in cerebral perfusion, measured by SPECT, are common. In one large study, 85% of middle-aged adults with diabetes showed hypoperfusion in one or more region of interest compared to 10% of controls; similarly, 58% of people with diabetes showed hyperperfusion, compared to 20% of controls [216]. Again, these effects were greatest in those with microvascular complications.

Changes in gray and white matter

Marked reductions in brain matter density are also associated with T1DM. Compared with a group of healthy individuals without diabetes, young adults with a childhood onset of diabetes manifested ~5% less gray matter in the right superior temporal gyrus, and in several left hemisphere regions, including the temporal gyrus, angular gyrus, medial frontal gyrus, inferior parietal lobule, and thalamus [217]. These structures are especially important for attention, memory, and language processing. The strongest predictor of gray matter density reduction was degree of chronic hyperglycemia; higher lifetime HbA_{1c} was consistently correlated with lower gray matter density.

A case–control study reporting similar findings, demonstrating that individuals with diabetic proliferative retinopathy manifest small reductions in gray matter density in the left middle frontal gyrus, the right inferior frontal gyrus, the right occipital lobe, and the left cerebellum. By contrast the gray matter values of people with diabetes without retinopathy were comparable to adults without diabetes [218]. Reductions in white matter volume have also been noted, with effects being greatest amongst adults with a longer history of chronic hyperglycemia and microvascular complications [219].

Retinopathy as a risk factor for CNS abnormalities

A long history of chronic hyperglycemia and the occurrence of microvascular complications is a robust risk factor for neurocognitive abnormalities. In a longitudinal study that followed a group of young and middle-aged adults with a childhood onset of T1DM over a 7-year period [220], those who had clinically significant proliferative diabetic retinopathy at baseline, or who developed retinopathy during the course of the follow-up period, showed a significant decline in psychomotor efficiency, compared to demographically similar people without diabetes. In contrast, those without retinopathy at either time showed no evidence of psychomotor slowing. The risk of cognitive change was predicted by four variables: the presence or development of proliferative retinopathy, the presence of autonomic neuropathy, elevated systolic blood pressure, and longer duration of diabetes. The resulting statistical model identified, with 83% accuracy, those who showed significant cognitive decline and explained 53% of the variance.

Cross-sectional studies of young adults have similarly demonstrated that background retinopathy is associated with white matter abnormalities on MRI and poorer performance on measures of attention, fluid intelligence, and information-processing speed [221]. Abnormal brain activation patterns during the performance of a working memory task have also been identified in people with clinically significant retinopathy [222]. Other microvascular complications, particularly peripheral neuropathy, are also associated with changes in brain function and structure [212, 214, 223, 224].

Given that middle-aged adults without diabetes who have retinal microaneurysms also show a pattern of cognitive decline that is characterized by psychomotor slowing [225], retinopathy may serve as a general marker of cerebral microangiopathy [181, 226]. This is quite plausible, given the well-known homology between the retinal and cerebral microvascular systems [227]. In those with clinically significant diabetic retinopathy, the resulting microangiopathy could lead to cerebral hypoperfusion

and thereby contribute to the development of abnormalities in brain structure and function by interfering with the efficient delivery of glucose and other key substances to neural tissue [181, 218]. The relationship often reported between peripheral neuropathy and brain dysfunction in individuals with diabetes may simply reflect the fact that microvascular complications tend to appear contemporaneously and have a common origin [228]. That is, microvascular disease may be the primary mechanism underlying the development of neurocognitive dysfunction in young and middle-aged adults [183].

Hyperglycemia and neurocognitive dysfunction in people with diabetes

Chronic hyperglycemia and the subsequent development of microvascular disease contribute to cognitive dysfunctions in people with T1DM or T2DM. Both T1DM and T2DM are associated with mental and motor slowing, and also with decreases in attention and executive functioning [229] and also with neural slowing, increased cortical atrophy and microstructural abnormalities in white matter tracts. In a meta-analysis, Biessels et al. studied the association between diabetes and incident dementia, using 14 longitudinal population-based studies. The incidence of "any dementia" was higher in individuals with diabetes, compared to those without diabetes. This elevated risk included both Alzheimer's disease and vascular dementia. These mechanistic studies suggest that vascular disease and also changes in glucose, insulin, and amyloid metabolism may underlie the pathophysiology [230].

HbA_{1c} is the best (albeit imperfect) predictor of impairment in older people with diabetes, although other diabetes-related conditions, (including hyperinsulinemia [231, 232] and hypertension [233]) are important. Many people with T2DM are beset with multiple medical problems or diabetic complications, some of which (e.g. cerebral atherosclerosis) may contribute to cognitive decline. Nevertheless, it is clear that factors other than vascular disease must play a part in the etiology of these cognitive impairments because they can be identified in otherwise healthy adults with T2DM who have no clinically apparent vascular complications.

Conclusions

One of the greatest problems facing people with diabetes is the failure, or inability, of many clinicians to empathize with how challenging it is to live with the daily self-care demands of a condition like diabetes, to identify those experiencing psychological distress quickly and provide appropriate support. From this chapter, it is clear that people with diabetes have a remarkable level of psychological resilience but, like anyone else, they may experience psychological distress, made more likely by having to cope daily with the demands of living with a chronic condition. Furthermore, it is evident that the behavioral change is unlikely if the person lacks the pre-requisite information, motivation and/or behavioral skills, and is unsustainable if such changes cannot be incorporated into the person's lifestyle (or if they compromise their quality of life). It is incumbent on all members of the healthcare team to recognize the psychological impact of diabetes and to continue to develop better ways of delivering healthcare and support in order to alleviate distress, improving both biomedical health outcomes and quality of life.

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57 Psychiatric Disorders and Diabetes

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Key points

- The interactions between diabetes and psychiatric disorders are complex: physical illness raises the risk of psychiatric disorder, but mental illness and its treatment with certain psychotropic medications also impact on the risks and outcomes of diabetes.
- Since mental health problems are more common among people with diabetes, heightened levels of awareness and knowledge are vital for the health professionals who work with them.
- Screening for mental health problems should form part of the holistic care of people with diabetes.
- The prevalence of diabetes is increased two- to threefold among those with mental illness, including depression and psychotic illnesses.
- The mechanisms underlying the association between diabetes and mental illness are multifactorial and include genetic and environmental factors as well as effects of the illness and its treatment.
- The presence of comorbid mental illness worsens the diabetes outcomes; the rates of microvascular and macrovascular complications, acute metabolic dysregulation and diabetes-related deaths are all higher in people with mental illness.
- The availability of mental health expertise in the settings where people with diabetes are treated is generally poor and should be improved.
- Tailored lifestyle interventions have been shown to reduce body weight in people with psychotic illness and are likely to reduce the incidence of diabetes.
- Effective diabetes management, incorporating primary care, diabetes services, and mental health teams, is essential to reduce the poorer health outcomes and current inequity experienced by people with mental illness and diabetes.

Introduction

The greatest challenge facing medicine in the 21st century is multimorbidity, defined as the co-occurrence of two or more diseases in the same individual. Whilst diabetes healthcare professionals are used to managing this increasingly common challenge, given the effects of diabetes on many body systems, the comorbidity of diabetes and mental illness is less well appreciated despite it being common and worsening the outcomes of both conditions. Psychiatric illness hinders an individual's ability to undertake the diabetes self-management that is central to the maintenance of health and prevention of complications and premature mortality. Therefore an understanding of the complex interaction between mind and body is crucial to the management and outcome of people with diabetes.

Both diabetes and psychiatric disorders are common conditions, and therefore a degree of co-occurrence would be expected purely by chance. There is considerable evidence, however, that diabetes is associated more frequently than expected with a range of psychiatric morbidity. In particular, it appears that people with mood and psychotic disorders are at increased risk of developing diabetes [1, 2], whilst those with diabetes go on to develop a range of psychological problems at increased rates compared to people without diabetes [1]. This was noted over a century ago; Henry Maudsley said in his celebrated textbook *Pathology of Mind*,

> *"Diabetes is a disease which often shows itself in families in which insanity prevails. Whether one disease predisposes in any way to the other or not, or whether they are independent outcomes of a common neurosis, they are certainly found to run side by side, or alternately with one another more often than can be accounted for by accidental coincidence or sequence" [3].*

Unfortunately in most countries, services are poorly equipped and organized to deliver good quality care for both the physical and psychological needs of patients in the same setting [4]. Clinicians need to be aware of the increased risks of comorbidity, and the need for screening. Diabetes healthcare professionals should be able to provide "first response" management, and recognize the needs of more complex patients for whom specialist management is essential. The topic of comorbidity has attracted interest from researchers, and considerable progress has been

Textbook of Diabetes, Fifth Edition. Edited by R. Holt, C. Cockram, A. Flyvbjerg and B. Goldstein.

Table 57.1 DSM-5 "Major" Depressive Episode.

A Five (or more) of the following symptoms have been present during the same 2-week period and represent a change from previous functioning; at least one of the symptoms is either (1) depressed mood, or (2) loss of interest or pleasure.
- Depressed mood most of the day, nearly every day, as indicated by either subjective report (e.g. feels sad or empty) or observation made by others (e.g. appears tearful).
- Markedly diminished interest or pleasure in all, or almost all, activities most of the day, nearly every day (as indicated by either subjective account or observation made by others).
- Significant weight loss when not dieting or weight gain (e.g. a change of >5% of body weight in a month), or decrease or increase in appetite nearly every day.
- Insomnia or hypersomnia nearly every day.
- Psychomotor agitation or retardation nearly every day (observable by others, not merely subjective feelings of restlessness or being slowed down).
- Fatigue or loss of energy nearly every day.
- Feelings of worthlessness or excessive or inappropriate guilt (which may be delusional) nearly every day (not merely self-reproach or guilt about being sick).
- Diminished ability to think or concentrate, or indecisiveness, nearly every day (either by subjective account or as observed by others).
- Recurrent thoughts of death (not just fear of dying), recurrent suicidal ideation without a specific plan, or a suicide attempt or a specific plan for committing suicide.

B The symptoms cause clinically significant distress or impairment in social, occupational or other important areas of functioning.

C The symptoms are not due to the direct physiological effects of a substance (e.g. a drug of abuse, a medication) or a general medical condition (e.g. hypothyroidism).

made in understanding the epidemiology and psycho-biological mechanisms involved. Efforts targeting psychiatric care providers have increased awareness of diabetes and metabolic problems in general, and have led to initiatives to increase routine screening and referrals for diabetes care, with varying degrees of success.

This chapter will provide an overview of the relationship between diabetes and mental illness, in particular focusing on the association with depression, psychotic illness (schizophrenia and bipolar illness), and eating disorders. Within each section, the epidemiology of the comorbidity, mechanisms underlying the association, and clinical implications will be considered.

Mood disorders

The association between diabetes and depression has been recognized for many years. In the 17th century, Thomas Willis described how "*diabetes is a consequence of prolonged sorrow*" [5]. Nevertheless it is a frequently ignored component of holistic diabetes care. Until the last decade, any discussion of mood disorders and diabetes would have concentrated solely on the increased rates of depression in people with diabetes, and is likely to have viewed such comorbidity as an "understandable" reaction to the difficulties resulting from living with a demanding and life-limiting chronic physical illness. We now understand that the relationship between the two conditions is more complex than this:

- At least in the case of type 2 diabetes (T2DM), the relationship between diabetes and depression is bi-directional as depression is a risk factor for the development of diabetes [6–8].
- Biological aspects of diabetes may contribute to the development of depression and vice versa.
- Other antecedent factors, such as the early nutritional environment or neighborhood, may contribute to the risks of both conditions [1].

Given the large numbers of people with diabetes and mental illness, approximately 8.3% and 10% of the total world's population, respectively, and the twofold higher rates of depression in people with diabetes [9], the comorbidity of these two conditions presents a major clinical challenge as the outcomes of both are worsened by the presence of the other. Quality of life is worse, diabetes self-management is impaired, the incidence of complications is increased and life expectancy is reduced [1]. The costs of treatment increase significantly for both individual patients and health economies but these costs do not necessarily result in significant improvements in disease or quality of life outcomes [10].

Case definition

Depressive symptoms exist on a continuum of severity. Standard definitions of "clinical" depression are based on symptom count and duration; the most widely used diagnostic criteria in current practice are those of the American Psychiatric Association DSM-5 "Major" depression [11] (Table 57.1). This definition approximates to a level of symptomatology which is associated with significant disability and dysfunction but it is important to note that depressive symptoms of lesser severity may still compromise self-care and outcomes in people with diabetes.

The clinical category of mood disorders includes both unipolar depression and bipolar (previously known as "manic-depressive") illness. This section will focus on unipolar depression; bipolar illness will be included in the section on psychotic disorders.

Epidemiology

Depression is common, affecting between 3–5% of the general population at any time. Its prevalence appears to be increasing and is predicted to become the second leading global cause of disability (after heart disease) by 2020 [12].

Considerable variability of measurement and use of terminology have contributed to heterogeneity and inconsistency in studies examining diabetes and depression [1]. The meaning of the term

depression spans relatively minor, occasional negative mood states (which should more accurately be termed *depressive symptoms*) to incapacitating and treatment-resistant disorders that fulfil all diagnostic criteria for depression. Many self-rating scales do not acknowledge the overlap between symptoms of diabetes and those of depression (e.g. fatigue, weight loss), leading to overestimates of the prevalence of "depression" in those with diabetes [13]. The "gold standard" for ascertainment of case status is a research diagnostic interview; at most rating scales can only give a probabilistic estimate of caseness. A further confounding factor is the construct of "diabetes-related distress" which captures the emotional distress associated with living with diabetes [14]. Diabetes-related distress correlates modestly with depressive symptoms with ~30% overlapping variance but remains distinct from depression in its association with self-management and glycemic control.

Studies have tended to ignore the heterogeneity of diabetes, studying mixed populations of different forms of diabetes (e.g. T1DM and T2DM). It is important to distinguish between these groups for several reasons:

- People with T2DM are generally older and depression prevalence varies with age
- Pathological mechanisms may differ
- The rates of diabetic complications and other comorbid conditions (e.g. obesity, heart disease) differ
- Management demands are different.

Studies have often been based on "convenience" samples of patients, usually drawn from specialist diabetes clinics, where referral patterns and the effect of other biases in sample composition, such as ethnicity, were unknown.

Finally the studies often had low or unknown response rates, and since the presence of depressive symptoms may reduce the likelihood of responding in such studies, this biases prevalence estimates further.

More recent studies, using better methods, and meta-analyses, have tended to report lower estimates of prevalence, with significant depressive symptoms affecting approximately 1 in 3–4 adults with T1DM and T2DM while a formal diagnosis of depressive disorders is made in approximately 10–15% of people with diabetes [9]. One review of the prevalence of comorbid depression in T1DM [15] concluded that clinical depression was present in 12%, compared with 3.2% in people without diabetes. Excluding studies without control groups and interview ascertainment led to a fall in estimated prevalence to 7.8%, a figure which was no longer statistically significantly different from healthy controls (OR 2.4; 95% CI: -0.7–5.4). A meta-analysis of 10 studies that included 9028 people with T2DM and 42,272 adults without diabetes found that rates of self-reported depression were significantly elevated in those with diabetes (18% vs. 10%) [16]. Recently the course of depression has been studied in 2460 people with T2DM in a primary care setting [17]. Over a 3-year period, 26% met the criterion for depression on at least one occasion, with incident depression present in 14%. Recurrence or persistence of depression was evident in 66% of those with baseline depression. Depression was more common in women and those with low education, non-cardiovascular chronic diseases, stressful life events, or a self-reported history of depression.

The association between diabetes and depression appears to be similar across many countries; in a study including 231,797 adults from 47 countries, people with diabetes were 2.36-fold more likely to have experienced an episode of depressive symptoms than those without (Figure 57.1) [18]. Similar associations were found in South America, Asia, and Europe but not Africa where case ascertainment may be less complete.

A meta-analysis of 11 cohort studies including ~50,000 people with T2DM but without depression at baseline indicated that the incidence of depression is 24% higher in people with diabetes [7] while another meta-analysis of 13 studies found incident depression was increased by 15% in people with diabetes at baseline [8]. The discrepancy between prevalence and incidence rates may be explained by greater persistence of depression and higher relapse rates in people with diabetes.

Although there have been few studies in children and adolescents with either T1DM or T2DM, depression rates (9–26%) also appear elevated [1].

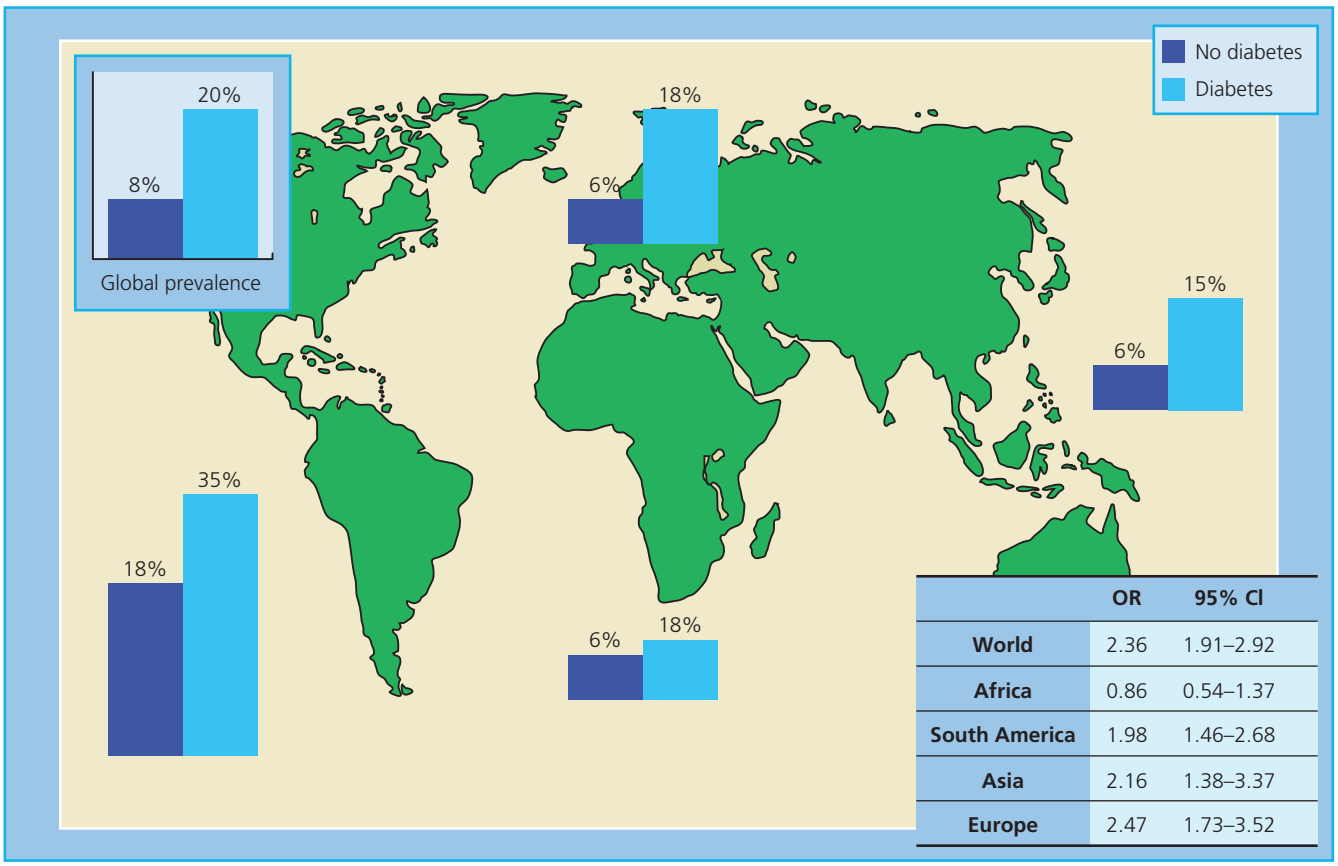
Who is likely to develop depression?

Risk factors for depression in otherwise healthy individuals, including female sex, marital status, childhood adversity and social deprivation, operate equally in people with diabetes and much depression in people with diabetes may be "independent" of the presence of the disease. However, there are both treatment- and diabetes-specific risk factors associated with depression. The use of insulin in T2DM is associated with higher rates of depression compared to non-insulin medications or dietary and lifestyle interventions alone [19, 20]. It seems unlikely that insulin causes depressive symptoms per se but insulin is associated with increased treatment demands and is generally used in people with more advanced disease. Recurrent hypoglycemia and poor glycemic control are both risk factors for depression and insulin therapy is usually associated with greater glycemic variability than other treatments. The intensive self-monitoring of blood glucose required with insulin therapy may also adversely affect depressive symptoms [20].

There is a well-recognized association between cardiovascular disease and depression but the development of microvascular complications, particularly sexual dysfunction and painful peripheral neuropathy, are also associated with depression [21]. In a specialized outpatient clinic, the presence of two or more complications more than doubled the risk of depression in people with T2DM, with neuropathy and nephropathy showing the strongest association with depression [22].

Depressive disorders as a risk factor for diabetes

A meta-analysis of nine cohort studies found that adults with depression had a 37% increased risk of developing T2DM [23] after accounting for factors common to both disorders including sex and body mass index. There is heterogeneity across studies which in part could be ascribed to ascertainment bias as people



	OR	95% CI
World	2.36	1.91–2.92
Africa	0.86	0.54–1.37
South America	1.98	1.46–2.68
Asia	2.16	1.38–3.37
Europe	2.47	1.73–3.52

Figure 57.1 Depressive episodes in people with and without diabetes. Odds ratios (OR) of an episode of depressive symptoms according to diabetes presence with 95% confidence intervals. Source: Data from Mommersteeg et al. 2013 [18].

with depression may be more likely to be screened for diabetes than those without.

Proposed mechanisms linking depression and diabetes

Several psychological, sociological and biological models have been proposed to explain the association between diabetes and depression. While there may be specific reasons why one condition pre-disposes to the other, recent research has also considered common antecedents to both (Figure 57.2) [1].

Common antecedents

An adverse intrauterine environment may predispose individuals to both T2DM and depression. There is a J-shaped relationship between birth weight and plasma glucose, insulin concentrations and T2DM while some but not all studies have shown that fetal under-nutrition is associated with adult depression [1]. One possible mechanism is programming of the hypothalamic-pituitary adrenal (HPA) axis as both depression and diabetes are associated with HPA dysfunction [24]. Adverse environmental factors in postnatal life, ranging from childhood adversity to neighborhood environment and poverty may also influence the predisposition to depression and diabetes.

Why diabetes may increase the risk of depression

The traditional view holds that depression is an understandable reaction to the challenges of living with a demanding chronic physical illness that is associated with disabling complications and premature mortality. This is supported by studies that found no increase in depression rates amongst those with undiagnosed diabetes or impaired glucose metabolism [25]. As depression rates only increase following a diagnosis of diabetes, this suggests that the knowledge of the diagnosis and the burden of managing the condition and its complications are important in the etiology of depressive symptoms; consequently healthcare professionals need to convey the diagnosis of diabetes sensitively and provide psychosocial support to mitigate against this effect.

The psychological model does not preclude other biological mechanisms and it is well recognized that both hypoglycemia and hyperglycemia affect brain function in areas of cognition and mood. Animal studies of diabetes have shown loss of hippocampal integrity and neurogenesis, which may contribute to mood symptoms while in humans, MRI studies have shown hippocampal atrophy. Prefrontal glutamate-glutamine-gamma-aminobutyric acid levels are increased in people with T1DM in a way that correlates with mild depressive symptoms [26].

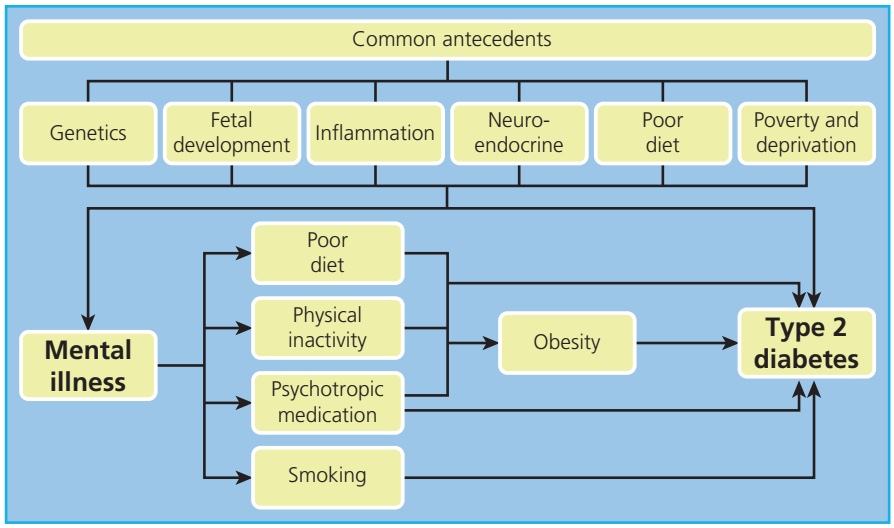


Figure 57.2 Mechanisms that explain why mental illness may predispose type 2 diabetes. There are a number of common antecedents that increase the risk of both conditions. Once an individual develops mental illness, further lifestyle changes may occur, which together with the effects of psychotropic medication may increase the risk of diabetes, either directly or indirectly through the development of obesity. Source: Adapted from Holt and Mitchell 2015 [2]. Copyright 2015 Nature Publishing Group.

Why depression may lead to diabetes

People with depression tend to be more sedentary and eat diets that contain more saturated fats and refined sugars and less fruit and vegetables than the general population [27, 28]. Other self-care behaviors may also be relevant; a meta-analysis found that people with depression were significantly less likely to follow diabetes treatment recommendations including missed medical appointments, medication use, glucose monitoring, and foot care [29]. This could lead to a vicious cycle whereby poorer self-care management leads to hyperglycemia which in turn worsens depressive symptoms and consequently contributes to decreased adherence to diabetes self-care. Depression is associated with disrupted sleep patterns [30], which may increase insulin resistance and risk of T2DM [31].

Pharmacological treatment of depression has also been implicated in the development of diabetes; some antidepressants may cause significant weight gain which may worsen insulin resistance [32]. Case reports and observational studies have shown a consistent association between the use of antidepressants and diabetes while randomized controlled trials have reported both hyperglycemic and hypoglycemic effects [33]. It is uncertain whether any or all antidepressants cause diabetes as their use may be a marker of individuals at high risk of diabetes.

Consequences of depression in diabetes

Comorbid depression adversely affects diabetes outcomes and decreases quality of life [34–36]. This is not explained by poor glycemic control as rather surprisingly and in contrast to diabetes-related distress, no consistent association between depressive symptoms and HbA_{1c} has been found [37–39]. Nevertheless treatment studies suggest that improved glycemic control may accompany a reduction of depressive symptoms.

Depression is associated with worsened severity of many diabetes complications although the direction and mechanisms that underlie this association are not fully understood [21]. The evidence that depression increases the risk of developing complications is less strong, although the associated impaired self-care would lead to this expectation. In one 10-year cohort study of individuals with childhood-onset diabetes, retinopathy severity was predicted by increasing duration of diabetes, with length of time spent in poor control and with overall proportion of time depressed [40]. Similar results have been seen in people with T2DM; in one longitudinal study, those with high depression scores at both baseline and 6-year follow-up were more likely to progress to diabetic retinopathy and to proliferative diabetic retinopathy than those with low depression scores [41].

One complication that may be particularly associated with depression is painful peripheral neuropathy. Recent studies suggest that not only is chronic pain a risk factor for depression, but the presence of depression may itself worsen the experience of pain [42].

Depression, even if mild, is also associated with premature overall and cardiovascular mortality [43]; in one study the annual mortality rate for those with diabetes and depression was 8%, 2.5-fold higher than those without either condition [44].

Management of people with diabetes and depression

The main aims of treatment are to reduce depressive symptoms and to improve self-care, glycemic control and diabetes outcomes. A major difficulty for most clinics is the lack of readily available specialist mental health input, and this has been a disincentive for services to engage actively in tackling this important clinical problem [45]. By contrast, guidelines now include psychological well-being. Most clinics should be able to provide "first response" management for simple depressive disorders, although specialist help will still be required for more complex cases, where there is diagnostic uncertainty, lack of response to initial treatment or suicide risk.

Screening and diagnosis of depression

The first step to the effective management of depression is its recognition and diagnosis. At present, screening and case finding

are not part of the routine management of people with diabetes; however, given the high prevalence of comorbid depression in people with diabetes, this seems worthwhile and healthcare professionals should ensure they have appropriate skills to diagnose mood disorders.

A formal diagnosis of depression requires a time-consuming validated interview and so quick and cheaper screening methods are needed for primary and secondary care settings [46]. Although there are many short questionnaires that screen for depressive symptoms, it is important to use one that has been evaluated adequately in people with diabetes because of the overlap of symptoms between diabetes and depression, such as lethargy, irritability, or weight change [13]. Questionnaires that rely heavily on these symptoms tend to overestimate the likelihood of depression.

The most widely used and validated questionnaire in T2DM is the Patient Health Question-9 (PHQ-9). It is also the shortest, containing nine questions and can be easily completed by the patient alone. The cut-off for major depression is ≥10 in primary care populations but it has been suggested that a higher cut-off of ≥12 points in people with diabetes may improve the discrimination between diabetes-related symptoms and depressive symptoms [47]. Other well-validated questionnaires for people with diabetes include the Beck Depression Inventory, the Center for Epidemiologic Studies Depression Scale, and the Hospital Anxiety and Depression Scale (HADS). These questionnaires should not be used to diagnose depression but to identify those who should undergo a diagnostic interview.

Another straightforward approach that can be used by diabetes healthcare professionals is to ask two simple questions:

- "During the past month, have you been bothered by having little interest or pleasure in doing things?"
- During the past month, have you been bothered by feeling down, depressed, or hopeless?"

If the answer to either is "yes," the person with diabetes should be asked if they want help with this problem. If the answer to this is also "yes," then the patient should be assessed by a diagnostic interview and offered appropriate referral and treatment.

While a necessary first step, screening alone is insufficient to improve clinical outcomes [46]. A Cochrane meta-analysis reported that depression screening in the general population had little or no impact on the detection and management of depression if used alone and recommended screening strategies could not be justified without organizational changes to ensure appropriate treatment if needed [48]. The importance of this for diabetes was demonstrated in a Dutch randomized controlled trial which investigated the benefits of depression screening [49]. Following screening, although written feedback was provided to both the person with diabetes and doctor neither utilization of mental health services nor depression scores improved. Furthermore without links to treatment, screening could lead to harm, including the stigma associated with depression, the risk of labeling transient distress as illness, and societal discrimination by insurance companies [50]. Several reasons might explain the observed low effectiveness of screening for depression in people with diabetes including a low acceptance of screening and subsequent referral to further care by people with diabetes, failure to screen those at highest risk of depression, reluctance by healthcare professionals and generally poor quality of depression care in primary care systems [50].

Treatment of depression in people with diabetes

Knowledge of appropriate counselling techniques and appropriate drug therapy is important for diabetes healthcare professionals, as well as an awareness of the need for prompt referral to specialists when psychological difficulties continue to interfere significantly with well-being or diabetes self-management.

Previously people with diabetes were specifically excluded from trials of depression treatment and so consequently, there were relatively few studies examining antidepressant and psychological treatment of depression in this population until recently. Nevertheless studies published over the two decades have clearly indicated that treating depression with either psychological therapies or antidepressant medication is effective [50].

Psychological treatment

A variety of psychological treatments, including cognitive behavioral therapy, problem-solving and psychodynamic techniques have been used to treat depression in people with diabetes. These have been delivered in a variety of settings both in primary and secondary care by different members of the healthcare team [50]. Others have used web-based and telephone contacts. The trials have a preponderance of people with T2DM and no trials have been conducted with only people with T1DM. Given the heterogeneity of interventions, varied levels of effectiveness were found making it difficult to compare trials. Nevertheless the consensus is that such interventions improve psychological distress, with a moderate to large effect size (standardized mean difference (SMD) ranging from -0.14 to -1.47). There is more debate about the effect on glycemic control with one systematic review reporting a reduction in HbA_{1c} of ~0.6% (6 mmol/mol) [51] while another reported a less pronounced and overall non-significant improvement in glycemic control (SMDs from 0.40 to –1.40) [52]. Four recent trials on psychological interventions found an improvement in glycemic control (SMD -0.25 to -0.68) [50]. Although web-based psychological therapies may be effective in treating depression in people with diabetes, they appear to have limited effects on glycemic outcomes.

The best response to psychological interventions occurs when these are combined with education that provides diabetes self-management skills as well as the psychological support to use these effectively. In these situations the boundary between educative approaches and formal psychotherapy can become blurred.

Pharmacotherapy

Effective and well-tolerated antidepressants are widely available and affordable and form an integral component of management for many people with depression. People with diabetes respond to antidepressants as the general population with amelioration of

depressive symptoms. Formal efficacy trials in people with diabetes are limited to a relatively small group of antidepressants, including nortriptyline, fluoxetine, buproprion, sertraline, paroxetine, and citalopram [50], leaving substantial gaps in the evidence for effectiveness, both depression and glycemic control, and safety for many commonly prescribed antidepressants. All antidepressants studied appear to have similar efficacy in terms of depression outcomes as long as adequate doses are used with effect sizes of -0.61 SMD [52] but no trial has reported the medium- and long-term sustainability of pharmacological interventions after treatment cessation.

The treatment of choice depends largely on the side-effect profile, patient preference, and individual response. Selective serotonin reuptake inhibitors (SSRIs) are less cardiotoxic than tricyclic antidepressants, are safer in overdose and consequently are widely used as first-choice agents. There are important drug–drug interactions between some members of this class and oral hypoglycemic agents through inhibition of the cytochrome P450 3A4 and 2C9 isoenzyme. For example, the use of fluoxetine may potentiate the effect of sulfonylureas precipitating hypoglycemia [53]. Some antidepressants, including mirtazapine, paroxetine and some tricyclic antidepressants, may cause undesirable weight gain [32]. By contrast, buproprion, which is available in the USA, is associated with weight loss. Furthermore, unlike SSRIs, it does not appear to worsen sexual function and therefore may have advantages for people with diabetes [54]. Several new antidepressant medications have been approved including vilazodone, vortioxetine, and levomilnacipran [55]. Differentiating these from most of those already available include a more benign weight gain profile for all three, fewer problems related to sexual functioning for vilazodone and vortioxetine, and potential relief of the cognitive dysfunction that can be associated with depression as demonstrated with vortioxetine. None of these drugs has been tested specifically in people with diabetes.

The clinical trials demonstrate a modest improvement in glycemic control with SSRIs (SMD -0.38). However, older studies have shown a mixed effect on glycemic control ranging from hyperglycemic effects with tricyclic antidepressant medications to euglycemic or slightly hypoglycemic effects with SSRIs and serotonin–noradrenaline reuptake inhibitors. Consequently the findings of improved glycemic control with certain antidepressants should not be extrapolated to other untried antidepressants [50].

Most guidelines recommend that there should be complete remission of depressive symptoms. To achieve this, treatment must be sustained at an adequate dose for at least 4–6 months after remission has been attained to consolidate recovery and reduce the risk of relapse and recurrence.

In addition to possible direct pharmacological effects, it should be remembered that treating depression may lead to a change in the patient's behavior and routine which may require adjustment of diabetes self-management. For example, if the patient's appetite improves, insulin requirements may increase; if the patient becomes more active, they may decrease.

Models of care

In most healthcare systems, depression is managed mostly within primary care and many diabetes healthcare professionals feel ill equipped to manage depression. In the United States, a case management model known as "collaborative care" has been developed, whereby a multidisciplinary team works together to identify and treat depression within primary care settings. The model incorporates identification of high-risk cases, problem-solving therapy delivered by trained nurse case managers, and pharmacological treatments using a stepped-care approach. The first study to evaluate this approach was the PATHWAYS study which showed improvements in depression symptoms but no change in glycemic control [56]. Subsequently, greater attention was paid to intervention strategies for diabetes resulting in improved glycemic and blood pressure control as well as improved depressive symptoms [57]. As well as being clinically effective, these models of care are also highly cost-effective [58, 59].

Psychotic disorders

Psychotic disorders include schizophrenia, psychotic depression and bipolar disorder and are often known as "Severe (and Enduring) Mental Illness" (SMI). The presence of psychotic symptoms, which include delusions and hallucinations, has a profound effect on well-being and functioning of many aspects of daily life. When they co-occur with a chronic physical illness, they create significant management challenges, and such patients are amongst the most complex that healthcare systems encounter.

Case definitions

Schizophrenia is characterized by psychotic symptoms (delusions, hallucinations), disorganization of speech and other behavior, and so-called "negative" symptoms which include loss of drive and blunting of affect (Table 57.2). Schizophrenia is also associated with cognitive decline. The illness tends to run a chronic clinical course, and most people with the condition will be under the long-term care of specialist mental health services.

Although bipolar disorder is often thought to be a disease whose hallmark is the occurrence of one or more episodes of mania (elevated mood; criteria for a manic episode are shown

Table 57.2 DSM-5 Schizophrenia.

1	Two or more of the following symptoms, at least one of these must be i, ii, or iii:
	i Delusions
	ii Hallucinations
	iii Disorganized speech
	iv Grossly disorganized or catatonic behavior
	v Negative symptoms (affective flattening, alogia, or avolition)
2	Social/occupational dysfunction
3	Features continuously present for at least 6 months

Table 57.3 DSM-5 Manic Episode.

1 A distinct period of abnormally and persistently elevated, expansive or irritable mood, and abnormally and persistently increased goal-directed activity or energy, lasting at least 1 week.
2 During the period of mood disturbance, three or more of the following symptoms have persisted (four if mood only irritable):
- i Inflated self-esteem or grandiosity
- ii Decreased need for sleep
- iii More talkative than usual or pressure to keep talking
- iv Flight of ideas or subjective experience that thoughts are racing
- v Distractibility
- vi Increase in goal-directed activity or psychomotor agitation
- vii Excessive involvement in pleasurable activities that have high potential for painful consequences (e.g. spending, sexual activity)

3 Marked impairment in occupational functioning or in usual social activities or relationships with others, or need for hospitalization to prevent harm to self or others, or psychotic symptoms.

in Table 57.3), bipolar disorder can be conceptualized as a predominantly depressive disorder, based on the amount of time people with bipolar disorder have depressive symptoms [60]. On average, the ratio of the number of depressive episodes to manic or hypomanic episodes is 3 : 1 for bipolar I disorder, and the ratio of depressive episodes to hypomanic episodes is 39 : 1 for bipolar II disorder. In addition, the strict diagnostic criteria for bipolar disorders are complex, and there is a degree of overlap with schizophrenia, such that some people may be diagnosed as having a "schizo-affective" disorder [61].

Epidemiology

Schizophrenia is estimated to have a point prevalence of between 1–7 per 1000 in the general population, with an annual incidence of 13–70 per 100,000, and a lifetime risk of 1–2%. There is little variation in incidence across the world. The clinical course of the illness is variable, ranging from a single brief episode (rarely) to a lifelong illness with marked deterioration over time. There are many theories about the causation of schizophrenia; it has a marked genetic risk profile, but is also associated with early cerebral insults (e.g. birth anoxia) and environmental stress.

Bipolar disorder is much less common than unipolar depression, with an estimated lifetime prevalence of 1% for bipolar I disorder and another 1% for bipolar II disorder. Again genetic factors are thought to play an important role in the etiology of bipolar disorders, which are among the most heritable of psychiatric disorders.

People with SMI have standard mortality rates that are approximately two- to threefold higher than the general population, equating to a loss of 10–20 years of life [62]. The average life expectancy for men and women with schizophrenia in the UK is 62.8 years and 71.9 years respectively [63]. While suicide and trauma account for the highest relative risk of death, the commonest causes of death are from physical illness, principally cardiovascular disease. Over the last 30 years, while the life expectancy of the general population has improved, this has not been experienced by people with SMI leading to a widening health inequality gap.

Diabetes and severe mental illness

It is challenging to obtain precise diabetes prevalence rates in people with SMI because of the high prevalence of undiagnosed diabetes, which is estimated to be up to 70% of all cases [2]. Nevertheless there is a general consensus that the prevalence of diabetes is two- to threefold higher than in the general population. A meta-analysis of 41 studies including 161,886 people found that the overall prevalence of diabetes was 9.0% with an odds ratio for diabetes among those with multiple episodes of psychosis of 1.99 [64]. The increased prevalence is driven by an excess of T2DM as there is no evidence of enhanced pancreatic autoimmunity. The incidence of diabetes is higher and the onset of diabetes appears to be 10–20 years earlier than in the general population [65] (Figure 57.3). As diabetes is uncommon in young healthy adults, the increased relative risk of diabetes is greatest in adolescents and young adults with SMI [2].

Although subtle metabolic abnormalities have been found in people with a first episode of psychosis, the majority of studies show that metabolic abnormalities develop rapidly after treatment initiation and two recent meta-analyses found no appreciable increase in diabetes in people prior to the initiation of antipsychotic treatment [64, 66].

People with SMI experience higher rates of microvascular and macrovascular complications, acute metabolic dysregulation and three- to fourfold more diabetes-related deaths [2]. In one study from Denmark, among those aged ≤50 years, 15.0% died within 7 years of a diagnosis of diabetes; the corresponding figures for those aged 50–69 years and ≥70 years were 30.7% and 63.8%, respectively. A third of deaths from physical causes were attributed to diabetes while 14% of deaths were attributed to the interaction between diabetes and SMI [67].

Why psychotic disorders are linked to diabetes

Unlike depression, there is no evidence that diabetes predisposes to psychotic illness but it has been noted for over a century that people with SMI are at increased risk of glucose abnormalities. An interest in the physical health of those with SMI was stimulated following the introduction of first-generation antipsychotics that for the first time allowed people with SMI to achieve reasonable control of their psychotic symptoms and live independently. Following concerns about metabolic side effects of the second-generation antipsychotics around the turn of the millennium, further effort was made to understand the link between SMI and diabetes and a greater understanding of the highly complex inter-relationship between the person with SMI, their treatment and environment and risk of diabetes has been gained. Although concerns about the side effects of antipsychotics triggered the resurgent interest in diabetes, to blame the antipsychotics alone for the increased risk of diabetes in people with SMI misses the

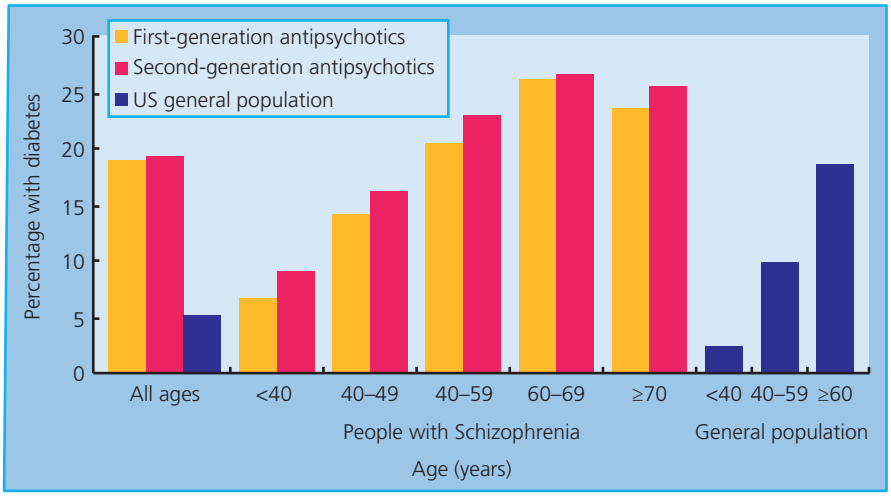


Figure 57.3 Age-specific prevalence rates of diabetes in people with schizophrenia, separated by treatment, compared with the general US population. Source: Data are adapted from Sernyak et al. 2002 [65] and National Health and Nutritional Examination Survey 2001–2002 (http://wwwn.cdc.gov/nchs/nhanes/search/nhanes01_02.aspx).

full picture and may hinder attempts to prevent and treat diabetes in this population.

Genetics

Both schizophrenia and T2DM are highly heritable disorders and it is conceivable that there may be genes that increase the risk of both conditions. Many schizophrenia genes are expressed in the brain and include those involved in glutamatergic neurotransmission and D_2 dopamine receptor (*DRD2* gene) while T2DM is associated with polymorphisms in genes that influence hepatic and peripheral insulin resistance, adipogenesis, and pancreatic β cell mass and function (see Chapter 14). Recent studies have identified at least 37 common genes that increase the risk of both T2DM and schizophrenia [68]. It is estimated that approximately 11% and 14% of these risk genes for T2DM and schizophrenia, respectively, may account for the risk of the other disease. Several candidate genes that may affect the risk of both conditions have been identified (Table 57.4) [68].

In addition to affecting an individual's risk of T2DM directly, genetic polymorphisms in various genes, including the promoter region of the 5-hydroxytryptamine$_{2C}$ receptor, leptin, methylenetetrahydrofolate reductase (*MTHFR*) and *MC4R* genes, appear to modify the risk of antipsychotic-induced weight gain [69]. Polymorphisms in the *HRH1*, *BDNF*, *NPY*, *CNR1*, *GHRL*, *FTO*, and *AMPK* genes may also affect the risk of weight gain.

Environment and biological effects of the illness

Many of the environmental factors that mediate the association between diabetes and depression are also relevant for the links between diabetes and SMI, including intra-uterine environment, adult lifestyle (diet and lifestyle), neighborhood environment, and poverty (Figure 57.2) [2]. A number of inflammatory and neuroendocrine changes, including HPA dysfunction, also occur in SMI.

Antipsychotic medication

Antipsychotics are an integral element of SMI treatment that comprises multidisciplinary psychological, social, and rehabilitation interventions. They are frequently taken over a long period to prevent relapse and hospitalization and to decrease mortality [70]. The first generation of antipsychotics was introduced in the 1950s but their use was blighted by a high incidence of a range of unwanted side effects, including hypotension, weight gain, sexual dysfunction, and sedation and extra-pyramidal side effects. In order to reduce the likelihood of these movement disorders, second-generation antipsychotics (also known as atypical

Table 57.4 Genes that have been linked to both diabetes and schizophrenia [2].

Gene	Function
Glycogen synthase kinase 3 (*GSK3*)	Regulates both glucose metabolism and cognitive function
Serine–threonine protein kinase *AKT1*	Reduced expression in lymphocytes and the frontal cortex in schizophrenia. Mediates insulin signaling and glucose metabolism; reduced action leads to diminished phosphorylation of its substrates, including *GSK3*.
Dopamine D_2 receptor (*DRD2*) gene	Implicated in obesity and T2DM, through alteration of insulin sensitivity and secretion. Affects risk of schizophrenia
Tyrosine hydroxylase gene	Associated with insulin resistance and schizophrenia
TCF7L2 gene	Encodes for a transcription factor involved in Wnt/beta-catenin signaling that has a role in pancreatic β cell function and is a susceptibility gene for T2DM. Wnt signaling pathway plays a role in CNS development and is associated with schizophrenia

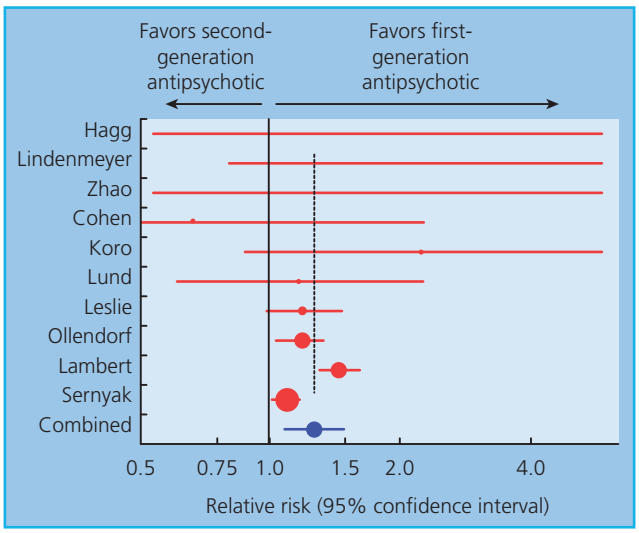


Figure 57.4 Forest plot of relative risks and 95% CIs for diabetes in patients with schizophrenia receiving first-generation antipsychotics compared with second-generation antipsychotics. Source: Adapted from Smith et al. 2008 [72].

antipsychotics) were developed. Although the second-generation antipsychotics are generally better tolerated, an association with weight gain and other metabolic abnormalities rapidly became apparent [2, 71].

Large pharmaco-epidemiological database studies reported that antipsychotics were associated with more diabetes than no treatment while treatment with a second-generation antipsychotic is associated with a small 32% (15–51%) increase in diabetes risk compared with first-generation antipsychotics (Figure 57.4) [72]. Overall the risk, however, appears to be low with the NNH estimates ranging from 19 to 333 for clozapine, 22 to 3333 for risperidone, 21 to 747 for olanzapine, and 24 to 500 for quetiapine (Figure 57.5) [73]. Although the risk of diabetes for the latest second-generation antipsychotics is widely believed to be lower, this has not always been apparent in pharmaco-epidemiology studies. For example, aripiprazole and ziprasidone were not associated with lower rates of diabetes than olanzapine, quetiapine, and risperidone in a pharmaceutical claims database [74], perhaps because of channeling bias whereby persons at higher risk for diabetes are prescribed antipsychotics that are perceived to be safer.

Although pharmaco-epidemiological studies are able to assess small risks in large populations who may be followed for a longer period of time than clinical trials, by design, they have a number of

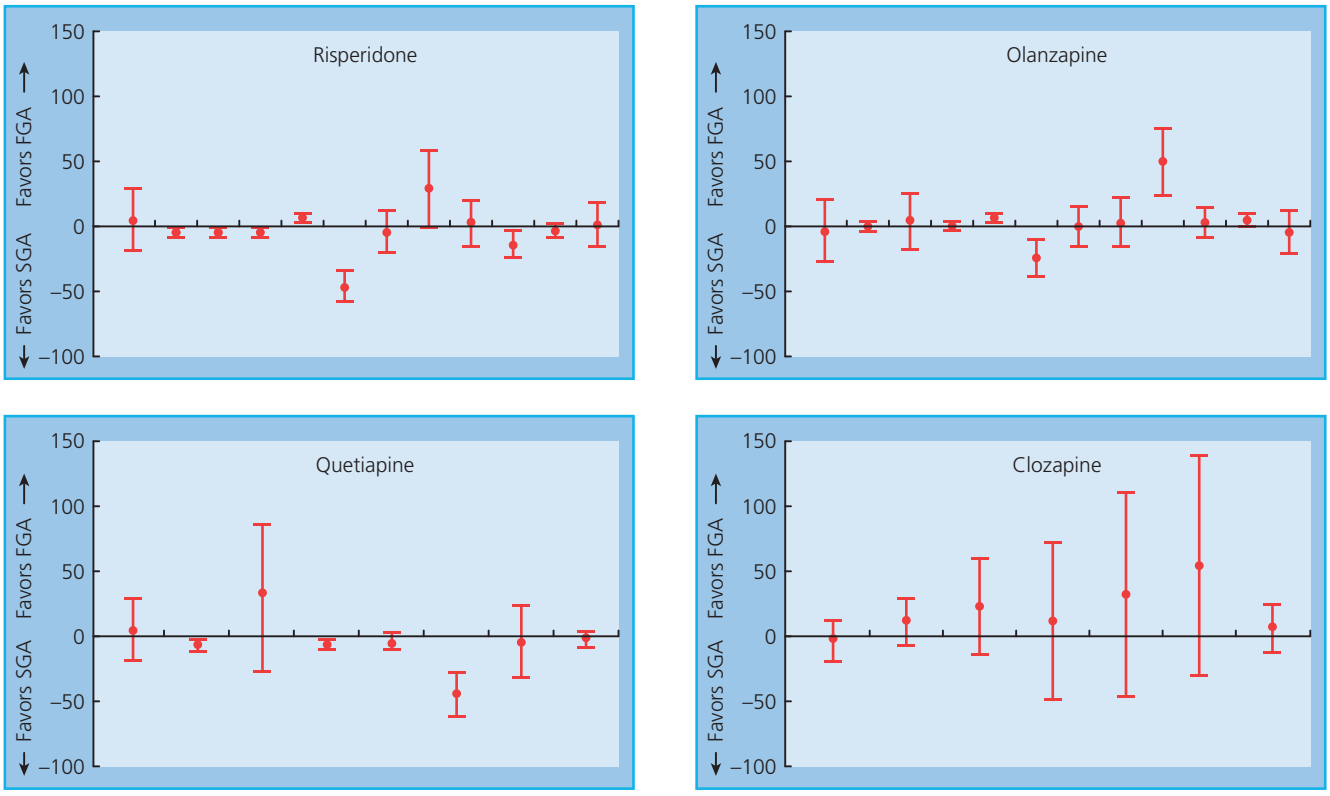


Figure 57.5 Number of cases of diabetes estimated to occur beyond those expected with first-generation antipsychotics (FGA) per 1000 patients treated with a second-generation antipsychotic (SGA), 95% CI. Source: Adapted from Citrome et al. 2007 [73].

methodological flaws that can affect the interpretation of results. They rely on data from administrative databases with inherent problems of data quality, such as convenience reporting of adverse effects, prescriber bias and omission of important confounding diabetes risk factors [75]. Furthermore individuals with either undiagnosed diabetes or those treated with lifestyle interventions alone will not be recorded in prescription databases.

Treatment assignment is not randomized and so differences in diabetes rates may be explained by factors other than the treatment. For example, clozapine is usually reserved as a second-line antipsychotic because of its risk to cause agranulocytosis, requiring ongoing monitoring of the white blood cell count. As a result, it is used in people with the most serious mental illness who are resistant to treatment with at least two other antipsychotics. By virtue of their illness, these individuals may be at higher risk of diabetes and so higher rates of diabetes among people treated with clozapine may reflect the person receiving the antipsychotic rather than treatment per se. Another potential reason for the observed increase with clozapine is "screening bias." People receiving second-generation antipsychotics, particular those receiving clozapine, are much more likely to be screened for blood glucose abnormalities than individuals receiving first-generation antipsychotics [76, 77]. Since there are high rates of undiagnosed diabetes in people with SMI, increased screening will inevitably result in an increased detection of diabetes without the need to invoke a causal relationship between drug and diabetes.

Randomized controlled trials (RCTs) are considered the gold standard when assessing the effect of an intervention but antipsychotic trials are under-powered to detect changes in incident diabetes and consequently most RCTs have reported no differences in incident diabetes [78]. Examining blood glucose changes is a more sensitive way of assessing an antipsychotic's metabolic effects and a systematic review of 48 head-to-head comparison studies found that a greater, albeit small, increase in glucose following treatment with olanzapine compared with amisulpride, aripiprazole, quetiapine, risperidone, and ziprasidone [79]. There were no differences in glucose changes between the other antipsychotics studied. Another systematic review found similar increases in glucose following treatment with the newer antipsychotics, asenapine, iloperidone, and paliperidone [80]. In the European First-Episode Schizophrenia Trial, which examined treatment effects in treatment naïve people with first episode psychosis, the mean change in glucose over a year ranged between 0.2–0.5 mmol/L with no differences between drugs [81]. Albeit small, these increases in glucose concentration may translate into meaningful differences in incident diabetes with the long duration of treatment needed to treat SMI.

There are several mechanisms by which antipsychotics increase the risk of diabetes. All antipsychotics may be associated with weight gain [71]; however, the effect size is markedly heterogeneous, with weight gain being less problematic for haloperidol, ziprasidone, and lurasidone in contrast to large effects observed with olanzapine, zotepine, and clozapine [82]. Overall 15–72% of people taking antipsychotics experience more than 7% of body weight gain in the first year of treatment [83]. From the short-term pivotal trials of the different antipsychotics, NNH versus placebo for weight gain of ≥7% from baseline ranges from 6 for olanzapine and quetiapine immediate-release to 67 for lurasidone [84]. Weight gain is most marked in people naïve to antipsychotics where weight gain is up to three- to fourfold greater than in those with chronic illness [85]. Most weight gain occurs early in treatment although people can continue to gain weight for at least 4 years after treatment initiation albeit at a slower rate gradually reaching a plateau.

Weight does not explain all the excess diabetes risk as some individuals develop diabetes without being overweight or gaining weight. Furthermore, as weight gain is likely to increase diabetes risk through increased insulin resistance, it does not explain why some people develop diabetic ketoacidosis which occurs as a result of markedly impaired insulin secretion. Through their interaction with multiple receptors, antipsychotics may affect insulin secretion by the β cells of the pancreas. Blockade of α_2 receptors may increase basal insulin secretion while blockade of 5-HT_{1a} and 5-$HT_{2a/c}$ receptors may decrease pancreatic β cell responsiveness to blood glucose (Figure 57.6). Central control of glucose homeostasis may also be affected by antipsychotics [86].

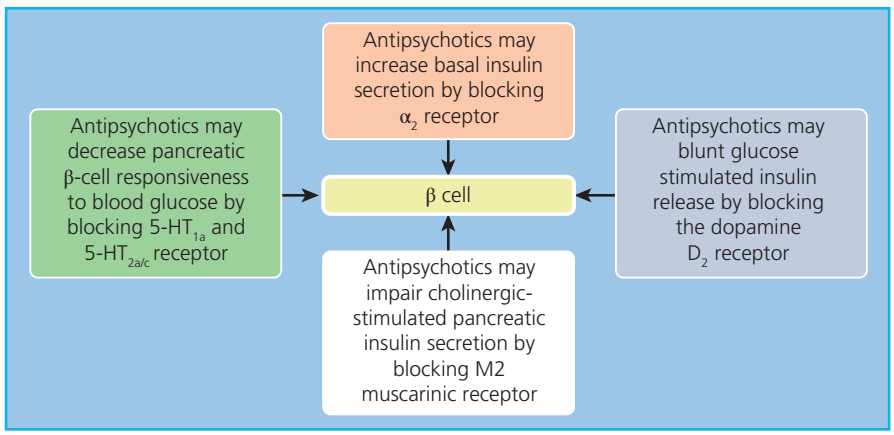


Figure 57.6 Possible pharmacological effects of antipsychotics on β-cell function.

In addition to these pancreatic effects, *in vitro* work suggests that antipsychotics may directly impair insulin action by inhibiting insulin-mediated glucose uptake and glycogen synthesis.

Contribution of different mechanisms

Given the complex pathophysiology of T2DM, it is perhaps unsurprising that multiple mechanisms are involved in the association between SMI and diabetes. It is also likely that the contributions of these risk factors operate differently between individuals. Overall, it appears that an excess of traditional diabetes risk factors, such as obesity, poor diet, physical inactivity, and family history, convey a higher risk than treatment, but this does not discount the possibility that antipsychotics are the major contributor to the development of diabetes in certain individuals, particularly where the onset of diabetes is rapid after treatment initiation and other risk factors are absent [2].

Screening of diabetes in those with severe mental illness

Given the large numbers with undiagnosed diabetes, there have been moves to screen at risk individuals in the general population for diabetes. As people with SMI constitute a high-risk group, several national and international guidelines have recommended regular screening for diabetes, regardless of treatment [87–90]. Although there are differences in detail, all guidelines recommend screening before the start or change of treatment, several months later to identify the few who develop diabetes rapidly after antipsychotic initiation and annually thereafter. Although the oral glucose tolerance test has been implemented successfully in some settings, this test is no longer widely used in the general population and measurements of fasting or random glucose, or glycated hemoglobin (HbA_{1c}) are more practical alternatives. There is a debate about the relative sensitivity and specificity of each of these tests but a pragmatic view should be taken; both random glucose and HbA_{1c} are more convenient and this probably outweighs any small loss of sensitivity. One caveat about HbA_{1c} is that it may be falsely negative if glucose concentrations are rising rapidly as may happen shortly after treatment initiation. In the setting, combining HbA_{1c} and glucose is a sensible option.

Despite clear guidance and potential benefit, screening has not been implemented into routine clinical practice (Figure 57.7) [90, 91], perhaps because people with SMI may be less likely to undergo opportunistic health screening. Professional barriers to screening including inertia or prejudice, lack of clarity about whose responsibility it is, lack of understanding about the most appropriate test and its interpretation and lack of access to necessary equipment may also be responsible for the poor screening rates within mental health settings [92].

Prevention of diabetes

There have been no specific diabetes prevention studies in people with SMI, but randomized control trials have shown that lifestyle interventions that aim to treat or prevent obesity, which encompass similar principles to diabetes prevention are

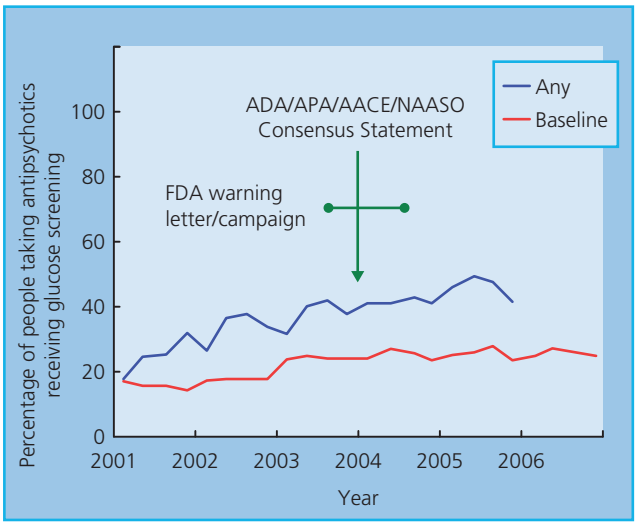


Figure 57.7 The effect of the American Diabetes Association; American Psychiatric Association; American Association of Clinical Endocrinologists; North American Association for the Study of Obesity consensus statement and U.S. Food and Drug Administration guidance on glucose testing in people receiving antipsychotic medication. Source: Adapted from Morrato et al. 2009 [91], Figs 1 and 2.

feasible in people with SMI. A meta-analysis of lifestyle interventions reported a mean reduction in weight of 3.12 kg over a period of 8–24 weeks with commensurate reductions in waist circumference and improvements in cardiovascular risk factors [93]. The interventions, which employed a variety of techniques including cognitive behavioral therapy and nutritional interventions, were beneficial in both individual or group settings and weight reductions were seen irrespective of duration of mental illness and treatment. Outpatient interventions appeared more effective than inpatient settings. The few studies with long-term outcomes suggest that benefits may persist for up to 1 year after the program's end, although others suggest that long-term behavior change may be difficult to maintain [94].

Several longer observational studies of weight management programs suggest that sustained weight loss can be achieved [2]. An 8-year observational study of a group intervention in well-motivated participants found that mean weight and BMI reduced progressively throughout follow-up [95]. The mean weight loss at 1 year was ~10% (~10 kg), with nearly two-thirds of participants achieving a 7% weight loss. By the end of the program, 92% had lost some weight with the only predictor of weight loss being the number of sessions attended.

A tailored and flexible program design of the intervention, outreach delivery in familiar locations, and effective inter-agency working are all important facilitators of behavior change while barriers include literacy difficulties, transient participant populations, low prioritization of diabetes prevention, and cost [96].

No pharmacological diabetes prevention trials in people with schizophrenia have been reported but short-term trials have shown that both metformin and orlistat reduce weight or

Table 57.5 Drugs that have been tested as potential agents to prevent or reduce weight gain.

Amantadine
Nizatidine
Topiramate
Metformin
Betahistine
Fluoxetine
Reboxetine (not available in the USA)
Sibutramine (withdrawn because of safety concerns)
Exenatide
Orlistat (approved for the management of obesity)
Lorcaserin (approved for the management of obesity in the USA)
Phentermine topiramate combination (approved for the management of obesity in the USA)
Naltrexone bupropion combination (approved for the management of obesity in the USA)
Liraglutide (approved for the management of obesity)

attenuate weight gain in people with schizophrenia receiving antipsychotics and improve insulin resistance (Table 57.5) [97]. A systematic review of studies to attenuate weight gain or promote weight loss reported that the mean difference between metformin and placebo was -3.17 kg [97]. In practice, orlistat is difficult to use because of its gastrointestinal side effects and so metformin is a more practical option. More research is needed to determine the long-term effectiveness of metformin but in the meantime, it can be considered for those who are unable or unwilling to make lifestyle changes or for those whose glucose concentrations continue to deteriorate despite lifestyle change.

Several other drugs, including d-fenfluramine, sibutramine (now withdrawn), topiramate, and reboxetine, have a modest effect on weight but there are insufficient data about efficacy or safety to recommend their use outside clinical trials (Table 57.5) [98]. Newly approved weight-loss agents such as lorcaserin, phentermine topiramate combination, naltrexone bupropion combination, and liraglutide have not yet been systematically studied among persons with SMI [99, 100].

Given the different propensities to weight gain and metabolic disturbance between antipsychotics [71], it is reasonable to consider whether switching antipsychotics may reduce the subsequent risk of diabetes. There is a lack of high-quality data to support this strategy but a Cochrane review of four studies including 636 participants showed that body weight reduced by a mean of 1.94 kg when people switched from olanzapine to either aripiprazole or quetiapine [101]. In addition there was a small but significant reduction in fasting blood glucose (0.1 mmol/L) reported in two trials. Any decision to switch antipsychotic must take account of the potential to affect the mental health of the patient.

Management of those with diabetes

The management of diabetes in people with SMI should follow currently available treatment algorithms for the general population but agents that induce less weight gain or promote weight loss, such as incretin-based therapies or SGLT-2 inhibitors, may have advantages given the high prevalence of obesity in people with SMI. Although the GLP-1 receptor agonists must be given by injection, the development of once-weekly preparations may allow these to be administered by mental health teams when the individual is unable to self-administer the injection.

Diabetes self-management is a key skill to achieving good control of diabetes and there are concerns that SMI may interfere with the lifestyle changes, regular monitoring and self-medicating that make up diabetes self-management. Consequently it is reassuring that a systematic review reported adherence rates among those with mental illness of between 51–85% with two studies finding higher rates of adherence than in the general population [102].

It is important that healthcare professionals, both in primary care and in mental health teams, ensure that people with SMI are not disadvantaged with regard to their diabetes care. Despite increased contact with primary care, there is increasing evidence that people with mental illness receive less education about diabetes, are less likely to be examined for retinopathy or diabetic foot complications, and are less likely to be screened for HbA_{1c} and other cardiovascular risk factors [4].

When an individual develops diabetes, while receiving an antipsychotic, it is important to assess what role this is likely to have played in the onset of diabetes in this individual. Under some circumstances, it may be appropriate to switch to an alternative antipsychotic if the patient's mental state will not be adversely affected [87].

Eating disorders

Case definitions

There are three main forms of eating disorder commonly diagnosed in adults [11].

- Anorexia nervosa (AN)
- Bulimia nervosa (BN)
- Binge eating disorder (BED).

Eating disorders exist on a continuum of severity, and there is a lack of good evidence on which to establish a formal boundary or cut-off for "clinical" significance. When an eating disorder co-occurs with a chronic disease such as diabetes, its significance may be increased by the potential for harm resulting from impaired self-care and glycemic control; thus eating disorders, which may be seen as "mild" in an otherwise healthy individual take on increased clinical importance. Because eating disorders are commonest in adolescents and young adults, there has been more research on the co-occurrence of eating disorders and T1DM; far less is known about such problems in the larger population with T2DM [103].

Diagnostic criteria for the common forms of eating disorder [11] are given in Table 57.6.

Table 57.6 DSM-5 Diagnostic criteria for Anorexia Nervosa, Bulimia Nervosa, and Binge Eating Disorder.

Anorexia Nervosa

Restriction of energy intake relative to requirements, leading to a significantly low body weight in the context of age, sex, developmental trajectory, and physical health. Significantly low weight is defined as a weight that is less than minimally normal or, for children and adolescents, less than that minimally expected.

- Intense fear of gaining weight or becoming fat, even though underweight.
- Disturbance in the way in which one's body weight or shape is experienced, undue influence of body weight or shape on self-evaluation, or denial of the seriousness of the current low body weight.

Bulimia Nervosa

- Recurrent episodes of binge eating. An episode of binge eating is characterized by (1) eating, in a discrete period of time (e.g. within any 2-hour period), an amount of food that is definitely larger than most people would eat during a similar period of time and under similar circumstances; and (2) a sense of lack of control over eating during the episode.
- Recurrent inappropriate compensatory behavior in order to prevent weight gain, such as: self-induced vomiting; misuse of laxatives, diuretics, enemas or other medications; fasting or excessive exercise.
- The binge eating and inappropriate compensatory behaviors both occur, on average, at least once a week for 3 months.
- Self-evaluation is unduly influenced by body shape and weight.
- The disturbance does not occur exclusively during episodes of anorexia nervosa.

Binge Eating disorder

- Recurrent episodes of binge eating. An episode of binge eating is characterized by (1) eating, in a discrete period of time (e.g. within any 2-hour period), an amount of food that is definitely larger than most people would eat during a similar period of time and under similar circumstances; and (2) a sense of lack of control over eating during the episode.
- The binge eating episodes are associated with three (or more) of the following: (1) Eating much more rapidly than normal. (2) Eating until feeling uncomfortably full. (3) Eating large amounts of food when not feeling physically hungry. (4) Eating alone because of feeling embarrassed by how much one is eating. (5) Feeling disgusted with oneself, depressed, or very guilty afterward.
  - Marked distress regarding binge eating is present.
  - The binge eating occurs, on average, at least once a week for 3 months.
  - The binge eating is not associated with the recurrent use of inappropriate compensatory behavior as in bulimia nervosa and does not occur exclusively during the course of bulimia nervosa or anorexia nervosa.

Clinical features

Anorexia nervosa (AN)

The hallmark of AN is weight loss, usually achieved by a combination of extreme dieting, exercise and, less commonly, self-induced vomiting. Misuse of laxatives and other weight-reducing substances (e.g. diuretics, thyroxine) may also occur. People with AN experience a characteristic set of attitudes and values concerning body shape and weight, which include intense feelings of fatness and extreme fear of loss of control over eating and consequent weight gain. Their body image is distorted and they express a level of dissatisfaction with their shape and weight, which is far beyond that seen in the general population. There is a tendency to judge their self-worth almost solely in terms of weight, shape, and ability to control food intake. AN is commonly regarded as being "egosyntonic," as individuals are unable to recognize that there is anything wrong and have little insight into the seriousness of their low body weight.

Anorexia nervosa usually begins in adolescence, although prepubertal and adult onset may occur. For some the natural body changes of adolescence appear to be a risk factor; weight loss associated with a diagnosis of T1DM and then commencement of insulin treatment and subsequent weight gain may act as a trigger.

The low weight of people with AN gives rise to the physiological and psychological features of starvation, including ritualized eating habits, cognitive rumination about eating, irritability, poor concentration, constant feelings of cold and misery, and decreased activity. Social withdrawal and isolation is common, and anxiety, obsessional features and suicidal thoughts sometimes occur. "Fattening" foods are typically avoided and the diet contains an average daily intake of calories in the region of 600–900 kcal per day, with very low fat and mineral intake. Most people with anorexia continue to feel hungry, and as such the term "anorexia" is a misnomer.

Common physical symptoms include gastrointestinal complaints (constipation, fullness after eating, bloating, and abdominal pain), lack of energy, reduced libido, early waking, and postural dizziness. Amenorrhea is often present, with infertility and osteopenia a significant risk. Those with pre-pubertal onset are often small in stature and show failure of breast development. Bradycardia, hypotension, and peripheral neuropathy are also reported, and a range of endocrine abnormalities may be found, including low sex hormone and tri-iodothyronine levels (with normal thyroxine and TSH), and raised growth hormone and cortisol.

Bulimia nervosa (BN)

Bulimia nervosa is characterized by recurrent episodes of binge eating in which large amounts of food are consumed (typically

≥2000 kcal) during which the individual feels unable to control the eating. This behavior is accompanied by a range of "compensatory" behaviors designed to prevent weight gain, including dietary restriction, vomiting, exercise, and laxative or diuretic misuse. People with BN have broadly the same set of attitudes and beliefs to those seen in AN. Although most individuals fall within the normal weight range, some have a past history of underweight, and may have previously met the diagnostic criteria for AN, while others are overweight. The vicious cycle of dieting, bingeing, purging, and fear of weight gain invariably has a detrimental impact on other aspects of functioning, such as work and social relationships, and can have financial implications resulting from the cost of the food. For some, binge eating seems to serve an important function by regulating unpleasant emotional states. Some sufferers have other impulse control problems and a history of interpersonal difficulties. Depression and self-harming behaviors such as cutting, overdosing or substance misuse may occur.

Physical complications of BN include enlargement of the parotid glands, erosion of dental enamel, and hypokalemia from vomiting, laxative or diuretic misuse.

Binge eating disorder (BED)

The cardinal feature of BED is regular episodes of binge eating. In the DSM-5, it is defined by recurrent episodes of binge eating (eating in a discrete period of time an amount of food larger than most people would eat in a similar amount of time under similar circumstances and a sense of lack of control over eating during the episode), occurring on average at least once a week for 3 months, and associated with marked distress. Binge episodes are also associated with ≥3 of the following:

- eating rapidly,
- eating until feeling uncomfortably full,
- eating large amounts of food when not feeling physically hungry,
- eating alone because of feeling embarrassed by how much one is eating,
- feeling disgusted with oneself, depressed, or guilty afterwards.

Unlike those with BN, persons with BED do not regularly engage in compensatory behaviors. Although many people with BED are obese, more than half have a BMI <30 kg/m^2, including 19% whose weight is normal [104].

Epidemiology

Binge eating disorder is the commonest eating disorder with an estimated lifetime prevalence of 2.6% among US adults, more than the prevalence for bulimia nervosa and anorexia nervosa combined, with a gender ratio that is far less skewed [104, 105]. In contrast, it is thought that about 1 in 250 females and 1 in 1000 males will experience AN, usually during adolescence or early adult life. BN is thought to be commoner with 0.5–1% of young women being affected in community studies. Longitudinal studies have shown that eating disorder diagnoses are often unstable over time, and cross-sectional studies underestimate the proportion of the population affected in the long term. Incidence rates in adolescent and young adults are higher than previously estimated.

Diabetes as a risk factor for the development of an eating disorder

Early case reports in the 1970s and 1980s highlighted the fact that people with T1DM omit insulin as a further means of weight control and there has been a strong clinical impression for many years that eating disorders are over-represented in people with diabetes. However, studies have produced conflicting results depending on the study population and eating disorder studied. There seems to be no difference in the prevalence of AN [106] but BN is 2.4-fold commoner in people with T1DM [107]. Intentional insulin omission occurs remarkably frequently increasing from 2% among girls aged 9–13 years, to 11% among girls aged 12–19 years, to 34–40% among young women aged 16–30 years old [108]. Such "self-induced glycosuria" is common but not universal, and is not confined to people with a frank eating disorder, being more widely observed as an occasional phenomenon in a range of weight-conscious individuals, more commonly women. As a means of weight control, the behavior produces rapid but often unsustainable weight loss, the main effect being via acute dehydration.

Some clinical features of disordered eating may persist into middle and later life and may be seen in people with T2DM. BED is often associated with obesity and is the most likely condition to occur.

Etiology

The causes of eating disorders are incompletely understood but dieting appears to be an important risk factor, although only a small proportion of all those who diet go on to develop a disorder. Other known risk factors include female gender, early puberty, a history of obesity or gaining weight, peer and cultural influences and certain personality traits including perfectionism and low self-esteem. Family relationships are often disturbed, although this may be either a cause or consequence of the disorder, or both. Several of these factors may be magnified by the demands of the diagnosis or management of T1DM. People with T1DM are encouraged to make dietary changes including restriction of high calorie fatty and sugary foods; this can lead to a preoccupation with food and body weight. Instead of relying on physiological cues related to hunger and satiety, food intake is brought under cognitive control; this can lead to feelings of low self-esteem and depression if self-imposed targets are missed. This in turn may drive further dietary restraint with a greater likelihood of subsequent failure, thereby causing a vicious cycle.

On average, people with T1DM are heavier than their peers and this may trigger dieting, weight preoccupation and altered body image perception. Furthermore there is a conflict between optimal diabetic and body weight control as weight tends to increase as HbA_{1c} comes down. Insulin treatment itself can lead to weight

gain and adjustment of insulin dose during puberty is notoriously difficult.

In contrast, there may also be protective factors; most notable of these is close medical and family surveillance during the period of highest risk of behaviors, such as vomiting and bingeing. However, in dysfunctional families, omission of insulin may be a tool used by the adolescent.

Impact on diabetes outcomes

Eating disorders, especially if persistent, are a major cause of poor outcome in people with diabetes [109]. In the short-term severe hypoglycemia, diabetic ketoacidosis, and hospital admission are all commoner in those with eating disorders [110]. Rates of serious micro- and macrovascular complications and mortality are significantly increased, even if the eating disorder is relatively short-lived. However, the incidence of long-term complications increases with the duration of insulin omission. Eighty-six percent of girls with T1DM and severe eating disorders developed retinopathy after 4 years compared to 24% of those without eating disorders [111]. In a 10-year follow-up study of females with T1DM, a quarter of those who reported insulin omission had nephropathy, compared with 10% of those who did not [112]. Mortality rates in girls with T1DM are increased nearly 16-fold in those with an eating disorder compared to those with diabetes alone (34.6 vs. 2.2 per 1000 person-years) in girls with T1DM [113].

Management of eating disorders

Detection

- Although some people with diabetes may volunteer information about eating problems, many will be secretive as a result of factors including denial, guilt, or shame. Thus an essential first step in management is successful detection of the problem. It is important to note that, although eating disorders are generally associated with poor self-care and erratic glycemic control, alternating periods of hypo- and hyperglycemia may be undetected by HbA_{1c}. Warning symptoms include:
- Marked weight fluctuation or loss.
- Symptoms of hyperglycemia (thirst or tiredness).
- Frequent episodes of ketoacidosis (often requiring hospital admission) or hypoglycemia leading to loss of consciousness.
- Growth retardation and pubertal delay may be seen in younger people with T1DM.

Most of these features are not specific for eating disorders and are only indicative of poor self-care. The only way to establish a diagnosis of an eating disorder is by a clinical interview, although brief self-report scales may be a useful means of screening.

General diagnostic questionnaires for detecting eating disorders are inappropriate for individuals with T1DM, as they do not identify features that are unique to T1DM, such as insulin omission. Furthermore some aspects of normal diabetes management may be viewed as disturbed eating in the general population. The revised Diabetes Eating Problem Survey (DEPS-R) is a 16-item diabetes-specific self-report measure of disordered eating that was designed specifically for people with diabetes [114] while the mSCOFF questionnaire is a simple five-item screening tool that is reliable, well validated, and can easily be used by diabetes healthcare professionals [115].

Treatment of eating disorders

There is a lack of primary research to guide the treatment of people with an eating disorder and diabetes, and advice is therefore based on existing guidelines for people without diabetes [116]. Dietary counselling by a dietician or specialist nurse may be a helpful first step, especially for those with milder disorders, but most cases will require specialist help. Guided self-help appears to be a viable option as a first step for people with bulimia. In all cases close liaison between the therapist managing the eating disorder and the diabetes team will be required. Eating disorder treatment needs to be enhanced with attention to:

- insulin or medication use
- glycemic control
- diabetes-related dietary restrictions
- relationships with family and medical staff
- feelings about having diabetes.

Although most people can be managed on an outpatient basis, the risk of impaired physical health necessitating inpatient admission is increased in those with diabetes. Regular physical monitoring is needed to manage the high risk of complications and mortality [117].

Anorexia nervosa

The evidence base for the treatment of AN with comorbid diabetes remains surprisingly weak but is likely to involve both psychosocial and biological aspects requiring a multidisciplinary team. A necessary first step for all patients is restoration of weight towards normal levels. During this process it is usually necessary to accept realistic rather than tight glycemic control. Diet should focus on healthy foods with a high satiety index. Severe hypo- or hyperglycemia must be avoided; as it is necessary to consume calories to prevent or treat hypoglycemia, this can cause patient anxiety. There is preliminary evidence that insulin pumps may decrease abnormal eating behavior and improve glycemic control because their use is associated with less weight gain and hypoglycemia [118]. As the insulin dose and blood glucose levels will change with eating habits and weight, it is essential that the eating disorder therapist understands the principles of diabetes treatment.

Bulimia nervosa

Treatment for BN, particularly by means of cognitive-behavioral therapy (CBT), is widely accepted, although there has been less study of its suitability for people with diabetes. The coexistence of diabetes with bulimia inevitably complicates management. Successfully engaging people in treatment may be more difficult, and approaches such as motivational interviewing may play a role [119]. Modification to standard treatment approaches includes the monitoring of self-care behaviors; again it is desirable that the

eating disorder therapist has knowledge and experience of the usual management of diabetes. Conflict may arise between the modifications to eating behavior advocated for BN treatment (promoting a more flexible approach to eating) and the dietary advice often given for diabetes management (regular controlled eating and avoidance of certain food groups). The development of structured education which offer a more person-centered approach may help this dilemma [120].

Other forms of treatment for BN include interpersonal psychotherapy, and the use of antidepressants. Fluoxetine has been approved for acute and maintenance treatment of binge-eating and vomiting behaviors in people with moderate to severe BN. A group educational program for people with bulimia and T1DM was better than "standard care" in improving eating behavior, but did not lead to improved glycemic control [121]. Inpatient treatment also appears to be successful, although the applicability of this approach in most healthcare systems remains to be tested.

Binge eating disorder

For the management of BED, psychological treatments such as cognitive behavioral interventions are recommended as first line and supported by meta-analytic reviews [122]. At present, only lisdexamfetamine, a stimulant that was originally approved for the treatment of attention deficit hyperactivity disorder, has been approved for the treatment of moderate to severe BED [123]. Treatment approaches for BED with comorbid diabetes have not been extensively studied but in one small study in T2DM, no significant difference was found in HbA_{1c} between those with and without BED [124].

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58 Social Aspects of Diabetes

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Key points

Driving

- Potential hazards facing the driver with diabetes include hypoglycemia, visual impairment, and disability from severe neuropathy or leg amputation.
- Hypoglycemia can severely disrupt driving skills by causing cognitive dysfunction and mood changes. Motor skills and judgment can become impaired when blood glucose falls below 3.8 mmol/L, often without inducing hypoglycemic symptoms. Impaired awareness of hypoglycemia is a relative contraindication to driving. Drivers with diabetes must take precautions to avoid hypoglycemia and know how to treat it if it occurs while driving.
- Corrected visual acuity that is worse than 6/12 in the better eye precludes driving in the general population. People with diabetes may fulfil this criterion, but still have significant visual impairment (e.g. field loss, poor night vision and perception of movement) secondary to retinopathy, laser treatment, or cataracts.
- In many countries, drivers with diabetes are legally required to declare the diagnosis for their driving license and motor insurance. Failure to do this will invalidate insurance claims.
- Driving licenses are often issued for fixed terms and only renewed following satisfactory medical review. In many countries, insulin-treated drivers are debarred from driving passenger-carrying vehicles and large goods vehicles, but the regulations have been changed in the European Union to allow this.

Employment

- Diabetes is not a bar to most occupations, and people with diabetes are protected in many countries by legislation against discrimination on the grounds of disability.
- People with insulin-treated diabetes are barred from certain occupations because of the risk of hypoglycemia. These include the armed forces, emergency services, commercial pilots, prison and security services, and jobs in potentially dangerous areas (e.g. at heights, underwater, and offshore).
- Severe hypoglycemia in the workplace is uncommon and shift work seldom compromises glycemic control. Depressive illness and poor glycemic control are associated with higher unemployment and sickness absence in people with diabetes.

Prison and custody

- Glycemic control may be suboptimal in prison because of restrictions in diet, exercise, and blood glucose monitoring. Intercurrent illness and metabolic abnormalities may not be recognized or treated promptly.
- Input from a diabetes specialist may improve the quality of care. Knowledge of diabetes among prison officers and staff of short-term custodial units is often limited and may be improved by liaising with local diabetes specialist services.

Insurance

- Diabetes should be declared to insurers, who may impose higher premiums or limited coverage. Many insurers' decisions are based on outdated actuarial data or misconceptions about the current prognosis of diabetes. National diabetes organizations can provide details of insurance brokers who do not weight policies against people with diabetes.
- Life expectancy in type 1 diabetes (T1DM) can be modeled from age, sex, and the presence of proliferative retinopathy and nephropathy. As the latter is a major determinant of survival, life insurance premiums should be reduced for all those who reach the age of 50 years without renal impairment.

Alcohol

- The association between excessive alcohol consumption, chronic pancreatitis, and secondary diabetes is well established. Alcohol excess is also associated with central obesity and poor adherence with medication; both could increase the risk of type 2 diabetes (T2DM) and compromise control of established diabetes. Most epidemiologic studies, however, have demonstrated a J-shaped relationship between alcohol consumption and diabetes, with moderate intake being associated with a lower risk of diabetes.

Textbook of Diabetes, Fifth Edition. Edited by R. Holt, C. Cockram, A. Flyvbjerg and B. Goldstein.

- In T2DM, moderate alcohol consumption is associated with a 35% reduction in total mortality and lower risk of cardiovascular disease compared to abstinence. Excessive alcohol consumption is associated with hypertriglyceridemia and resistant hypertension; affected individuals have an increased vascular risk.
- Ethanol inhibits hepatic gluconeogenesis and increases the risk, severity, and duration of hypoglycemia. Alcohol obscures the ability, both of the individual and of observers, to recognize and treat hypoglycemia, and intoxication can simulate hypoglycemia.

Recreational drugs

- Approximately one-third of young people with diabetes use recreational drugs at some time. The most common class of drug taken is cannabis, but amfetamine-type stimulants (including "ecstasy"), cocaine, and opiates are also used.
- Recreational drug use is associated with a sixfold higher risk of death from acute metabolic complications of diabetes. Intravenous drug use is uncommon but is dangerous and is associated with omission of insulin therapy, frequent hospital admissions (usually with diabetic ketoacidosis), and high mortality.
- Cocaine and amfetamine-type stimulants can have profound hemodynamic effects through sympatho-adrenal activation. In addition to an increased risk of cardiac arrhythmias and myocardial ischemia, the sympathetic activation antagonizes the action of insulin and can precipitate diabetic ketoacidosis.

Travel

- Diabetes is not a bar to traveling, but changes in meals, physical activity, and antidiabetes drug treatment en route and after arrival all need careful consideration. Important issues include travel insurance, medical identification, supplies and storage of medication and monitoring equipment and immunizations.
- During long flights, blood glucose should be monitored frequently and glycemic control relaxed to avoid hypoglycemia. Insulin injection schedules may require in-flight adjustment, especially if the time-shift exceeds 4 hours.

Leaving home

- In the Diabetes UK Cohort Study, "living alone" was associated with a more than fourfold increase in risk of death from acute metabolic complications of diabetes.
- Leaving home is potentially a period of high risk for young people with diabetes; particular concern has been expressed about the welfare of university students with T1DM.

Introduction

Diabetes influences many aspects of daily life, principally through the effects of treatment and its potential side effects, particularly hypoglycemia. The development of diabetic complications, such as neuropathy and retinopathy, can also affect everyday activities, particularly when these are severe with clinical manifestations, or require time-consuming treatment such as dialysis for chronic renal failure.

Driving

Driving is an everyday activity that demands complex psychomotor skills, visuospatial coordination, vigilance and satisfactory judgment. Although motor accidents are common, medical disabilities are seldom responsible. Diabetes is designated a "prospective disability" for driving because of its potential to progress and cause complications, while side effects of treatment (principally hypoglycemia) can affect driving performance. In most high-income countries, the duration of the license of a driver with diabetes is period-restricted by law, and its renewal is subject to review of medical fitness to drive. The problems associated with diabetes and driving and the limitations of relevant research data have been reviewed [1, 2].

The main problems for the driver with diabetes are hypoglycemia and visual impairment resulting from cataract or retinopathy. Rarely, peripheral neuropathy, peripheral vascular disease, and lower limb amputation can present mechanical difficulties with driving (Table 58.1), but these problems may be overcome by adapting the vehicle and using automatic transmission systems.

Despite these challenges, drivers with diabetes do not appear to be involved in more accidents than their counterparts without diabetes [3]. Population studies have shown no excess in accident rates among drivers with diabetes in Northern Ireland [4], Scotland [5], England [6], Germany [7], Iceland [8], or Pittsburgh in the USA [9], while a large survey of over 30,000 drivers in Wisconsin, USA found only a modest increase [10]. In most surveys, however, incidents were self-reported and probably underestimated, while fatal accidents (in which a diabetes-related cause, such as hypoglycemia, could have had a role) were excluded. Accident rates may also have been lowered by regulatory authorities

Table 58.1 Reasons for drivers with diabetes to cease driving.

Newly diagnosed people with diabetes, especially insulin-treated, should not drive until glycemic control and vision are stable
Recurrent daytime hypoglycemia (particularly if severe)
Impaired awareness of hypoglycemia, if disabling
Reduced visual acuity in both eyes (worse than 6/12 on Snellen chart)—note use of mydriatics for eye examination will affect visual acuity
Severe sensorimotor peripheral neuropathy, especially with loss of proprioception
Severe peripheral vascular disease
Lower limb amputation

Table 58.2 Advice for drivers with diabetes.

Inform licensing authority* (statutory requirement) and motor insurer of diabetes and its treatment
Do not drive if eyesight deteriorates suddenly
Check blood glucose before driving (even on short journeys) and at intervals on longer journeys
Take frequent rests with snacks or meals; avoid drinking alcohol
Keep a supply of fast-acting and complex carbohydrate in the vehicle for emergency use
Carry personal identification to indicate that driver has diabetes (and is prone to hypoglycemia)
If hypoglycemia develops, stop driving, switch off engine, leave the driver's seat and then treat with carbohydrate
Do not resume driving for 45 minutes after blood glucose has returned to normal (delayed cognitive recovery)

* In the UK, the licensing authority is the Driver and Vehicle Licensing Agency (DVLA), Swansea, SA99 1TU, UK.

debarring high-risk drivers and by drivers with advancing diabetic complications who stop driving voluntarily [4, 5]. Practical advice for drivers with diabetes is given in Table 58.2.

Hypoglycemia

Drivers with insulin-treated diabetes often experience hypoglycemia while driving [4, 5, 11] and this can interfere with driving skills by causing cognitive dysfunction, even during relatively mild hypoglycemia that does not induce symptoms. Studies of people with T1DM using a driving simulator showed that driving performance often became impaired at blood glucose concentrations of 3.4–3.8 mmol/L, and deteriorated further at lower levels [12]. Problems included poor road positioning, driving too fast or too slow, inappropriate braking and causing "crashes" by stopping suddenly. Alarmingly, most did not experience hypoglycemic symptoms or doubt their competence to drive; only one-third treated the hypoglycemia, and only when blood glucose had fallen below 2.8 mmol/L [12]. In the UK, the Driver and Vehicle Licensing Agency (DVLA) does not distinguish between type of diabetes, and the restrictions are based on the use of insulin as therapy, as this can cause hypoglycemia in any person using this treatment. The risk of hypoglycemia in insulin-treated T2DM rises with duration of insulin therapy.

Judgement and insight become impaired during hypoglycemia, and some drivers with diabetes describe episodes of irrational and compulsive behavior while at the wheel [11, 12]. Hypoglycemia also causes potentially dangerous mood changes, including irritability and anger [13]. In addition, asymptomatic hypoglycemia impairs visual information processing and contrast sensitivity, particularly in poor visibility [14, 15], which may diminish driving performance.

Poor perception of hypoglycemia is also potentially dangerous. Many drivers with diabetes subjectively overestimate their current blood glucose level and feel competent to drive when they are actually hypoglycemic [16]. Impaired awareness of hypoglycemia, often associated with more frequent severe episodes, is potentially hazardous and is a common reason for revocation of the driving license. It is not an absolute contraindication to driving if it can be demonstrated, by frequent self-monitoring, that there is prolonged freedom from hypoglycemia [17].

Hypoglycemia is a recognized cause of motor vehicle accidents, but its true frequency and causal relationship to a particular incident are often difficult to ascertain. Blood glucose is seldom estimated immediately after a road traffic accident, and evidence for preceding hypoglycemia is often circumstantial. Hypoglycemia was the main cause of non-fatal motor vehicle accidents in the Diabetes Control and Complications Trial (DCCT); hypoglycemia was three times more common in the intensively treated participants, but the rate of major accidents was no higher, perhaps because of better precautionary advice [18]. Other studies have found that the frequency of hypoglycemic episodes during driving correlates with the total number of accidents [4, 5] and hypoglycemia-related driving mishaps are related to the frequency of severe hypoglycemia in the preceding year [19]. The frequency of hypoglycemia-related accidents is substantially lower than those caused by alcohol and drugs.

Avoiding and treating hypoglycemia while driving

General measures to avoid hypoglycemia are discussed in Chapter 35. All drivers with insulin-treated diabetes should keep some fast-acting carbohydrate in the vehicle; disturbingly, some do not [20, 21]. Each car journey, no matter how short, should be planned in advance to anticipate possible risks for hypoglycemia, such as traffic delays. It is advisable to check blood glucose before and during long journeys, and to take frequent rest and meals. Unfortunately, these measures are seldom undertaken [22]. Driving expends energy and—as with other forms of exercise—prophylactic carbohydrate should be taken if the blood glucose is <5.0 mmol/L and driving should be avoided if <4.0 mmol/L [23].

If hypoglycemia occurs during driving, the car should be stopped in a safe place, and the engine switched off before consuming some glucose. In the UK, the individual should vacate the driver's seat and remove the keys from the ignition, as a charge can be brought for driving while under the influence of a drug (insulin) even if the car is stationary. Driving should not be resumed for at least 45 minutes after blood glucose has returned to normal, because cognitive function is slow to recover after hypoglycemia [13].

Many features of hypoglycemia resemble alcohol intoxication, and mentally obtunded hypoglycemic drivers with diabetes are sometimes arrested on the assumption that they are drunk. Drivers with insulin-treated diabetes should therefore carry a card or identity bracelet stating the diagnosis. Individuals with newly diagnosed insulin-treated diabetes may have to stop driving temporarily until their glycemic control is stable.

Insulin secretagogues, the sulfonylureas and glinides, are the only oral antidiabetes drugs that may cause hypoglycemia while driving, and people treated with these agents should be informed

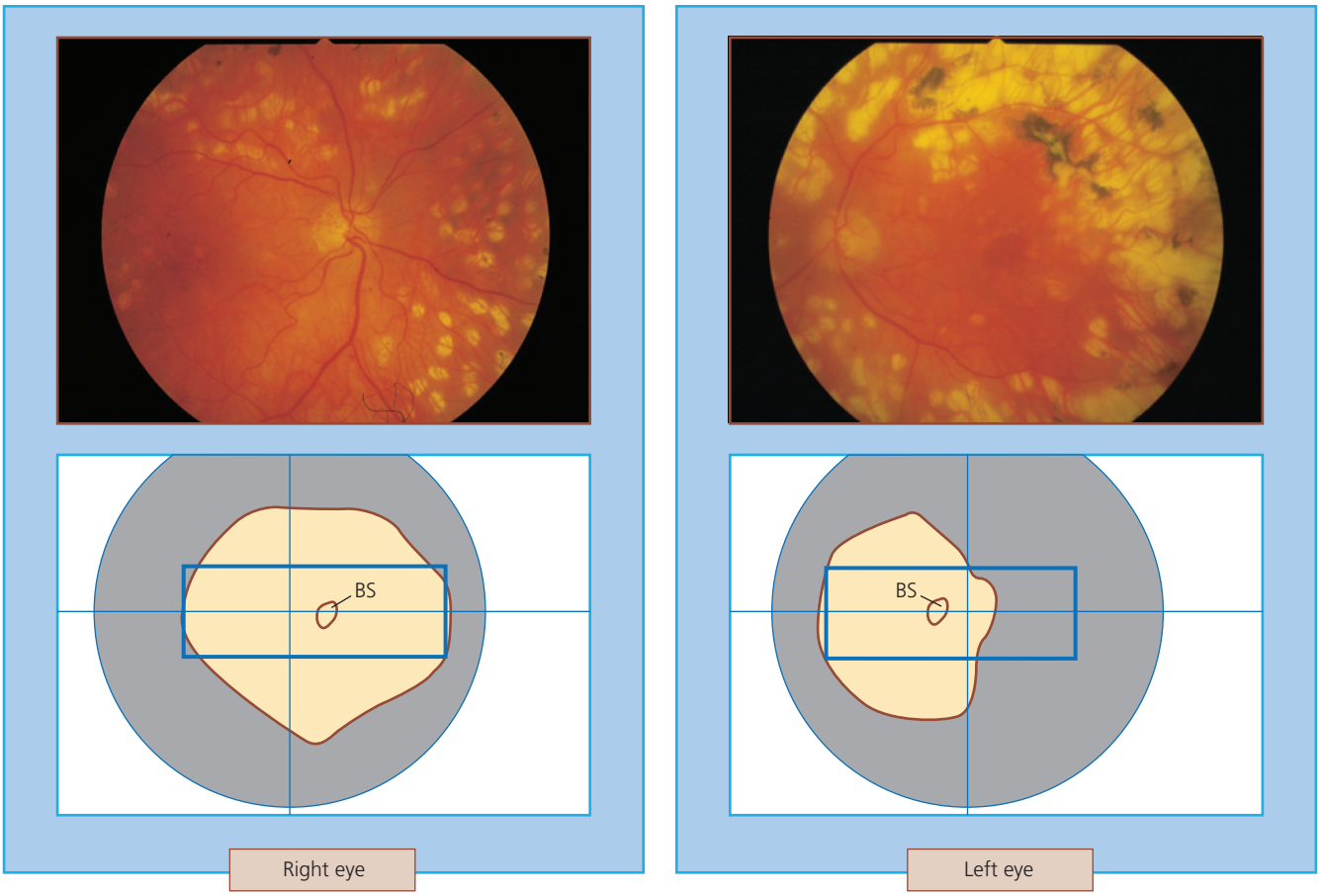

Figure 58.1 Visual field loss caused by photocoagulation. This 60-year-old man with diabetes needed extensive laser photocoagulation to the temporal retina of the left eye, causing nasal visual field loss which caused this eye to fail the standard test for driving. The right eye required less intensive laser treatment and the visual field was adequate for driving. BS, blind spot. Blue rectangle: minimum area recommended for safe driving. Source: Courtesy of D. Flanagan, Addenbrooke's Hospital, Cambridge, UK.

of this possibility. While GLP-1 receptor agonists alone are not associated with a risk of hypoglycemia, this may be a problem when used in combination with a sulfonylurea. Blood glucose testing in relation to driving is not a requisite for drivers with Group 1 driving licenses (see below), but may be required for holders of Group 2 driving licenses who are taking this treatment combination.

Visual impairment

In the UK, monocular vision is accepted for driving, provided that the person meets the minimum legal requirement, that is, to be able to read a number plate with letters 8.9 cm (3.5 inches) high at a distance of 30 m (75 feet), wearing spectacles if necessary. This corresponds to a distance visual acuity of approximately 6/10 on the Snellen chart. The number plate test has deficiencies: it is poorly reproducible under clinical conditions and does not assess visual fields, night vision, or the ability to see moving objects. All of these may be severely reduced by retinal ischemia in preproliferative retinopathy [24], while visual field loss can be caused by extensive laser photocoagulation for diabetic retinopathy [25, 26] or macular edema (Figure 58.1) [27]; careful containment of laser burns can preserve vision [28]. Cataracts often accentuate glare from headlights, and in such cases driving in the dark should be avoided.

Previous surveys have identified very few drivers with diabetes who would fail the standard eyesight test. Impaired vision is an uncommon reason for the driving license to be refused or revoked, although many people stop driving voluntarily because their eyesight is deteriorating. Worsening vision from diabetic (or other) eye disease should be reported by the individual to the licensing authority.

Eye screening is a crucial part of assessing medical fitness to drive. Pupillary dilatation for fundoscopy or retinal photography temporarily reduces visual acuity, particularly if the usual binocular visual acuity is 6/9 or worse [29]. Patients should be told not to drive for at least 2 hours after the use of mydriatics. The driving regulatory authorities require perimetry to assess the visual fields of people who have had photocoagulation (Figure 58.1).

Statutory requirements for drivers with diabetes

In most developed countries, drivers with insulin-treated diabetes are required by law to declare their diabetes to the relevant

regulatory authority (in the UK this is the DVLA). The statutory requirements for ordinary and vocational (professional) driving licenses vary considerably around the world; the national licensing authority should be contacted for details. Licensing restrictions have been criticized as being draconian and discriminatory against people with diabetes, but the civil rights of the person with diabetes have to be balanced against the need to safeguard public safety.

European driving licenses

Ordinary driving licenses (Group 1)

The European Union (EU) member states all use the same classification for driving licenses but this is not applicable to other parts of the world. In the UK, the DVLA must be informed when a person with insulin-treated diabetes applies for, or renews, a driving license, or if insulin dependence develops in a driver with diabetes. Failure to do this constitutes "concealment of a material fact," which can incur a fine, but more importantly can invalidate a claim to the motor insurers; professed ignorance of the law is not accepted as an excuse. The onus to declare rests with the individual driver, but doctors who provide diabetes care, including general practitioners, have a responsibility to inform their patients of this legal requirement, and should offer practical advice (Table 58.2). Drivers with diabetes who are treated with diet alone or with oral antidiabetes medications do not have to notify the DVLA unless they have visual impairment or other diabetes-related problems that could affect medical fitness to drive. In the UK, a driving license is "period-restricted" and is usually issued for a maximum of 3 years, and is renewed after completion of a medical questionnaire. The DVLA request further medical reports in some cases, and always when an applicant reports a medical problem that may seriously affect driving (e.g. recurrent hypoglycemia). GLP-1 receptor agonists (given by injection) can be used without restriction, other than when used in combination with a sulfonylurea for drivers with Group 2 (vocational) licenses, when this must be notified to the DVLA and requires assessment of medical fitness to drive.

The member states of the EU have an agreed policy on restrictions on driving licenses for people with insulin-treated diabetes, and these were changed after publication of the Third Directive on driving (Annex III to European Directives 91/439/EEC and 2006/126/EC: Driving Licence Standards for Diabetes) in 2006 and implemented thereafter. The main provisions are:

1 The interval between regular medical reviews should not exceed 5 years; stricter rules (3-yearly review in the UK) are allowed.

2 A driver must not experience more than one episode of severe hypoglycemia within the preceding 12 months. The time of day has not been specified, and so nocturnal episodes of severe hypoglycemia occurring during sleep are presently included but are to be ignored in future as this requirement is to be amended following legislation that will take effect in January 2018. This criterion raised concerns that it may lead to deliberate concealment of severe hypoglycemia by insulin-treated drivers, which has been suggested by a Danish study [30].

3 A driver must not have impaired awareness of hypoglycemia. No definition of this syndrome was given, and so its interpretation has been left to the discretion of individual states. In the UK it has been defined as "an inability to detect the onset of hypoglycemia because of a total absence of warning symptoms," which is rare in clinical practice.

Vocational driving licenses (Group 2)

It is extremely difficult to estimate the risk and likely outcome of a motor accident as many factors can be involved. Professional drivers have a much higher annual mileage than ordinary car drivers and a higher rate of driving mishaps overall. In the absence of scientific evidence, risk and hazard are gauged by the size of vehicle being driven, which is perhaps not unreasonable, given the potential consequences of a hypoglycemic person losing control of a large heavy vehicle. Before 2010 drivers with insulin-treated diabetes could not be issued with a Group 2 vehicle driving license except in (undefined) "exceptional circumstances," subject to (unspecified) authorized medical opinion and were debarred from driving Group 2 vehicles, with the exception of C1 vehicles (3.5 to 7.5 tonnes). However, in some European countries "exceptional cases" appeared to be the norm and the inconsistent application of EU regulations, inadequacy of assessment of medical fitness to drive, and lack of harmonization between states were very unsatisfactory. As these professional drivers were able to cross state borders and drive in countries with much stricter regulations for Group 2 driving licenses, this was politically unacceptable. The EU Regulations on driving have been relaxed and now allow all drivers with insulin-treated diabetes to apply for a Group 2 driving license, provided they meet strict criteria including having no episodes of severe hypoglycemia, normal hypoglycemia awareness, and undertaking frequent blood glucose monitoring at times relevant to driving (Annex III to European Directives 91/439/EEC and 2006/126/EC).

Oral antidiabetes medication is not a bar to holding a vocational driving license in the UK. In practice, however, many public transport companies restrict the employment of drivers with T2DM who take sulfonylureas; metformin or treatment with GLP-1 receptor agonists is not a contraindication, but medical assessment is usually necessary. Progression to insulin therapy usually terminates the employment of bus and train drivers. Taxi, ambulance and police pursuit drivers are not covered by the statutory regulations. In the UK, taxi licenses are issued by local authorities, which vary considerably in how medical fitness to drive is assessed, although many have now adopted Group 2 licensing standards. The employment of insulin-treated drivers in these other categories is determined by employers who usually seek advice from occupational health physicians.

Driving outside Europe

Outside Europe, the regulations in different countries range from a complete ban to no restriction other than a medical

examination for prospective or current drivers who require insulin [31]. Differences in approach between countries are influenced by the level of economic development and the prevalence of insulin-treated diabetes; many low- and middle-income countries impose no restriction on vocational driving licenses for people with insulin-treated diabetes [31]. The American Diabetes Association has published a position statement with valuable practical recommendations about how to evaluate risks to driving associated with diabetes in individuals, and how these should influence licensing decisions in the USA [32]. Drivers with insulin-treated diabetes are prohibited from driving commercial motor vehicles across state borders in the USA, but within most states, drivers with insulin-treated diabetes can drive commercial vehicles with the exception of lorries transporting hazardous materials and passenger-carrying buses [33].

In most other countries, insulin treatment alone is targeted by legislation, even though hypoglycemia can occur with other glucose-lowering drugs. A Canadian survey of crashes involving truck and commercial vehicle drivers with diabetes revealed an increase in risk for drivers with T2DM treated with sulfonylureas [34], the presumption being that unsuspected hypoglycemia is a causal factor. Similarly, an insurance-based study in the USA of people with T2DM treated with (unspecified) non-insulin therapies showed that those who had made claims for hypoglycemia had greater rates of motor vehicle accidents requiring hospital treatment [35], indicating that hypoglycemia-related mishaps also occur in people with T2DM who are not being treated with insulin.

Aircraft pilot licenses

Pilots with insulin-treated diabetes have been employed for several years by a Canadian commercial airline without any incidents, but in Europe pilots on insulin are not allowed to fly commercial aircraft. However, the UK Civil Aviation Authority, in collaboration with the Republic of Ireland Aviation Authority, is currently using an agreed protocol to certify individual pilots with insulin-treated diabetes to fly commercial aircraft, provided they meet strict medical fitness criteria and fly along with a co-pilot without diabetes. This trial will provide data for further consideration by the European Aviation Safety Agency, with the possibility of allowing certification of insulin-treated pilots in other EU countries. Private pilot licenses can be issued to individuals with diabetes treated with sulfonylureas (provided that they have a safety license endorsement), but not with insulin. People with insulin-treated diabetes cannot work as air traffic controllers.

Employment

With a few provisos, people with diabetes can successfully undertake a wide range of employment. There remains some prejudice against people with diabetes, but employment prospects in the UK and many other countries have improved with the introduction of legislation that makes it unlawful to treat a disabled person less favorably.

The main concern when considering people with diabetes for employment is the risk to safety associated with the condition or its treatment. Employers often fail to make the crucial distinction between a "hazard" (something with the potential to cause harm) and a "risk" (the likelihood that such harm will occur). The potential problems of diabetes relevant to employment are the hazards of acute hypoglycemia related to insulin and sulfonylureas, poor control of diabetes, and the development of serious diabetic complications that may affect ability to work or interfere with performance at work.

Employment is generally restricted where hypoglycemia could be hazardous to the worker with diabetes, their colleagues, or the general public. Employment-related issues, however, are not confined to people with T1DM. The rising prevalence of T2DM in the population of working age, along with the increasing use of insulin, has become an issue for occupational health assessment. Access to employment may be limited through discriminatory employment practices and restrictions posed by companies (rather than by legislation) because of perceived problems associated with diabetes or to job-sensitive issues related to the potential risks of hypoglycemia or to visual impairment. Diabetes can also affect employment through increased sick leave and absenteeism and by adversely influencing productivity. Diabetes in general has a negative long-term influence on the economic productivity of the individual; health-related disabilities can cause work limitations, especially in older employees in whom early retirement is more common on medical grounds.

A prospective survey in Edinburgh of 243 people with insulin-treated (mainly type 1) diabetes in full-time employment found that hypoglycemia occurred uncommonly at work (14% of all severe episodes) and had few adverse effects [36]. The study cohort, however, may have been subject to selection bias in terms of occupational diversity and many had suboptimal glycemic control; surprisingly few participants had impaired awareness of hypoglycemia. An internet survey of the effects of non-severe hypoglycemia in people with T1DM and T2DM in employment has suggested that work time and productivity are lost by around one in five people when hypoglycemia occurs at work, though such an uncontrolled study may be open to over-estimation of the magnitude of the problem [37].

For some occupations (e.g. train drivers) any risk of hypoglycemia is considered unacceptable. Elsewhere, the case for employment restrictions may be less clear-cut. Jobs that restrict the employment of workers with insulin-treated diabetes are listed in Table 58.3. People treated with insulin are not usually permitted to work alone in isolated or dangerous areas, or at unprotected heights. Shift-work is not necessarily a contraindication: one study in a car assembly plant found no difference in glycemic control between day and night-shift workers with diabetes, although control deteriorated if shift rotas were changed frequently [38].

In one British survey, the prevalence of diabetes in the workforce was 7.5 per 1000, including a lower-than-anticipated rate of

Table 58.3 Forms of employment from which people with insulin-treated diabetes are generally excluded in the UK.

Vocational driving
Large goods vehicles (LGV)
Passenger-carrying vehicles (PCV)
Locomotives and underground trains
Professional drivers (chauffeurs)
Taxi drivers (variable; depends on local authority policy)
Civil aviation
Commercial pilots and flight engineers (licensing currently under trial)
Aircrew (as above)
Air-traffic controllers
National and emergency services
Armed forces (army, navy, air force)
Police force
Fire brigade or rescue services (some exceptional cases)
Merchant navy
Prison and security services
Dangerous areas for work
Offshore: oil-rigs, gas platforms
Moving machinery
Incinerators and hot-metal areas
Work on railway tracks
Coal mining
Heights: overhead lines, cranes, scaffolding

Source: Data from Waclawski [38] and Waclawski and Gill [56].

2.6 per 1000 for people treated with insulin [39]. Employment is generally debarred in the armed forces, emergency work such as fire-fighting, civil aviation, jobs in the off-shore oil industry, and in many forms of commercial driving [39]. Workers with diabetes seldom conceal their medical condition from their employers, and any blanket policy that debars workers with diabetes from a specific occupation may be inappropriate or even discriminatory. Individual assessment is crucial, as employment regulations may not differentiate between different types and treatments of diabetes. Some bureaucratic regulations have been successfully challenged on medical grounds: for example, active fire fighters in the UK and a US air traffic controller were reinstated following appeals against dismissal.

In some cases, entering or persevering with a specific occupation may not always be in the individual's long-term interests (e.g. with the advance of disabling complications). This is clearly a difficult issue, which may require sympathetic medical counseling because of possible repercussions on the individual's income, self-esteem, future quality of life, and the financial support of dependants.

Unemployment, sickness and diabetes

According to a British survey, employers do not generally believe that diabetes per se limits employment prospects, because most workers with diabetes have few medical problems and can tackle a wide range of occupations [40]. Discrimination by employers, however, may affect hiring practices. Some British and Dutch surveys reported no apparent excess of unemployment among people with diabetes as compared with the general population [41–44], but other studies in the UK [45, 46] found that relatively more people with diabetes were not earning because of inability to work, intercurrent illness, early retirement or by being housewives. Although in many cases there was no apparent reason why an individual with diabetes could not obtain employment [46], depressive illness is strongly associated with unemployment and difficulties with work performance [47]. Adolescents with diabetes appear more likely than their peers without diabetes to lose jobs, or to fail to follow their desired occupation or cope with shift-work [48]. Reduced employment and income in workers with diabetes in North America have been related to disability, which was seven times more common than among a sibling control group, was mainly related to diabetic complications [49, 50], and was associated with lower employment income [51, 52]. Sickness absence rates among employees with diabetes are moderately to substantially higher than in workers without diabetes [53–56], which has economic and social consequences. Workers with insulin-treated diabetes and good glycemic control had fewer sickness absences than those with poor control [57]; poor control itself (HbA_{1c} >86 mmol/mol, 10%) is associated with a high rate of sickness absence [58].

Prison and custody

Imprisonment and short-term custody are unusual but troublesome life situations that can interfere with the management of diabetes. Hypoglycemia can occur if food is withheld after arrest, and may be confused with intoxication by alcohol or drugs. Diabetes is generally managed badly in prison because of the unsuitability of prison diets, lack of exercise, and the practical difficulty of using some insulin regimens (e.g. basal bolus); also, self-monitoring may be prohibited, and glucose to treat hypoglycemia may be unavailable during long "lock-up" periods. Most prison medical personnel have no specialist knowledge of diabetes and there may be no access to specialist supervision during custody.

Some prisoners with diabetes deliberately manipulate their treatment (e.g. by omitting insulin to induce ketoacidosis to have themselves removed to hospital which arguably offers a more amenable environment [59]). By contrast, treatment of intercurrent illness may be delayed by prison staff, who think that the prisoner is "misbehaving."

In some cases, withdrawal of alcohol, better dietary adherence and weight loss may actually improve glycemic control while in prison, and structured diabetic care can be provided effectively by an attending specialist physician [60, 61]. Facilities for people with diabetes in police custody are generally limited, with an inability to measure blood glucose, treat diabetic emergencies or to provide insulin and appropriate meals [62]. A Scottish liaison initiative between a specialist diabetes department and the local police force identified and successfully addressed deficiencies in

their custody facilities, including the provision of glucose monitoring equipment and the training of police staff [62]; this has been assisted by the development of a forensic nursing service.

Insurance

In many societies, insurance is viewed as essential to protect individuals and their families from the financial risk of unexpected events or illness, and insurance is often necessary to secure a financial loan, as for house purchase. People with diabetes are sometimes refused insurance or have to accept higher premiums and limited coverage, because the disorder is associated with reduced life expectancy, the risk of complications, and greater use of healthcare services. Several factors are important for insurance underwriting, including the severity and duration of the diabetes, the extent of diabetic complications and other concurrent medical disorders. It is reasonable for an insurer to be cautious in dealing with applicants who have poorly controlled long-standing diabetes and established complications.

There is wide variation in insurance terms and premiums among different European countries [63], in the USA [64] and even within the UK [65], which suggests that insurers work from assumptions about diabetes rather than using scientific evidence from actuarial studies. The presence of T1DM may be the only factor considered by insurers [64], and many still base potentially discriminatory decisions on outdated information that reflects the poor outcome of diabetes diagnosed and treated decades ago. There are no standardized guidelines, nor is there any uniformity in the approach to diabetes and insurance [65], although risk classifications for life insurance have been published [66]. Some companies do not accept applicants with diabetes, while others do so without financial penalty. People with diabetes seeking insurance cover should therefore request quotations from several companies, and should be supported by a medical assessment from a physician who is competent in the specialty. Many national patient organizations have negotiated favorable terms with insurance brokers and will provide details on request.

The prognosis of people with diabetes (particularly T1DM) has improved considerably during the last 50 years, and the impact of this on life insurance for people with T1DM has been analyzed in Scandinavia [67]. In the last 30–40 years, median life expectancy has increased by over 15 years, largely because of substantial reductions in diabetic nephropathy. It has therefore been suggested that life insurance in T1DM should focus entirely on the risk of developing diabetic nephropathy [68], and a model to calculate insurance terms has been proposed, based on current age, age at diagnosis, sex, presence of nephropathy or proliferative retinopathy and other pre-existing disease [67]. As the risk of developing new nephropathy falls after 25 years of diabetes, all people who reach the age of 50 years without nephropathy should have their insurance premium reduced. This approach has been adopted by most insurance companies in the Nordic countries, and by some in other European countries. To avoid penalizing people with diabetes, there must be regular updating of mortality and life expectancy data, and this information must be transmitted to actuarial advisers and insurance underwriters.

People with diabetes also face higher premiums for accident insurance, which is unjustified because there is no evidence that they have more accidents or permanent disability than the general population [69]. Neither is there any rationale for higher motor insurance premiums [64, 65, 70], particularly for those not treated with insulin, because no excess in road traffic accidents has been demonstrated (see earlier). A US study of the insurance cost of employees with diabetes showed that while healthcare expenditure was three times higher than all healthcare consumers, it was not more expensive than other chronic illnesses such as heart disease, asthma, and cancer [71].

Diabetes must always be disclosed to the insurer: concealing the diagnosis constitutes the withholding of a material fact, which nullifies the contract with the insurer and thus the insurer's liability in the event of a claim.

Alcohol

Many people enjoy drinking alcohol and diabetes should not be a barrier to social drinking. Accumulating data suggest that moderate alcohol consumption not only reduces the risks of developing T2DM but improves metabolic control and restricts diabetic complications. By contrast, alcohol can promote hypoglycemia and chronic excessive consumption may be deleterious both to long-term diabetes management and general health.

Alcohol consumption and risk of diabetes

Chronic high consumption of alcohol can predispose to the development of secondary diabetes. Alcohol has a direct toxic effect on the pancreas resulting in both acute and chronic pancreatitis. Diabetes complicates about 45% of cases of chronic pancreatitis (see Chapter 21). Insulin treatment is usually required to control hyperglycemia in people with chronic pancreatitis, although diabetic ketoacidosis is rare. This may be because the pancreatic damage also destroys the α-cells that secrete glucagon, which is an essential factor in ketogenesis (see Chapters 15 and 36). Insulin therapy can be particularly challenging in this situation, as many individuals with alcohol-related chronic pancreatitis have chaotic lifestyles, with poor diet and ongoing excess alcohol consumption. A heavy alcoholic binge, with concomitant low food intake, can result in alcoholic ketoacidosis.

By contrast, modest alcohol consumption appears to protect against T2DM, reducing risk by up to 30% [72, 73]. A J-shaped relationship has been observed between alcohol consumption and risk of T2DM (Figure 58.2). Moderate alcohol consumption is associated with enhanced insulin sensitivity, which may in part explain the relationship. The pattern of drinking behavior also appears to be important, with binge drinking associated with an increased risk of T2DM [74].

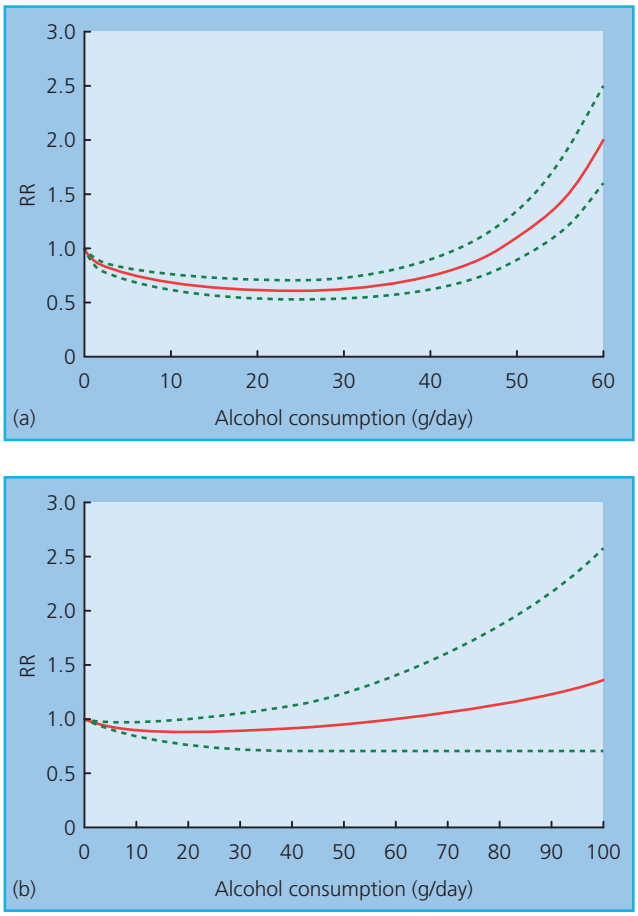

Figure 58.2 Relationship between alcohol intake and risk of diabetes in (a) women and (b) men. Solid lines represent the pooled and fitted relative risk estimates and the dotted lines are the 95% confidence intervals. Source: Pietraszek et al. 2010 [74]. Copyright 2010 Elsevier.

Alcohol and glycemic control

Hypoglycemia

Ethanol has marked metabolic effects on the liver, which metabolizes over 90% of an alcohol load. Gluconeogenesis is suppressed, even at blood alcohol levels that are not usually associated with intoxication [75–77], while the processes of recycling carbon as glucose and lactate between hepatic gluconeogenesis and muscle glycolysis [76] and fatty acid oxidation are also inhibited by alcohol. Thus, alcohol has the potential both to predispose to hypoglycemia and to inhibit glucose recovery. In individuals without diabetes, total hepatic glucose production is not reduced by alcohol, despite the inhibition of gluconeogenesis [77], and alcohol-induced hypoglycemia only occurs if hepatic glycogen stores are already depleted; for example, by fasting for at least 36 hours [78].

In people with diabetes, alcohol consumption may impede recovery from insulin-induced hypoglycemia. This effect is often delayed, occurring up to 24 hours after alcohol ingestion and may occur during the night or the following day [79]. Those with a deficient glucagon response to hypoglycemia (see Chapter 35) may be at greater risk, because they are unable to increase hepatic gluconeogenesis. The signs of hypoglycemia may be missed or mistaken for those of alcohol intoxication by the individual or by observers and even moderate alcohol consumption increases the cognitive impairment that occurs during hypoglycemia [80]. People with insulin-treated diabetes should be advised not to drink *any* alcohol before driving.

Overall, alcohol is an important contributory factor to many episodes of hypoglycemia in people with diabetes—an estimated 20% in one study [81]. Hypoglycemia-induced brain damage is rare, but when it occurs, it is often preceded by excessive alcohol consumption, which presumably promotes protracted neuroglycopenia. Severe hypoglycemia caused permanent neurologic damage after binge drinking in five alcoholic patients with insulin-treated diabetes, two of whom died [82].

Hyperglycemia

Excessive alcohol consumption is associated with central obesity [83], which may be a consequence of the adverse lifestyle factors that tend to accompany high alcohol intake. It should also be noted that alcohol provides 7 kcal energy per gram (1 unit = 10 g alcohol) in an easily consumable form and can therefore provide a substantial caloric intake, particularly as beer and lager. This is a commonly overlooked source of calories in obese, middle-aged men with T2DM, who are having difficulty in achieving weight loss by dietary means. The caloric content of spirits is much lower but may be augmented by adding sugar-rich mixers to drinks. Low-carbohydrate beers and lagers (such as Pilsner) have been marketed as being suitable for people with diabetes but should not be recommended because of their high alcohol content.

Heavy drinking has also been linked with poorer adherence to medications, outpatient follow-up, and self-blood glucose monitoring [84, 85]. Despite this, and the association with increased central obesity, excessive alcohol consumption does not appear to be associated with poorer glycemic control. Indeed, in most studies, there is a linear inverse relationship between glycemic control and alcohol consumption [74, 86]. However, people with very heavy alcohol consumption tend to be underrepresented in such studies.

Alcohol and diabetic complications

Moderate alcohol consumption in people with T2DM is associated with a 35% reduction in total mortality compared with non-drinkers (i.e. a similar magnitude to the effect of moderate alcohol on the risk of developing T2DM) [87] (Figure 58.3). These favorable effects of alcohol consumption may be a consequence of enhanced insulin sensitivity, lower blood pressure, and favorable changes in lipids and hemostatic factors [74]. These observations again do not include data on substantive numbers of very heavy drinkers and it is well established that excessive alcohol consumption increases serum triglyceride concentrations in

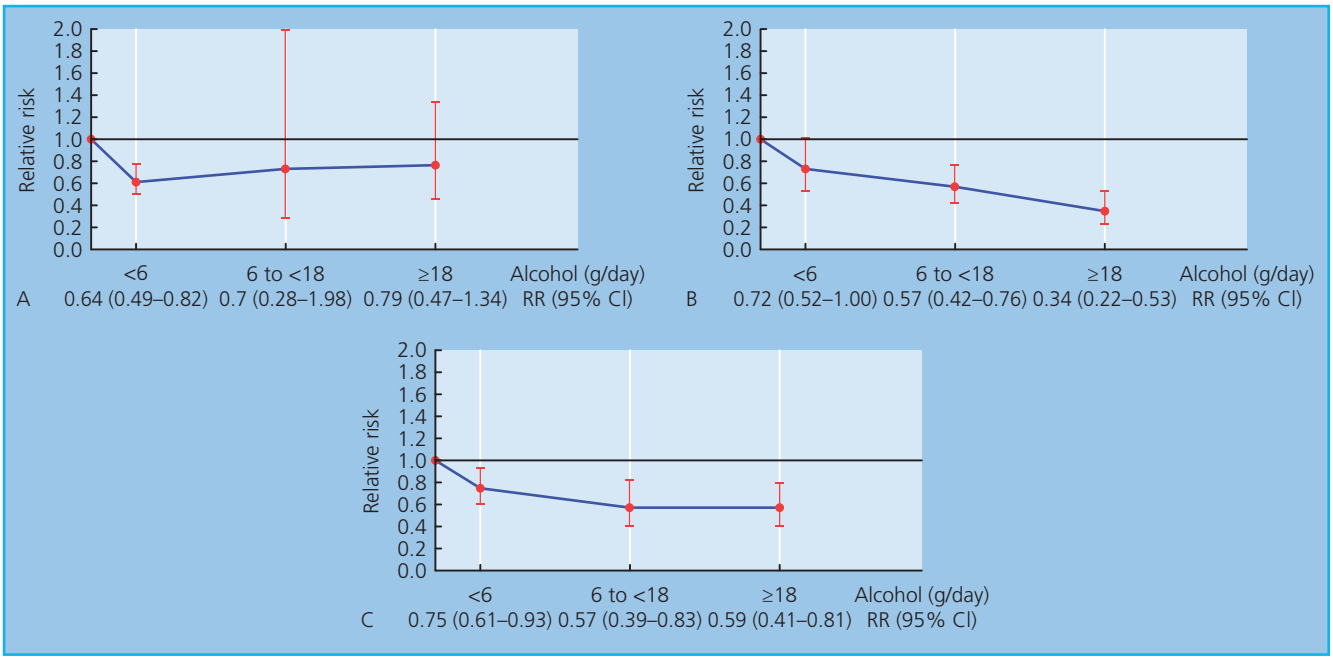

Figure 58.3 Pooled relative risk estimates (with 95% confidence intervals) of: (a) total mortality; (b) coronary heart disease mortality; and (c) coronary heart disease incidence for three alcohol consumption categories, with non-drinkers as the reference. Source: Koppes et al. 2006 [87]. Reproduced with permission of Springer.

susceptible individuals and raises blood pressure; excess alcohol consumption is an important cause of hypertension failing to respond to treatment (see Chapter 42). In the ADVANCE trial, mortality and risk of cardiovascular events was indeed higher in people with T2DM who drank more than the UK-recommended limits [88].

With regard to microvascular complications, a J-shaped relationship is observed between risk and alcohol consumption [89]. Moderate consumption (30–70 g/week) is associated with a 40% reduction in risk of proliferative retinopathy and neuropathy in T1DM, and over 60% reduction in risk for macroalbuminuria. Conversely, chronic excessive consumption of alcohol in people with diabetes is associated with peripheral neuropathy and exacerbation of neuropathic symptoms, erectile dysfunction, and increased risk of foot ulceration [90]. This may be in part a direct toxic effect of alcohol on the nervous system, though acute alcohol intoxication also impairs erectile function, while poor self-care and hygiene behaviors may contribute to the association between alcohol and foot ulceration.

Recommended alcohol intake

Recommendations for average alcohol intake in people with diabetes are comparable with advice given to the general population, that is, women with diabetes should drink no more than 2 units of alcohol per day and men no more than 3 units. General advice from Diabetes UK given to people with diabetes regarding alcohol is summarized in Table 58.4.

Recreational drugs

Use of recreational drugs is a serious problem in the general population, but can pose particular difficulties for people with diabetes [91]. The main classes of drugs involved are cannabis, amfetamine-type stimulants (including "ecstasy"), cocaine and opiates, with cannabis being the most commonly used drug by far.

Regulation

In the UK, drugs that are associated with dependence or misuse are regulated under the Misuse of Drugs Act, 1971. This Act specifies a classification system for drugs according to harm associated with misuse and specifies controls over manufacture, supply, and possession (Table 58.5). The list of drugs within each class can be amended by order of the Home Secretary. The Misuse of Drugs Regulations, 2001 define the classes of individuals who are authorized to supply and possess controlled drugs and lay down the conditions under which these activities may be carried out. Drugs are classified under five schedules, which specify the requirements governing import, export, production, supply, possession, prescribing, and record keeping. Cannabis and lysergide (LSD) are classified as Schedule 1 as they have no medicinal use, while opiates, cocaine and amfetamine are classified as Schedule 2 and are subject to full controlled drug requirements.

Table 58.4 General advice on alcohol for people with diabetes.

Moderate amounts of alcohol can be drunk shortly before, during or soon after a meal without affecting short-term blood glucose control and can be beneficial for the heart
Alcohol should never be drunk on an empty stomach as the alcohol will be absorbed too quickly
Alcoholic drinks should not be substituted for usual meals or snacks as this may cause hypoglycemia
Severe hypoglycemia can occur with larger quantities of alcohol, particularly when taken by people treated with insulin and especially if insufficient carbohydrate has been eaten
Hypoglycemia may occur up to 16 hours after heavy drinking
A hypoglycemic episode can be confused with being drunk. Tell people you have diabetes and wear some form of diabetes identification.
Check your blood glucose levels regularly; take treatment for hypoglycemia with you and have a starchy snack before going to bed.
Continuous heavy drinking can lead to raised blood pressure
All types of alcoholic drinks contain calories and may contribute to weight gain or failed dietary effort
Drinking alcohol can worsen neuropathy and aggravate associated symptoms
Drinking low carbohydrate beers and cider offer no benefit because of their higher alcohol content
Low alcohol wines are often higher in sugar than ordinary ones, so intake should be restricted
Mixer drinks should be "diet" or "sugar-free" such as diet tonic water and diet cola
Drinking and driving should be avoided.

Source: Adapted from Diabetes UK Website.

Table 58.5 Classification of controlled drugs.

Class A includes:*
Cocaine
Diamorphine (heroin)
Methadone
Methylenedioxymethamfetamine (MDMA, "ecstasy")
Morphine
Opium
Pethidine
Class B includes:
Oral amfetamines
Barbiturates
Codeine
Cannabis
Ketamine
Class C includes:
Most benzodiazepines
gamma-Hydroxybutyric acid (GHB)
Cathinone (Khat)
Zolpidem
Androgenic and anabolic steroids

Source: Data from UK Misuse of Drugs Act 1971.
* Includes Class B substances when prepared for injection.

Prevalence of recreational drug use

On a global scale, it is estimated that in 2012 between 3.5–7% of the world population aged 15–64 years (162–324 million people) had used illicit drugs at least once in the preceding year [92]. In England and Wales in 2013–2014, 8.8% of adults aged 16–59 years had taken an illicit drug in the preceding year, but this figure rose to 18.9% in adults aged 16–25 years [93]. Approximately one-third of adults have used recreational drugs at least once in their lifetime [93]. Trends in recreational drug use have changed over the years with a decline in the use of LSD and solvents and an increase in the use of amfetamine-type drugs and ketamine, particularly associated with the night-club and "rave" culture. Cannabis and powder cocaine remain the most commonly used illicit drugs in the UK. The Internet, and in particular the so-called "dark-net," has facilitated the manufacture, sale, and distribution of a plethora of new psychoactive chemicals. The rapid proliferation of these chemicals is a challenge for authorities, not the least in determining which should be subject to legal controls. Other legal drugs are also being used increasingly for their psychoactive properties, including nitrous oxide and salvia.

Data specifically about the use of recreational drugs by people with diabetes are sparse. Two uncontrolled questionnaire surveys of young adults with T1DM, one from the USA and one from the UK, have reported a similar prevalence and pattern of recreational drug use to that observed in the general population [94, 95]. In the UK survey, approximately 30% of respondents had used recreational drugs, with cannabis (28.2% of respondents), amfetamine-type stimulants (13%), and cocaine (12%) being used most commonly [95]. Many (15% of respondents) used more than one drug. A report from Chile has suggested that use of recreational drugs was lower in school-aged adolescents with T1DM than in the general population (9.6% vs. 22.2%), although this difference disappeared during later years at school [96]. In all studies examining prevalence of recreational drug use, underreporting by respondents is highly likely, related in part to fear of retribution.

Impact of recreational drug use on diabetes

In the Diabetes UK Cohort Study, acute metabolic complications (diabetic ketoacidosis and, to a lesser extent, severe hypoglycemia) were the most common causes of death in adults with T1DM under the age of 30 years, closely followed by accidents and violence [97]. In that study, a history of previous drug abuse was associated with a nearly sixfold increase risk of death from acute complications. More than 50% of young adults presenting with diabetic ketoacidosis to a tertiary referral hospital admitted to using recreational drugs; a history of recreational drug use was volunteered by only 20% on initial questioning [98]. Drug misuse has also been identified as a major cause of death in young people with T1DM [99]. Substance abuse co-occurring with mental illness is associated with a particularly high mortality [100].

Intravenous drug abuse

Recreational drug use often disrupts normal lifestyle and a person with diabetes may abandon the daily routine of regular meals

and insulin injections. Recreational drug use may also be only one aspect of a chaotic lifestyle associated with other high-risk behaviors. This can result from the use of any recreational drug, but intravenous drug abuse (particularly of opiates, but also amfetamines) is particular damaging and is strongly associated with poor social support, criminality, and mental illness. Intravenous drug use is uncommon in people with diabetes (as it is in the general population), but is associated with omission of insulin therapy, frequent admissions to hospital and high mortality, both from diabetic ketoacidosis and deliberate or accidental opiate overdose [101]. Unsurprisingly, intravenous drug abusers with diabetes may also present with complications related to the route of drug administration: deep venous thrombosis and abscesses at groin or limb injection sites. Intravenous drug abusers often default from outpatient clinic attendance (this may be associated with imprisonment) and maintaining contact with such individuals is usually difficult.

Cocaine and amfetamines

Cocaine and amfetamine-type stimulants can have dramatic effects on the cardiovascular system through activation of the sympathetic nervous system [102]. Cocaine is a sympathomimetic that inhibits reuptake of norepinephrine and dopamine at sympathetic nerve terminals. Amfetamine and ecstasy potentiate the release of norepinephrine, dopamine, and serotonin from the central and autonomic nervous systems. Cocaine toxicity may be potentiated by cannabis, while amfetamine toxicity is enhanced by alcohol. Drug-induced sympathetic activation leads to tachycardia, vasoconstriction and hypertension. Myocardial ischemia and infarction, supraventricular and ventricular tachyarrhythmias, and severe hypotension can all occur. Prolonged use can result in a dilated cardiomyopathy. The sympathetic activation produced by these drugs antagonizes the action of insulin and cocaine use has been identified as an independent risk factor for diabetic ketoacidosis [103]. The risk of diabetic ketoacidosis may be increased by the omission of insulin before discos and parties to avoid the potential risk and embarrassment of hypoglycemia.

Ecstasy is also associated with severe hyponatremia, secondary to a combination of inappropriate secretion of antidiuretic hormone, polydipsia, and a proximal renal tubulopathy [95, 98].

Ketamine

Ketamine acts as an N-methyl-D-aspartate receptor antagonist and so reduces excitatory neurotransmission. It induces a state of relaxation and dissociation ("K-land"), but hypertension, hyperthermia, tachycardia, and seizures can occur in severe intoxication. Ketamine can precipitate diabetic ketoacidosis, with a metabolic acidosis that is severe and disproportionate to the degree of ketosis. It can also be associated with metabolic acidosis without ketoacidosis and rhabdomyolysis [98].

Cannabis

Cannabis is not known to affect glucose metabolism but its effects on the central nervous system may increase appetite and impair recognition of hypoglycemia. Use of cannabis in low doses is associated with sympathetic activation and tachycardia; at high doses, parasympathetic activation may predominate, resulting in bradycardia and hypotension. In the absence of any structural heart disease, these effects are usually well tolerated.

Hypoglycemia

While the association between recreational drug use and diabetic ketoacidosis is well established, there are few data suggesting any association with hypoglycemia. Such drugs, however, are often taken in conjunction with alcohol and may be associated with poor oral intake of carbohydrate both of which will increase the risk of hypoglycemia. Moreover, amfetamine-like stimulants can induce frenetic behavior at night clubs and raves which can induce hypoglycemia in people treated with insulin [104]. The hallucinatory, or central nervous system, depressant effects of recreational drugs may impair an individual's ability to recognize and treat hypoglycemia. Furthermore, the sympathomimetic effects of cocaine and amfetamine-type stimulants may mimic the autonomic signs and symptoms of hypoglycemia.

Advice on recreational drug use in diabetes

Recreational drugs cause significant morbidity and are hazardous for people with diabetes. Their dangers must be emphasized to people with T1DM (particularly teenagers and young adults), but advice must be given in a sensitive and non-judgmental manner. When exposed to recreational drugs and alcohol, modest reductions in insulin dosage and regular consumption of carbohydrate-based snacks or non-alcoholic sugary drinks are required, particularly if strenuous dancing is to be undertaken. In such situations, significant dehydration can occur and water should be regularly consumed. Music festivals are increasingly popular and the ready availability of alcohol and recreational drugs pose additional risks due to the more prolonged nature of the events over several days, poor sanitation, limited food choices, and the potential for significant peer pressure. People with T1DM attending such events should be advised of the potential hazards and the need to moderate consumption of alcohol and recreational drugs, while maintaining a regular intake of food and non-alcoholic beverages. Regular monitoring of capillary glucose should be strongly advised, although the reality is that frequent monitoring is likely to fall by the wayside during the excitement of the event.

Travel

Diabetes should not be regarded as a bar to short- or long-distance travel, although careful planning may be required to avoid metabolic disturbances and other problems of diabetes that could have particularly serious consequences away from home. Diet and an adequate fluid intake may be disrupted while travelling or staying abroad, and local differences in climate, food, endemic diseases, and medical facilities may compromise

diabetes control. Blood glucose levels should be monitored frequently during travel and holidays, and people with diabetes must be able to take a pragmatic approach to deal with contingencies (e.g. loss of insulin, delays during travel) that could perturb their diabetes. Occasionally, specific diabetic complications or other medical disorders such as uncontrolled hypertension or ischemic heart disease can jeopardize health and safety during travel and periods away from home.

Preparation for travel

Personal identification

Travelers with diabetes should carry a doctor's letter stating the diagnosis and treatment, and ideally some other form of identification such as medical identification jewelry or tags (these contain personalized medical information and are recognized worldwide). These should also allay the suspicions of airline security, immigration and customs officials who discover syringes and drugs in luggage. Many national diabetes associations provide an identification card that shows the person's photograph, doctor's name and contact telephone number.

If a prolonged stay abroad is intended, it is useful to carry a prescription letter listing all medications (with generic names, as brand names often vary between countries), insulin-injection devices, and blood-testing items.

Insurance and medical care abroad

Comprehensive medical insurance is essential to cover accidents and illness that require medical assistance, and loss of medical equipment and drugs. The insurance policy must cover diabetes and other pre-existing medical conditions, as claims relating to these may otherwise be rejected. Most travel policies contain exclusions, which frequently include diabetes; a person with diabetes may not be covered for conditions such as a stroke or myocardial infarction for which diabetes is a recognized risk factor. When appropriate, insurance must be adequate to cover any dangerous sporting activities (when hypoglycemia could be particularly hazardous), and the costs of emergency air transport home in the event of a serious accident or illness.

Most countries in the EU provide emergency medical attention free or at reduced rates to visitors from other member states, although immediate payment for treatment may be demanded in some countries, such as France. Travelers from the EU can obtain a European Health Insurance Card (EHIC) in their home country, which confirms their entitlement to this scheme, although full medical travel insurance is still recommended. Some non-EU countries (e.g. Australia and Russia) offer free or reduced-rate medical care for EU members. In the USA, emergency medical treatment can be extremely expensive, and insurance premiums are correspondingly high. A list of insurers who do not load premiums against people with diabetes can be obtained from national diabetes associations.

Irrespective of medical insurance cover, it should be appreciated that emergency medical care available in some countries is suboptimal or even potentially dangerous for a diabetes-related emergency. In some parts of the world, insulin is not readily obtainable and intravenous fluids are in short supply. These considerations may influence the choice of holiday destination for people with diabetes.

Table 58.6 Checklist of essential items for travelers with insulin-treated diabetes.

Health checks
Diabetes "annual review"—if prolonged travel
Vaccinations
Visit GP for prescriptions, including possible antibiotics and anti-diarrheal agents
Documents
Diabetes identity card/bracelet
Document stating diagnosis and treatment; letter from insulin pump company regarding X-ray machines and scanners
Copy of repeat prescription
Medical insurance and EHIC
Insulin pump company care-line number
Insulin pump settings
Equipment
Insulin vials or cartridges (also required by those on pump therapy)
Syringes and needles/pens and spare pen needles
Flask or cool bag for insulin storage
Blood glucose meter; spare meter and batteries; ketone meter (if used)
Finger pricking device and spare lancets; container for used needles
Spare insulin pump, batteries and consumables
Hypoglycemia treatment
Quick-acting carbohydrate:
Glucose drinks (screw-top container; no more than 100 mL if flying)
Glucose tablets/confectionery
Slow-acting (complex) carbohydrate:
Biscuits or cereal bars

Drugs and equipment

Essential items for the traveler with diabetes are listed in Table 58.6.

- *Immunization.* Routine recommendations should always be followed for the relevant destination. Occasionally, a severe reaction to a vaccine may cause a temporary rise in insulin requirements.
- *Medication.* Air travelers treated with insulin should carry an ample supply in their hand luggage. Preferably, another supply of medication should be carried by a relative or friend in case of loss or theft. When travelling by air, medication and blood monitoring equipment should not be consigned to the hold, because of the risk of losing luggage and the deleterious effects of extremely low hold temperatures on the insulin. During travel, insulin can be carried in an insulated cool bag. Treatment for hypoglycemia should also be carried in the hand luggage; this is best in the form of dextrose tablets or sweets as the regulations on the amount of liquid that may be carried through airport security may pose difficulties.

- *Insulin pumps.* People using continuous subcutaneous insulin infusion should carry spare batteries for their pump, vials of long-acting insulin and syringes (or pens) as a back-up in case of pump failure and the contact details of the pump manufacturer so that a replacement can be ordered. Some insulin pump manufacturers will provide users with the temporary loan of a spare pump for a holiday. It is important that insulin pump users carry a written note of their insulin pump settings, including basal rates, bolus ratios, sensitivity factor, blood glucose targets, and active insulin time, as well as the consumable types and the pump serial number. Some insulin pumps should not be passed through X-ray security or body scanners as these may interfere with the electronic software in the pump; pump manufacturers will provide an explanatory letter, which can be shown to security staff. Insulin pumps can pass safely through security metal detectors. The delivery of insulin from a pump may be increased if the atmospheric pressure is reduced suddenly because bubble formation displaces insulin from the cartridge, and may provoke hypoglycemia. If cabin depressurization is severe, this could increase insulin delivery by as much as 8 units [105]. Even during normal ascent and descent, there can be slight increases and decreases respectively in the amount of insulin administered. Insulin pumps can also be targets for theft, as they may be mistaken for mobile phones or other electronic devices; it is important to check that travel insurance covers theft of the insulin pump.
- *Blood glucose and ketone monitoring.* Extremes of temperature and high altitude can disable some blood glucose meters and affect the accuracy of blood glucose test strips, although the cabin pressure of passenger aircraft (equivalent to an altitude of up to 8000 feet) should not pose problems [106]. While on holiday, it is sensible to carry a spare glucose meter (and blood ketone meter if used), test strips, and a replacement meter battery. If a new glucose meter is purchased overseas, it is important to remember that its default display could be in different units to the standard for an individual's home country, that is, mg/dL instead of mmol/L. Continuous glucose monitoring systems use wireless technology to link with a monitor or insulin pump device. This can be an issue for some airlines and current advice is that people with diabetes should discuss any medical devices that they intend to take on board an airplane with their airline.
- *Other considerations.* Those prone to motion sickness should take an anti-emetic to prevent nausea and vomiting from disrupting glycemic control. Antidiarrheal agents and a broad-spectrum antibiotic should be carried, particularly if travelling to regions with a high risk of acquiring gastroenteritis. People with peripheral sensory neuropathy should take comfortable and appropriate footwear for travel and for holiday use, as foot ulceration may be caused by wearing ill-fitting sandals or walking barefoot across rocks or even hot sand.

Long flights and crossing time zones

These pose several potential problems, ranging from the timing and composition of airline meals to ensuring that insulin dosages will cover the flight and adjust to local time on arrival.

Meals

Times of serving in-flight meals after take-off can usually be obtained from the airline. In-flight meals can be supplemented with a personal supply of suitable carbohydrate, but it is impractical to carry large quantities, not least because of the limits of what foods may be imported into many countries. Allowance may have to be made for delayed flights or long intervals between meals, while fatigue or travel sickness may blunt appetite.

Alcohol

Drinking alcohol before and during air travel is best avoided because of the risk of hypoglycemia; also, the diuretic effects of alcohol favor dehydration, which has been implicated in deep venous thrombosis and pulmonary embolism during long-haul flights (although diabetes does not appear to confer greater risk) [107]. Water or non-alcoholic sugar-free drinks should be drunk liberally.

Blood glucose

Blood glucose levels should be monitored frequently while in transit and when changing time zones. It is often safer to allow in-flight blood glucose values to be slightly higher than usual to avoid the risk of hypoglycemia.

Insulin treatment

There is no evidence-based information on how to adjust insulin dosages during flights that cross several time zones, and this probably accounts for the variability in the advice that is given [108]. Each case should be discussed individually, taking into account the duration of the flight and the change in time zone, the usual insulin preparations and dosages, the size and timing of meals, and the results of glucose monitoring. Some general guidelines are suggested in Table 58.7 and Figure 58.4.

Guiding principles are:

- Do not aim for strict blood glucose control while flying. A few hours of mild or moderate hyperglycemia will do no harm and, as long as glucose levels are monitored regularly, it is safer to reduce usual insulin dose and use small additional insulin dosages rather than risk hypoglycemia.
- Blood glucose levels should be checked every 2–3 hours.

Table 58.7 Management of diabetes during long-distance air travel.

Obtain advice from the diabetes clinic before traveling
Obtain essential information, including the local time of departure, flight duration, and local time of arrival
Inform the airline that you have diabetes, especially if treated with insulin
Carry extra supplies of carbohydrate
Anticipate that delays may occur
Time zone travel may necessitate two consecutive morning or evening insulin doses, before and after the flight
Ensure that you can monitor your blood glucose frequently during travel
Do not strive for meticulous control of blood glucose while traveling
Adjust insulin doses if necessary

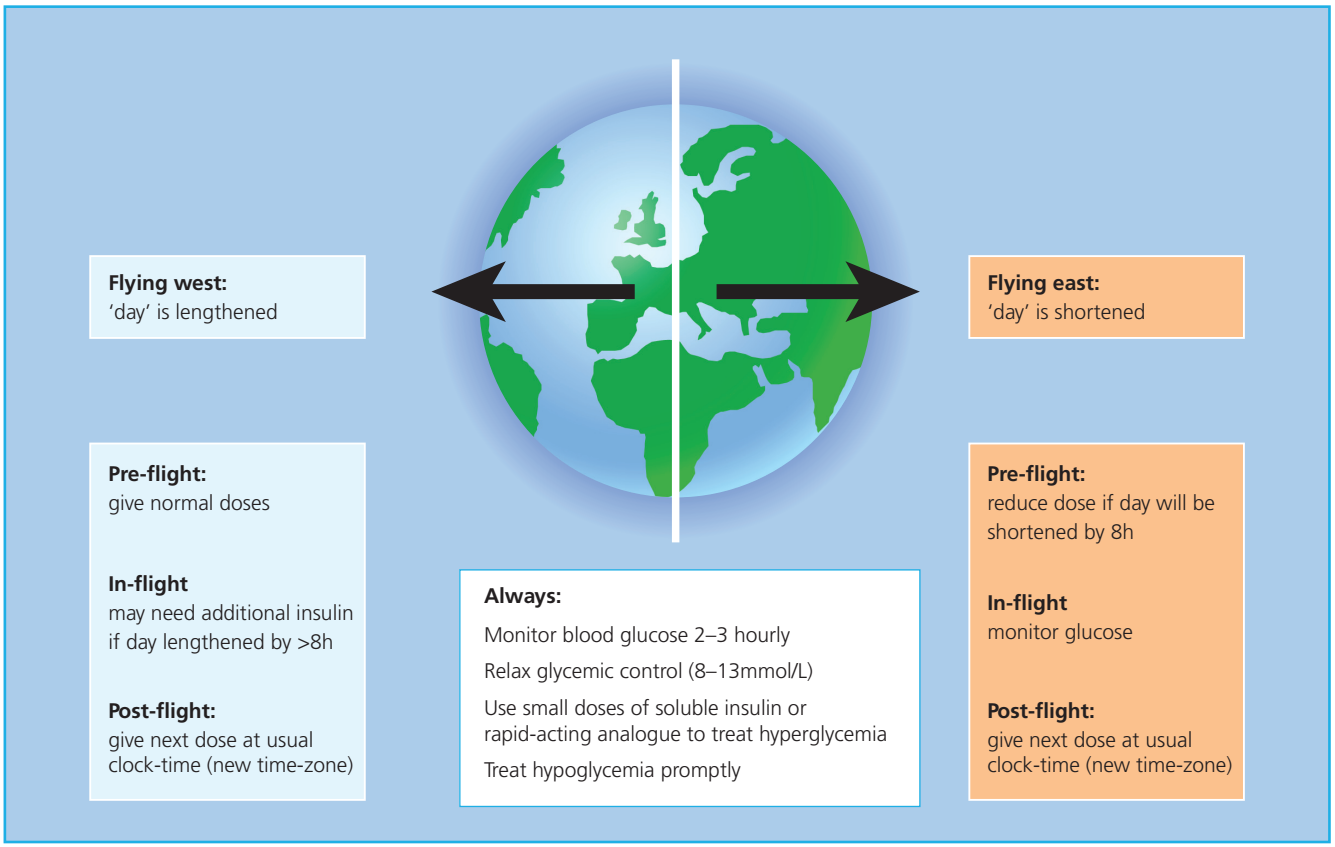

Figure 58.4 Scheme for adjusting insulin dosages during flights that cross time zones.

- Time changes of less than 4 hours in either direction usually need no major adjustment of the usual insulin schedule: simply give the next dose of insulin at its usual clock time, using the destination's time zone.
- Westward flights lengthen the "day." Give the next dose of delayed-acting or premixed insulin at its usual clock time (using the destination's time zone). If this injection is delayed by more than 12 hours, then additional insulin with food will be needed in the interim. The most convenient way to do this is with small doses (usually a few units) of soluble insulin or a rapid-acting analog, injected every 4 hours or so on the basis of blood glucose measurements.
- Eastward flights shorten the "day." The next dose of delayed-acting or premixed insulin should again be given at its usual clock time (destination time zone), but because this injection will effectively be earlier than usual, the previous dose of delayed-action insulin should be reduced if the interval between the injections is less than 12 hours.
- Extremely long flights with a time shift of 12 hours or more may require two "morning" or two "evening" insulin dosages to be injected consecutively, before and after the flight.
- Any additional insulin needed to fill in long gaps between delayed-action injections or to correct hyperglycemia is best given as small doses of soluble or a rapid-acting analog, ideally using a pen injection device.
- Travelling across time zones is generally easier to manage when using insulin pump therapy. The "temporary basal" feature can be helpful, depending on the length of the flight and activity levels, and it is easier to administer correction boluses. It is important to adjust the clock time on the pump to the local time, to ensure that the correct basal rates of insulin are being administered [109].

Oral antidiabetes agents

Additional doses are not usually required to cover an extended day.

Insulin treatment in hot climates

An individual's insulin requirements may change markedly in different countries, the main factors being differences in diet and daily physical activity. Subcutaneous insulin absorption can be accelerated by high ambient temperatures, such as in a sauna (see Chapter 29), and this effect has variable clinical significance in very hot climates.

Modern formulations are quite stable, but sometimes denature if exposed to high temperatures and shaken; in this case, discolored particles or a granular appearance (distinct from the normal cloudiness of delayed-action preparations) may be seen when the insulin is resuspended. Sometimes, there are no visible changes, but the insulin appears to lose its effect, with the usual dosages failing to lower blood glucose. Particularly in hot countries, insulin is

best stored in a refrigerator; if one is not available, insulin can be protected by a damp flannel or a porous clay pot containing some water or wet sand, placed in a cool part of the room. Even these measures may be unnecessary, as most insulin preparations can survive being kept at 25 °C or more for up to 6 months, and will retain most of their biologic activity [110].

Food and drink

When traveling abroad, it is essential to know the basic form of carbohydrate that is eaten locally, and useful to learn to judge quantities of foods such as pasta or rice. Items selected from local menus can be supplemented with bread, biscuits, or fruit. Sugar-free drinks are difficult to obtain in many countries but bottled water is safe and usually available.

Quick-acting carbohydrate to treat hypoglycemia should always be carried and stored appropriately: dextrose tablets may disintegrate or set hard in hot and humid climates unless wrapped in silver foil or stored in a suitable container, while the temperature-dependence of chocolate is well known. Cartons of fruit juice cannot be reused once opened; a plastic bottle with a screw top is preferable. Sealed packets of powdered glucose may be the best option for hot damp climates.

Traveling companions should carry a supply of quick-acting carbohydrate (and glucagon) for emergency use, and should know how to test the blood glucose and how to treat hypoglycemia.

Intercurrent illness

Any intercurrent infection should be treated promptly and appropriately, with adequate replacement of fluids and carbohydrate in the form of drinks if possible. Insulin therapy must never be discontinued and dosage may have to be increased, and blood glucose should be checked every 3–4 hours, with testing for urinary ketones if possible. The "sick-day" rules described in Chapter 29 should be followed.

Recreational activities

The impact of physical exercise and sport on diabetes is discussed in Chapter 26. People need advice about strenuous and unaccustomed exercise during holidays, such as beach sports or prolonged and vigorous dancing. Swimming alone should be avoided. The risks of alcohol and recreational drugs have been described earlier.

Leaving home

As a child with diabetes grows up, inevitably parental input to the day-to-day management of diabetes is reduced with increasing autonomy of the adolescent. In teenage years this is often manifest by a deterioration in glycemic control (Chapter 60). Even in adolescence, parents or guardians still have a very important role with the provision of regular meals and in the recognition and treatment of hypoglycemia, particularly at night. Therefore, the eventual move away from the parental home can pose problems, especially if the individual with T1DM is living alone and if they move to another town. Social isolation may exist until new friends are made and access to alcohol and recreational drugs may increase, with the attendant risks that have been highlighted. Sexual activity may commence or increase, introducing issues of sexual health and pregnancy, and novel forms of exercise may be more readily available. On leaving the parental home, individuals often become removed from the familiar support of the healthcare professionals in their local diabetes center and initially do not have the similar contact and immediate access to advice from doctors and nurses about diabetes, precisely at a time it may be most needed. It is a disturbing fact that "living alone" was associated with a more than fourfold increase risk of mortality from acute metabolic complications of diabetes in the Diabetes UK Cohort Study [98].

Students with diabetes

Particular emphasis has been placed on the welfare of students with T1DM who have left home to attend university or college. In part, this has been because of high-profile instances where individuals with T1DM have died shortly after commencing university [111]. Several surveys have suggested that students find diabetes more difficult to manage, although this does not necessarily translate into a rise in glycated hemoglobin concentrations [112–117]. Barriers to diabetes control include fear of hypoglycemia, diet, irregular schedules, lack of parental involvement, limited finances, recreational drugs, and alcohol. There is a natural desire for students with diabetes not to appear different from their peers and this may lead them to assign a lower priority to diabetes management than they would normally and to undertake potentially high-risk activities [118].

Diabetes services need to be responsive to the needs of adolescents and young adults who are leaving home. Such individuals are often poorly informed about the inherent risks associated with, for example, alcohol and drugs [95, 117] and these and other needs may not be addressed in the context of a routine diabetes consultation [116]. Before the individual leaves home, a formal re-education program should be offered in which alcohol, drugs, exercise, sex, and sick-day management are discussed [119]. Individuals leaving home need to think about their mealtimes; it can be difficult for someone living alone to motivate themselves to prepare substantial meals and many adolescents have limited cooking skills. Regular meals are provided in university halls of residence, but the nature and content of the food, particularly the carbohydrate content, may not be ideal. Students should be advised to monitor blood glucose levels frequently during examination periods. Many students report that studying and undertaking examinations can cause marked fluctuations in glucose levels; this may partly be associated with stress or varying carbohydrate intake. Both acute hypoglycemia and hyperglycemia impair cognitive function and can cause mood changes and may affect examination performance adversely. Therefore, students should try to optimize glucose control during examinations and ensure that a supply of rapid-acting carbohydrate is available during an examination.

Many students may prefer to remain under the care of their "home" diabetes team, but it is important that they know how to contact local specialist diabetes services in the university town for advice or assistance. Medical practitioners in university health services have a duty to ensure that students with diabetes are offered regular diabetes follow-up. The student should be encouraged to confide at an early stage with a reliable friend or colleague about their diabetes and the potential problems that may arise [119]. It may cause embarrassment talking to recent acquaintances about having diabetes. University authorities have a pastoral responsibility for students with diabetes [112].

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11 Diabetes in Special Groups

59 Diabetes in Childhood

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Key points

- An estimated 700,000 children have diabetes worldwide; 100,000 new cases are diagnosed annually; the incidence has been increasing by up to 5% annually, over decades.
- Type 1a (autoimmune) diabetes mellitus (T1aDM) accounts for almost all cases in children younger than 10 years, for >90% among older children of European ancestry, and for 20–70% of diabetes in children older than 10 years from other ethnic groups.
- The presence of two or more of the islet autoantibodies predicts the development of diabetes in those less than 10 years, in most cases; despite enormous research effort, prevention of T1aDM is still elusive.
- Diabetes in children is diagnosed based on polyuria, polydipsia, weight loss, fatigue, and random blood glucose >200 mg/dL (11.1 mmol/L). Oral glucose tolerance testing is rarely needed.
- Diabetic ketoacidosis (DKA) in a thin dehydrated child with Kussmaul breathing, abdominal pain, vomiting, and impaired neurologic status is present at diagnosis in fewer than 30% of cases in high-income countries today.
- There are significant differences in management of DKA in children, compared with adults, with the primary focus on prevention of cerebral edema.
- After diagnosis, childhood diabetes is managed in the outpatient setting by a team including a pediatrician specializing in diabetes, a diabetes nurse educator, a dietitian, a pediatric social worker, and/or a pediatric psychologist trained in childhood diabetes.
- In-depth initial and continuing education of parents and children in the self-management of diabetes is the cornerstone of lowering the risk of acute and long-term complications.
- Insulin pump or basal bolus multiple daily injections are the standard of insulin therapy in children.
- Nutrition planning should be based on carbohydrate counting or exchange system; the macronutrient and micronutrient composition of the diet is similar to that for healthy children without diabetes.
- While regular exercise is recommended for all children with diabetes, it requires careful planning of insulin and nutritional management to prevent severe hypoglycemia.
- Severe hypoglycemia is largely preventable, but is still the most common serious complication of childhood diabetes.
- Healthcare providers should equip families with the tools necessary to avoid dehydration, uncontrolled hyperglycemia or DKA, and hypoglycemia during routine infections.
- HbA_{1c} levels below 58 mmol/mol (<7.5%) are the target currently recommended and achievable by most children and adolescents; the gap between recommended and actual HbA_{1c} levels is the widest among adolescents.
- Age-specific psychologic care should include screening for and treatment of family dysfunction, developmental maladjustments, and communication problems, disordered eating and sleep patterns, as well as psychiatric disorders both in the children and their care providers.
- All children with diabetes should be screened at an appropriate age and duration of diabetes for dyslipidemia, microalbuminuria, elevated blood pressure, retinopathy, celiac, thyroid and Addison disease.

Spectrum of diabetes in children

In Europe and North America, 1 in 300 children develops diabetes by the age of 20 years. While the rates are lower elsewhere, there are an estimated 700,000 children with diabetes worldwide and 100,000 new cases are diagnosed annually. Diabetes is a heterogeneous disease at any age. Newborn babies and infants rarely develop the disease (1 in 250,000 in those younger than 6 months) and the etiology is not autoimmune, but usually monogenic (see Chapter 18). From the age of 9 months to 10 years, almost all diabetes is caused by islet autoimmunity (see Chapter 10). With the increasing prevalence of obesity in the general population, a significant proportion of children with T1aDM present with a phenotype that masquerades for T2DM. Measurement of autoantibodies to insulin, GAD_{65}, IA-2, and ZnT8 at diagnosis, C-peptide after the initial metabolic stabilization and HLA-DR,DQ typing may be necessary to assess appropriate long-term treatment.

Textbook of Diabetes, Fifth Edition. Edited by R. Holt, C. Cockram, A. Flyvbjerg and B. Goldstein.

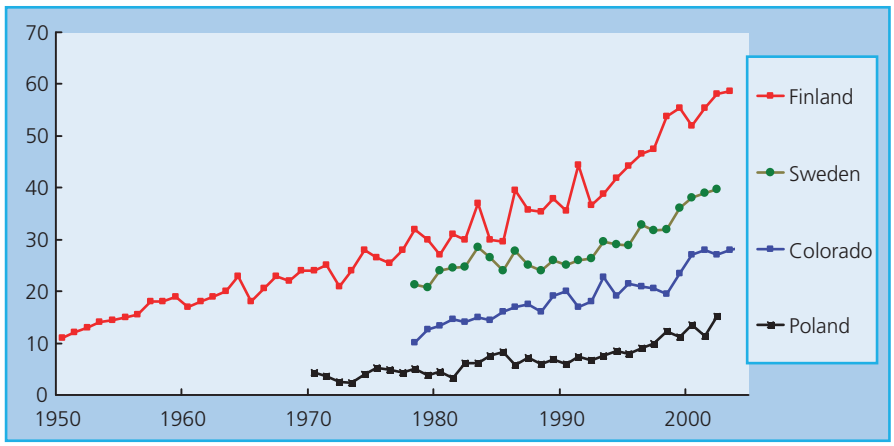

Figure 59.1 Incidence of T1DM has been rising about 3–5% per year.

This chapter focuses on the practical aspects of the management of T1aDM in children, while Chapter 60 addresses management of diabetes in adolescents and transition to adult care. For type 1b diabetes (clinical presentation as in T1aDM, but absent islet autoantibodies) and monogenic diabetes see Chapters 11 and 18, respectively. The epidemiology and etiology of T1aDM are addressed in Chapters 3 and 10, respectively. Briefly, T1aDM is caused by the interplay of genetic and environmental factors. The initial step—development of islet autoimmunity marked by the presence of islet autoantibodies—is believed to be driven by one or more environmental triggers [1]. Over the past 40 years, the incidence of childhood T1DM worldwide has increased by 3–5% annually (Figure 59.1). Elimination of the environmental trigger(s) responsible for this epidemic would be the most efficient approach to primary prevention; however, there is lack of consensus about which environmental factors initiate and promote islet autoimmunity. Efforts to prevent T1DM have been recently reviewed elsewhere [2]. After the initiation of islet autoimmunity, most people have a long preclinical period that offers an opportunity for secondary prevention of the progression to clinical diabetes. The presence of more than one of the autoantibodies combined with susceptibility HLA-DR,DQ genotypes identifies those at high risk of developing diabetes. There may be a "point of no return" in the autoimmune destruction of the islets, rendering some interventions effective only at the earlier stages of the process. Once tolerance is broken to more than one of islet autoantigens, most individuals progress to diabetes within 10 years. A period of mild asymptomatic hyperglycemia, detectable by oral glucose tolerance testing (OGTT) [3] or HbA_{1c} [4], may precede by months or years overt insulin dependence among those with islet autoantibodies. Intervention at this "dysglycemic" stage may also theoretically preserve endogenous insulin secretion and prevent the acute and long-term complications of T1DM. Preservation or regaining of residual insulin secretion after diagnosis of diabetes might also help, but the immunomodulatory agents used so far in tertiary prevention carry unacceptable long-term risks.

Manifestation, diagnosis, and initial treatment

Clinical presentation and diagnosis

The cardinal symptoms at the diagnosis of diabetes include polyuria (96% of children, often with nocturia or bed-wetting), polydipsia, weight loss (61%), and fatigue [5]. The classic presentation of diabetic ketoacidosis (DKA) in a thin dehydrated child with Kussmaul breathing, abdominal pain, vomiting, and impaired neurologic status affects fewer than 30% of cases presenting in high-income countries today [5, 6]. With the increasing community recognition of diabetes, most children present with milder hyperglycemia of shorter duration; however, 75% of the children (63% below age 5 years) have the symptoms for more than 2 weeks, suggesting that the diagnosis could be made earlier in many cases. A young child may have a less specific presentation, for example, with vomiting or rapid breathing during the course of an infection. Diabetes should always be considered in ill children; urine or blood testing for glucose and ketones leads to an early diagnosis and may prevent DKA and hospitalization. Nearly all children admitted with severe DKA have been seen hours or days earlier by healthcare providers who missed the diagnosis.

While most children do not require intravenous fluids or insulin infusion at the diagnosis of diabetes, many are hospitalized for a few days. These hospitalizations could be avoided if safe outpatient alternatives and adequate reimbursement existed for this initial care. For instance, the availability of a US outpatient care center has helped to decrease hospitalization at diagnosis from 88% in 1978–1982 to 46% in 1998–2001, with the proportion of hospitalizations secondary to DKA increasing from 44% to 63% [6].

The diagnostic criteria are the same in children and adults (see Chapter 2); however, most children are quite symptomatic and do not require an extensive work-up. In a symptomatic child, plasma glucose ≥11.1 mmol/L (200 mg/dL) at any time of day, without regard to time since the last meal, or fasting plasma glucose ≥7.0 mmol/L (126 mg/dL) is diagnostic. Blood glucose results

obtained using a glucose meter should be immediately confirmed in a laboratory, before the initiation of insulin treatment. By contrast, if marked hyperglycemia and blood or urinary ketones are present, treatment is urgent; waiting another day to confirm the diagnosis may be dangerous if DKA is allowed to develop. In a well child, the diagnosis must not be based on a single plasma glucose test or borderline results obtained using a glucose meter. In such cases, the authors check the HbA_{1c} level; if this is normal, further monitoring of the fasting and/or 2-h postprandial blood glucose is recommended for several days. In children progressing to overt diabetes, hyperglycemia after dinner is usually the initial abnormality detectable by self-monitoring of blood glucose at home. OGTT should not be performed if fasting, random, or postprandial criteria are met as it is unnecessary and excessive hyperglycemia can result.

Hyperglycemia detected incidentally or during acute infection, trauma or other illness may be transient, especially if typical symptoms of diabetes are absent or equivocal. Children with transient hyperglycemia may be more likely to develop diabetes, but the reported progression rates vary from 0% to 32%. Testing for islet autoantibodies helps to rule in diabetes in cases with mild presentation; however, it is important to consider that the quality of commercial assays for islet autoantibodies varies widely and testing for at least three autoantibodies (to insulin, $GAD_{65,}$ and IA-2) provides 80% predictive value.

The possibility of other types of diabetes should be entertained in children who have negative diabetes autoantibodies and any of the following features:

- diagnosis at <6 months of age,
- autosomal dominant family history of diabetes,
- mild fasting hyperglycemia which does not progress,
- associated syndromic features, or
- a history of exposure to drugs known to cause β-cell toxicity or insulin resistance [7].

Impaired glucose tolerance (IGT) and impaired fasting glucose (IFG) may also be detected in a child with islet autoimmunity progressing to overt diabetes [3]. OGTT is rarely needed in prepubertal children, however, except to reassure the family that a metabolic decompensation is not imminent. In older children, especially obese teenagers with equivocal symptoms, the OGTT may have a role in the earlier diagnosis of T2DM, IGT, and IFG.

Diabetic ketoacidosis

The clinical presentation of DKA includes abdominal pain, nausea, and vomiting which can mimic an acute abdomen. The children are mildly to moderately dehydrated (5–10%), may have Kussmaul respiration and become progressively somnolent and obtunded.

DKA results from absolute or relative deficiency of circulating insulin and a corresponding increase in the levels of counter-regulatory hormones, such as catecholamines, cortisol, glucagon, and growth hormone (see Chapter 36). This combination leads to a catabolic state with increased glucose production by the liver and kidneys, increased lipolysis, ketogenesis with ketonemia, and metabolic acidosis. Absolute insulin deficiency occurs in children with previously undiagnosed T1DM or in those with an established diagnosis through omission of or inadequate insulin regimens. Relative insulin deficiency occurs during acute illness and stress if the increase in counter-regulatory hormones is not balanced by an appropriate increase in insulin dosage. The severity of DKA is categorized by the degree of acidosis:

- Mild: venous pH 7.2–7.3 or bicarbonate <15 mmol/L
- Moderate: venous pH 7.1–7.2 or bicarbonate <10 mmol/L
- Severe: venous pH <7.1 or bicarbonate <5 mmol/L.

Diabetic ketoacidosis at diagnosis of diabetes

In the USA, in those diagnosed with T1DM and T2DM younger than 20 years, 29% and 10% of the cases, respectively, presented in DKA [6]. In Europe, the rates for T1DM cases ranged 15% to 67% correlating inversely with the local incidence of T1DM [8]. DKA is more often found among younger children and in children with lower socioeconomic status who encounter barriers in accessing medical care [6]. Intensive community intervention to raise awareness of the signs and symptoms of childhood diabetes among school teachers and primary care providers may help to reduce the prevalence of DKA at diagnosis [9].

Diabetic ketoacidosis in children with established T1DM

In a large cohort of children with established T1DM, on average, eight per 100 developed DKA every year [10]; however, nearly 60% of the DKA episodes occurred in 5% of children with recurrent events. Recurrent DKA was predicted by omission of insulin, poor metabolic control, intercurrent gastroenteritis with dehydration, psychiatric and eating disorders, difficult family or social circumstances or limited access to medical care, peripubertal/adolescent girls, and insulin pump therapy.

Treatment of ketoacidosis

Children with DKA should ideally be cared for in a unit with nursing staff trained in management of DKA in children, written guidelines for DKA management in children and access to a laboratory capable of providing frequent and timely biochemical results. Hydration status should be assessed and fluid deficit and osmolality calculated to help guide fluid and electrolyte replacement. Serum electrolytes, glucose, blood urea nitrogen, creatinine, calcium, magnesium, phosphorous and blood gas testing should be repeated every 2–4 hours or more frequently in severe cases. The calculations are shown in the Box 59.1.

Children with DKA have a 5–10% deficit in extracellular fluid volume which has developed slowly. Avoid rapid or overzealous fluid replacement. Initial volume expansion should occur over the first 1–2 hours with intravenous (i.v.) infusion of 10–20 mL/kg normal saline (0.9%) or Ringer solution. The bolus rarely needs to be repeated and should not exceed a total of 40 mL/kg over the first

Box 59.1 Calculations of Anion gap, corrected sodium and serum osmolality

Anion gap = $Na - (Cl + HCO_3)$

Corrected Na = measured Na + [(plasma glucose − 100 mg/dL)(1.6)/100]

Serum osmolality = 2(Na + K) + glucose/18 + Blood urea nitrogen/2.8(mOsm/L)

4 hours of treatment. Subsequent fluid deficit replacement should occur over the next 48 hours using $^1/_2$ to $^3/_4$ normal saline, in addition to electrolytes (see Box 59.2).

Once blood glucose concentrations reach 250 mg/dL (14 mmol/L), 5–10% dextrose should be added to the i.v. solution to maintain the blood glucose concentration between 150 and 250 mg/dL (8–14 mmol/L) and avoid saline overload and hyperchloremic acidosis.

Continuous i.v. insulin infusion (typically consisting of diluted regular insulin) at a dose of 0.05–0.1 units/kg/h should commence after the child has received initial volume expansion. An i.v. bolus of insulin is unnecessary and may increase the risk of cerebral edema [11]. The insulin infusion should allow for a gradual decrease in blood glucose concentration by 50–100 mg/dL/h. If the blood glucose levels decrease too quickly or become too low before acidosis has resolved, i.v. dextrose concentration may be increased to 12.5% to prevent hypoglycemia while continuing to correct the metabolic acidosis with insulin. Unless the child is truly hypoglycemic, the insulin infusion rate should not be decreased to less than 0.05 units/kg/h as this is likely to prolong the time needed to suppress ketogenesis. Bedside monitoring of blood ketones (β-hydroxybutyrate) is more helpful than blood gases in adjusting insulin and glucose infusion rates.

Total body potassium is usually depleted, but serum levels at presentation may be normal or high secondary to efflux of intracellular potassium into the extracellular space in the presence of acidosis. Once the serum potassium is found to be normal or low, and urine output is confirmed, i.v. fluids should include 20–40 mEq/L potassium in the form of K acetate, K_2HPO_4, or a combination of these. No more than half of the potassium replacement should be given as K_2HPO_4 because excessive phosphorous administration may result in hypocalcemia following the suppression of parathyroid hormone.

Similar to serum potassium levels, serum phosphorus levels may be initially elevated only to fall rapidly during treatment of DKA. Clinical problems resulting from low phosphorus levels have not been substantiated; however, severe hypophosphatemia (<1 mg/dL) should be treated. If hypocalcemia develops, administration of phosphate should be decreased or stopped.

Severe acidosis is reversible with fluid and insulin replacement. Bicarbonate therapy may paradoxically cause CNS acidosis and hypokalemia from rapid correction of acidosis and is a risk factor for cerebral edema. Bicarbonate therapy is not recommended unless the acidosis is profound (pH < 6.9) and likely to interfere adversely with the action of epinephrine during resuscitation. If bicarbonate is considered necessary, 1–2 mmol/kg can be cautiously administered over 60 min.

Box 59.2 Estimate of 24-hour maintenance fluid volume

Estimation based on age:
- 0–2 years = 80 mL/kg
- 3–5 years = 70 mL/kg
- 6–9 years = 60 mL/kg
- 10–14 years = 50 mL/kg
- >15 years = 35 mL/kg

Estimation based on body weight:
- 100 mL/kg for the initial 10 kg body weight, plus
- 50 mL/kg for the next 10 kg body weight, plus
- 20 mL/kg for each additional kg body weight

For example, a child weighting 30 kg needs 1000 + 500 + 200 = 1700 mL maintenance water for 24 hours or 70 mL/h, not counting past or ongoing losses

Cerebral edema

Cerebral injury is the major cause of morbidity and mortality in children with cerebral edema accounting for 60–90% of all deaths due to DKA while up to 10–25% of survivors have significant residual morbidity [11]. Neurologic status must be monitored at frequent and regular intervals. Subclinical cerebral edema occurs in most children with DKA. Severe clinical edema affects 0.5–1% of the children and is fatal in over 20% [12]. Typically, cerebral edema occurs at 4–12 hours, but has been reported as late as 24–28 hours, after the initiation of i.v. fluid treatment. Potential risk factors for symptomatic cerebral edema in children include:
- More profound dehydration, hyperventilation, and acidosis at presentation;
- Bicarbonate therapy;
- Excessive and rapid fluid administration, especially if initial serum osmolality is >320 mOsm/L;
- Failure of serum sodium to rise as hyperglycemia resolves; and
- Initial i.v. insulin bolus or too early initiation of insulin infusion.

Signs and symptoms of cerebral edema include headache, change in mental status or behavior, incontinence, focal neurologic findings, sudden normalization of heart rate in a previously tachycardic dehydrated child, or a worsening clinical course in a child with improved laboratory values. Bradycardia, hypertension and irregular respiration (Cushing triad) are signs of greatly increased intracranial pressure. Early intervention is essential. Treatment includes administration of mannitol (1 g/kg over 30 min), decreasing fluid rate to 75% or less of maintenance rate, and elevation of the head of the bed. Mannitol therapy may need to be repeated. Intravenous hypertonic saline has also been used as an alternative to mannitol. However, a recent 11-year retrospective cohort study suggests that hypertonic saline as a sole agent may be

associated with an increased risk of mortality [13]. Radiographic studies (such as head CT), if necessary, should be obtained after rather than during treatment of cerebral edema.

Frequent monitoring of blood glucose levels should prevent hypoglycemia. For acute hypoglycemic episodes while on continuous insulin infusion, the insulin infusion may be temporarily discontinued for up to 15 min if necessary.

Transition to subcutaneous insulin regimen

Children may be transitioned to an appropriate subcutaneous insulin regimen once DKA has resolved and they are able to eat. To prevent rebound hyperglycemia, the insulin infusion should not be discontinued until 15–30 min after the first subcutaneous injection of rapid-acting insulin has been administered. Long-acting insulin analogs achieve therapeutic levels able to replace insulin infusion 4–6 hours after the subcutaneous injection. Bedside monitoring of blood ketones helps to titrate insulin dose and prevent a relapse.

Hyperglycemic hyperosmolar syndrome

Hyperglycemic hyperosmolar syndrome (HHS) can occur in children, primarily in the setting of T2DM and is defined as:

- Plasma glucose concentration 600 mg/dL (>33.3 mmol/L);
- Venous pH > 7.25 or arterial pH > 7.30;
- Serum bicarbonate >15 mmol/L;
- Small urine ketones or absent to small blood ketones;
- Serum osmolality >320 mOsm/kg.

Presentation of HHS can have a more insidious onset than DKA, and polyuria and polydipsia may continue until profound dehydration occurs, with approximately 50% of cases having altered consciousness or seizures. Compared to DKA, children with HHS need greater amounts of fluids to avoid intravascular collapse, which contributes to the mortality seen in HHS.

Goals of HHS treatment include:

- Gradual decrease of sodium concentration, often by titrating the sodium content in fluids.
- Decrease in glucose of 90 mg/dL per hour (5 mmol/L per hour) or less, after first few hours of therapy (initial treatment with bolus fluids causes a greater fall in glucose initially, but this should not persist).
    - Insulin therapy is delayed until glucose is falling less than 50 mg/dL (3 mmol/L) per hour and should be initiated at 0.025–0.05 units/kg/h and adjusted to maintain a decrease in serum glucose of 50–75 mg/dL per hour (3–4 mmol/L).
- Monitor potassium every 2–3 hours and phosphate and magnesium every 3–4 hours. Treat hypokalemia, hypophosphatemia, and hypomagnesemia if they are present.
- Check creatine kinase every 2–3 hours to monitor for rhabdomyolysis.

Complications of HHS include venous thrombosis associated with use of central venous catheters, rhabdomyolysis, and malignant hyperthermia. Cerebral edema is rarely seen. Children can have a mixed picture of DKA and HHS, and in these cases typically more fluids are given than usual for DKA, and insulin is started sooner than in HHS, but treatment should be based on the individual clinical presentation [14].

Pediatric ambulatory diabetes care

Diabetes is primarily managed in the outpatient setting by a team including a pediatrician specializing in diabetes, a diabetes nurse educator, a dietitian, a pediatric social worker trained in childhood diabetes and/or a pediatric psychologist with knowledge of childhood diabetes and chronic illness. In communities with low population density and low prevalence of childhood diabetes, such a care team may not be available and care will primarily be provided by the child's primary care physician. In these instances, these physicians should work closely with and have access to a regional diabetes care team. When available, telemedicine utilizing two-way video-computer technology and local medical staff offers a way for more efficient and effective care from afar.

Healthcare providers and the diabetes care team must always be cognizant of and sensitive to the cultural needs and barriers to care that may arise with minority children of recent immigrants. Interpreters should be utilized when needed.

Initial education

Initial education should provide a basic understanding of the pathophysiology of diabetes and its treatment to ensure that families feel confident in providing diabetes care at home (Table 59.1) [15].

At many institutions, initial education at time of diagnosis occurs in an inpatient setting regardless of whether or not the child presents acutely ill in DKA. In some centers with appropriate outpatient resources, initial diabetes education and initiation of insulin therapy can occur in the ambulatory setting, which has been shown to be cost effective.

Continuing education

In the first 6 months following diagnosis, close contact in the form of frequent outpatient visits, home visits, telephone communication and other methods of communication is essential for

Table 59.1 Initial education curriculum.

An explanation of how the diagnosis was made and reason for symptoms
Discussion regarding normal blood glucose levels and targets, the need for immediate insulin treatment and its mechanism of action
Practical skills including how to draw up and administer insulin, blood glucose testing, blood and urine ketone testing
Basic dietary guidelines
Simple explanation of symptoms and management of hypoglycemia
Diabetes at school
Importance of medical alert identification
Psychologic adjustment to the diagnosis
Emergency telephone contacts

Table 59.2 Continuing education curriculum.

Insulin types, actions, and adjustments based on self-monitoring of blood glucose
Monitoring and treatment goals
Mechanisms for coping with and adjusting to the diagnosis of diabetes
Nutrition, including carbohydrate counting
Management of diabetes during illness
Management of hyperglycemia and ketosis and prevention of DKA
Prevention, recognition, and management of hypoglycemia
Exercise, travel and holiday planning
Microvascular and macrovascular complications of diabetes and their prevention
Up-to-date information on research in diabetes and new therapies and technologies in diabetes care
When age-appropriate, discuss diabetes and driving, smoking, alcohol, drugs, college, and employment

DKA, diabetic ketoacidosis

addressing the frequently changing requirements during this time (Table 59.2) [15].

Diabetes education is a continuous process and must be repeated to be effective. It must be adapted and appropriate to the age of the child. Infants and toddlers often have unpredictable eating and activity patterns. There is often more difficulty in distinguishing normal behavior from mood swings related to hypoglycemia or hyperglycemia. Needle phobia can present a significant issue with the perception of pain inflicted by the caregiver. Hypoglycemia is more common in this age group and the prevention, recognition, and management of hypoglycemia is a priority. School-aged children will have increased understanding and involvement with their diabetes management. Providers should address school-aged children directly in addition to speaking with their parents or care providers. Education includes monitoring of blood glucose levels and injections at school, particularly during meal times, exercise and extracurricular activities. There should be increased recognition and awareness of hypoglycemic symptoms. Education should also focus on age-appropriate stepwise handover of diabetes responsibilities. This becomes particularly important in adolescence during which there is a critical balance between promoting independent responsible management of diabetes while maintaining parental involvement.

Once established, it is common practice for children to be seen in the ambulatory setting at least every 3 months; visits should be more often if the child does not meet the treatment goals or intensifies treatment, for example, if insulin pump treatment is initiated. During these visits, overall health and well-being is assessed, growth and vital signs are monitored, and a physical examination is performed. There should be routine screening for diabetes-associated complications and comorbidities. Blood glucose records, including a check of HbA_{1c}, medications and school plans are reviewed. This will allow the insulin doses to be adjusted and provide a template for continued diabetes education. Age appropriate diabetes-specific knowledge should be assessed and reviewed.

The dietitian may review dietary habits and provide ongoing nutrition education as needed. The social worker or psychologist assesses and monitors psychosocial problems and family dynamics and the impact of diabetes care. At the conclusion of these visits, an individualized plan should be developed for each child and their family and a written copy of this plan should be provided.

The advent of new technology including downloadable glucometers, insulin pumps and continuous glucose sensors, and electronic smartphone apps has made it increasingly possible for the diabetes care team to gain insight into home management of diabetes; however, this should not replace self-monitoring and regular review of blood glucose data at home by the child and their family.

Diabetes management in school

Children with diabetes spend a significant portion of their day in school; therefore, diabetes management in school is a critical portion of their diabetes management plan [16]. The child has the right to receive adult support for diabetes care from school personnel during school hours, outdoor school activities and school-sponsored events away from school. School personnel must be trained to provide or supervise all diabetes care prescribed by the diabetes team, be supportive of providing diabetes care and encourage diabetes management during school hours, including:

- Insulin administration by injection or with an insulin pump;
- Testing blood glucose in young children and older, newly diagnosed children and adolescents until they are capable of performing the task independently; and
- Identification and treatment for hypoglycemia, both mild–moderate and severe.

Children with diabetes should have a school health plan in place. The health plan should include contact information for the child's family as well as their diabetes care providers. It should also contain information regarding routine management of diabetes (blood glucose monitoring, insulin administration and dosing, snack times) and an emergency plan for management of hypoglycemia and hyperglycemia. Issues specific to insulin pumps include remembering to activate insulin bolus with food, disconnecting the pump during vigorous exercise or in the event of severe hypoglycemia, pump failures, and pump alarms.

Extracurricular activities are an important component of a child's school experience and children with diabetes should be allowed to participate and their needs accommodated accordingly. Field trips, field days and overnight trips often require advanced planning, but a child's diabetes should never be a cause for exclusion from any school-sanctioned activity.

Insulin treatment

The overarching goal of insulin replacement is to provide just enough insulin at an appropriate time to provide sufficient basal

insulin levels as well as higher insulin levels after meals [17]. The choice of insulin regimen depends on the individual's age, duration of diabetes, dietary and activity patterns, ability to cope, and metabolic targets. Patient and family preferences should also be respected.

Subcutaneous insulin injection regimens

Injections regimens, in order of worsening HbA_{1c} outcomes, include:

- Basal bolus regimen: 40–60% of the total daily dose as basal insulin analog (e.g. glargine, detemir) in 1–2 doses a day with rapid-acting insulin analog 10–15 min before each meal; soluble human insulin is less preferable and requires administration at least 20–30 min prior to each meal.
- Intermediate-acting human insulin twice daily and soluble human insulin 20–30 min prior to each meal.
- Two injections daily of a mixture of short- or rapid- and intermediate-acting insulin before breakfast and before the evening meal.
- Three injections using some variation of the following: a mixture of short- or rapid- and intermediate-acting insulin before breakfast, rapid or soluble human insulin before the afternoon snack or evening meal, and intermediate or basal/long-acting insulin before bed.

Basal insulin analogs, include glargine, which lasts for 20–24 hours and detemir, which lasts between 6–23 hours and is often given as twice daily injections (see Chapter 29). Longer acting insulins include degludec, which can last up to 72 hours [18] and is currently only approved for adults in the USA. In Europe insulin degludec is licensed for children with diabetes aged 1–17 years old. Intermediate-acting insulins include NPH, which is often given twice daily, and have greater inter- and intra-individual variability than the long-acting insulin analogs. Common rapid-acting insulin analogs include aspart, lispro, and glulisine, which are given before a meal and to treat hyperglycemia. Regular human insulin is a short-acting insulin that has a longer onset of action and later peak of action, but is still used commonly in many places around the world.

Intermediate-acting insulins, such as NPH, are often mixed with soluble human (regular) or rapid-acting analogs (aspart, lispro, or glulisine). If children are using needles and syringes, in place of insulin pen devices, they and their families should be taught how to mix the insulin properly to avoid contamination. It is generally taught to draw up the clear (regular or short-acting) insulin before drawing up cloudy insulin (NPH). As per the manufacturer's instructions, glargine or detemir insulins should not be mixed with any other insulin.

Premixed insulins contain a mixture of regular (or rapid-acting) insulin and NPH insulin in various fixed ratios. These preparations may be useful for children who do not want to draw insulin from separate vials prior to injecting. They may also be useful in reducing the number of injections when adherence is an issue, especially among teenagers. Premixed insulins are also available for use in pen injector devices. The main disadvantage to using premixed insulin preparations is the lack of flexibility in adjusting the separate insulin doses, which is often necessary with varied food intake or during illness or exercise.

Insulin pump therapy

Insulin pump therapy is the best way to restore the body's physiologic insulin profile. The pump delivers a variable programmed basal rate that corresponds to the diurnal variation in insulin needs. Prepubertal children require a higher basal rate in the early part of night, while post-pubertal adolescents who experience the "dawn phenomenon" require higher rates in the morning.

The user initiates bolus doses before meals and to correct hyperglycemia. Most pumps can receive wireless transmission of test results from glucose meters, but the child or caregiver must still manually enter the amount of carbohydrate being consumed. The pump calculates the amount of insulin needed for a meal or correction based on previously entered variables, which include: insulin : carbohydrate ratios, insulin sensitivity factor, glycemic target, and duration of insulin action (set at 2–8 h to protect from accumulating too much insulin). The user may accept or override the suggestion.

Rapid-acting insulin analogs perform better in pumps than soluble human insulin, both in terms of mimicking the first-phase insulin release after meal and avoidance of postprandial hypoglycemia. Even with the analogs, however, insulin has to be administered at least 10–15 min before meal to reach effective levels in time. A longer lead time may be needed if pre-prandial blood glucose is higher than 150 mg/dL. Young children, picky eaters and those with lack of organization may struggle with these requirements. In addition, children are often unable to predict the size of the meal. In these cases, one may administer half of the usual meal bolus in advance, with the other half, if needed, after meal. Adherence problems include infrequent blood glucose testing, not reacting to elevated blood glucose, incorrect carbohydrate counting or missing boluses altogether.

Children and their families must be instructed on troubleshooting and treatment of hyperglycemia, particularly if ketones are present, as this may be an indication of a pump malfunction. If the flow of insulin becomes interrupted, ketonemia will develop within 4 hours; this is particularly dangerous at night as there is no long-acting insulin on board. Syringes or insulin pens should always be available so that insulin may be administered via injection in the event of a pump failure.

Most clinical trials have demonstrated better HbA_{1c} and less severe hypoglycemia with pump therapy, compared with multiple daily injections. Pump therapy can improve the quality of life in children who have trouble with injections or who desire greater flexibility in their lifestyle (e.g. with sleeping in, sports, or irregular eating). Insulin pumps can be particularly helpful in young children or infants who have multiple meals and snacks and require multiple small doses of rapid-acting insulin. The newer generation of insulin pumps can deliver as little as 0.025 units/hour, but higher rates using diluted insulin may be needed for uninterrupted flow.

Currently, the most frequent complications of insulin pump treatment include failures of insulin delivery because of a displaced or obstructed infusion set, local skin infections, and DKA. Insulin pump treatment is significantly more expensive than regimens based on injections. For some children, pumps may be too difficult to operate or follow the multiple testing and carbohydrate counting requirements, or may be unacceptable because of body image issues or extreme physical activity (e.g. swimming, contact sports) [16].

Continuous glucose monitors (CGM) have been used in children with pumps and on multiple daily injection therapy (see "Monitoring and goals of diabetes management" section later in this chapter). Sensor-augmented pump therapy linking CGM to pumps is currently available, and an automatic shut-off of a pump overnight to prevent hypoglycemia was recently approved and is in use. Fully "closed-loop" systems, allowing the insulin pump to be directed automatically by a continuous glucose sensor with minimal human input, are being tested [19].

Nutrition

Nutritional management in children with diabetes remains a key component of diabetes care and education; if available, a pediatric dietitian should be a part of the diabetes care team. A key strategy should be prevention of overweight and obesity. The management does not require a restrictive diet, just a healthy dietary regimen from which the children and their families can benefit. Current guidelines target optimal glycemic control, reduction of cardiovascular risk, psychosocial well-being, and family dynamics [20, 21]. A thorough dietary history should be obtained including the family's dietary habits and traditions, the child's typical meal times and patterns of food intake.

Weight loss or poor weight gain may be a sign of illness (such as infection, celiac disease, or hyperthyroidism), insulin omission, or disordered eating [22].

Insulin pump and multiple daily injections therapy utilize carbohydrate counting in which the grams of carbohydrate to be eaten are counted and a matching dose of insulin is administered. This plan allows for the greatest freedom and flexibility in food choices, but it requires expert education and commitment and may not be suitable for many families or situations (e.g. school lunches, teenagers). Books and apps are now available to help calculate carbohydrate intake more accurately. Exchange planning teaches that it is not necessary to count precise grams. Exchanges are taught as either 10- or 15-g servings of carbohydrate. The exchange plan can enable a more consistent daily intake of carbohydrate. The constant carbohydrate meal plan was used often in the past with insulin regimens based on NPH and regular insulin, where carbohydrate intake and the amount of insulin were kept relatively constant from day to day. It has been perceived as too restrictive and a potential source of conflict.

The use of the glycemic index has been shown to provide additional benefit to glycemic control (see Chapter 25). Low glycemic index carbohydrate foods, such as wholegrain breads, pasta, temperate fruits, and dairy products may lower postprandial hyperglycemia. A glycemic load approach to predicting the postprandial blood glucose response, based on the glycemic index of the food and the portion size, has not been fully explored in children. Regardless of which meal plan is chosen, helpful principles are shown in Table 59.3.

Table 59.3 Principles of dietary planning in children with diabetes.

1. Eat a well-balanced diet, with daily energy intake distributed as follows:
   - Carbohydrate 50–55% (sucrose intake up to 10% total energy)
   - Fat 30–35% (up to 20% monounsaturated fat; <10% polyunsaturated fat; <10% saturated fat and trans fatty acids; n-3 fatty acids 0.15 g/day)
   - Protein 10–15%.
2. Eat meals and snacks at the same time each day, if possible.
3. Use snacks to prevent and treat hypoglycemia, but avoid overtreatment:
   - Young children often have a mid or late morning snack
   - Most people will have a mid or late afternoon snack
   - Many children require a bedtime snack, particularly if the bedtime blood glucose is below 130 mg/dL (7 mmol/L) or if they have been active during the day.
4. Gauge energy intake to maintain appropriate weight and body mass index:
   - Overinsulinization, "forced" snacking and excess food intake to prevent or treat hypoglycemia promote excessive weight gain and should be avoided
   - Eating disorders are common in teenagers with diabetes, particularly girls.
5. Recommended fiber intake for children older than 1 year: 3.3 g/MJ; children older than 2 years should eat = (age in years + 5) g/day fiber.
6. Avoid foods high in sodium that may increase the risk of hypertension; target salt intake to less than 4 g/day (sodium chloride).
7. Avoid excessive protein intake (athletes should not require protein supplements).
8. Children with diabetes have the same vitamin and mineral requirements as other healthy children; however, hypovitaminosis D is common and screening and supplementation are recommended.
9. There is no evidence of harm from an intake of artificial sweeteners in doses not exceeding acceptable daily intakes.
10. Specially labelled diabetic foods are not recommended because they are not necessary, are expensive, are often high in fat and may contain sweeteners with laxative effects. These include the sugar alcohols such as sorbitol.
11. While alcohol intake is generally prohibited in youth, teenagers continue to experiment with and sometimes abuse alcohol. Alcohol may induce prolonged hypoglycemia in young people with diabetes (up to 16 hours after drinking). Carbohydrate should be eaten before, during and/or after alcohol intake. It may be also necessary to lower the insulin dose, particularly if exercise is performed during or after drinking (e.g. dancing).
12. Approximately 10% of children with type 1 diabetes have serologic evidence of celiac disease. Those with positive intestinal biopsy or symptomatic have to be treated with a gluten-free diet. Products derived from wheat, rye, barley, and triticale are eliminated and replaced with potato, rice, soy, tapioca, buckwheat, and perhaps oats. While most of the children are asymptomatic, the long-term consequences of untreated celiac autoimmunity may warrant a gluten-free diet.

Age-specific advice

Breastfeeding in infants should be encouraged. Insulin pump therapy should be considered, particularly in children who require very small doses of insulin. Toddlers are often picky eaters and are more likely to eat frequent smaller meals throughout the day; their insulin regimen should match this eating pattern. Food refusal can be a significant source of distress, particularly if an insulin dose has already been administered. In school-aged children, meal plans may need to be adjusted depending on the school schedule. Food intake among teenagers is often chaotic. Breakfasts are skipped and binges may happen at any time of day or night. Weight loss or failure to gain weight may be associated with insulin omission for weight control and may be indicative of a disordered eating behavior. While insulin pump or multiple daily injections treatment may help some, simplification of the management plan to avoid extreme mismatches between food intake and insulin are sometimes the only viable option.

Exercise

Children with diabetes derive the same health and leisure benefits from exercise as children without diabetes and should be allowed to participate with equal opportunities and equal safety [23]. Physiologically, during exercise in children without diabetes, there is a decrease in pancreatic insulin secretion and an increase in counter-regulatory hormones resulting in an increase in liver glucose production (see Chapter 24). This matches skeletal muscle uptake of glucose during exercise, maintaining stable blood glucose concentrations under most conditions. In children with T1DM, there is no pancreatic regulation of insulin in response to exercise and there may be impaired counter-regulation. These factors combine to increase the risk of hypoglycemia and hyperglycemia during exercise. It is helpful to keep an exercise record noting the most recent insulin dose, timing and type of exercise, blood glucose levels before and after exercise, snacks eaten and the time of any episode of hypoglycemia.

Factors affecting a child's response to exercise include:

- Duration, type, timing and intensity of activity;
- Overall metabolic control and ambient blood glucose level;
- Type and timing of insulin injections and its absorption;
- Type and timing of food;
- Muscle mass and conditioning; and
- Degree of stress/competition [23].

Preventing hypoglycemia

Blood glucose levels should be checked before, during, and after the exercise. Children should consume carbohydrates prior to exercise, with the amount depending on the blood glucose level prior to exercise and the duration and intensity of exercise. For short duration activity, sports drinks with simple sugars provide optimal absorption and usually prevent hypoglycemia for the next 30–60 min. For activity of longer duration, solid foods containing carbohydrates are digested more slowly and should be consumed in addition to a liquid with simple sugars. Extra snacks should always be available to the child during exercise. The child's coaches and teammates or other responsible adults and peers should be aware of the signs and symptoms of hypoglycemia. Often, children will require adjustments to their insulin dosing when exercise is anticipated. The site of insulin injection should also be taken into account. Exercise increases blood flow in the part of the body being used, increasing insulin absorption if that area is where the insulin injection was administered. For example, prior to running the insulin dose should not be administered in the legs.

Insulin adjustments

For exercise anticipated within the first hour after eating, the dose of rapid-acting insulin before the meal may need to be decreased by 25–75% (depending on the intensity of the exercise). For evening exercise, reduction of the evening meal rapid-acting insulin by 25–75% as well as ingesting 10–15 g of fast-acting carbohydrate before the activity can help avoid hypoglycemia. For day-long activities (such as camps, hiking, or skiing), consider a 30–50% reduction in the long-acting insulin dose (or in the basal rate if using an insulin pump) the night before and on the day of the activity. For children using insulin pumps, there are numerous options for insulin adjustments with exercise. If the pump will be worn during exercise, a reduction of the basal rate by 20–50% starting 90 min before activity and lasting until the end of exercise can help to avoid hypoglycemia. For day-long activities, the basal rate can be reduced by 30–50% during the day of and the night after activity [23]. For some types of activities (e.g. contact sports), children may need to disconnect from the pump and do one of the following:

- Bolus part of the basal insulin to be missed prior to exercise (particularly if the pre-exercise blood glucose level is elevated) and the remainder after exercise;
- Bolus half of the insulin missed while disconnected after exercise;
- Bolus all of the insulin missed while disconnected after exercise.

In general, the pump should not be disconnected for longer than 2 hours. If necessary, the pump should be reconnected briefly and a bolus administered prior to disconnecting again.

New technologies with low glucose suspend may help with decreasing risk of hypoglycemia during and after activity.

Delayed hypoglycemia

Hypoglycemia can occur up to 24 hours after exercise secondary to increased glucose transport into the skeletal muscle, the late effect of increased insulin sensitivity, and the delay in replenishing liver and muscle glycogen stores. Blood glucose levels must be monitored for several hours following exercise, at bedtime and sometimes during the night on days with strenuous exercise. Consider a longer lasting snack (containing a solid carbohydrate, protein, and fat) at bedtime and reducing the insulin dose as discussed earlier.

Ketones and exercise

In situations of poor insulin intake or increased insulin resistance, whether it be from poor glycemic control or from illness, exercise may be dangerous because of the effect of uninhibited action of the counter-regulatory hormones. Children with diabetes should not participate in strenuous exercise if the pre-exercise blood glucose level is high (250 mg/dL, >14 mmol/L) and urine ketones (small or more) or blood ketones (≥0.5 mmol/L) are present. Treat ketones and postpone exercise until ketones have cleared.

Hypoglycemia

Hypoglycemia is the most common acute complication in the treatment of T1DM and responsible for a significant proportion of deaths in people with diabetes aged under 40 years of age (see Chapter 35) [24]. Blood glucoses of <60–70 mg/dL (<3.3–3.9 mmol/L) are considered to place an individual with T1DM at risk of severe hypoglycemia. A threshold value of 70 mg/dL (<3.9 mmol/L) is used as the value for identifying and treating hypoglycemia in children with diabetes because of the potential for glucose levels to drop further [24]. Severe hypoglycemia happens to one in five children every year on average, but 80% of the events occur among the 20% of children who have recurrent events [6]. Younger age, longer diabetes duration, barriers in access to care, and presence of psychiatric disorders or chaotic family environment increase the risk. While lower HbA_{1c} is generally a risk factor for hypoglycemia, appropriate intensive insulin treatment can lower the risk by improving timing of insulin in relationship to food intake and exercise [25].

Signs and symptoms

- *Autonomic signs and symptoms:* shakiness, palpitations, sweatiness, pallor.
- *Neuroglycopenic signs and symptoms:* difficulty concentrating, blurred or double vision, disturbed color vision, difficulty hearing, slurred speech, poor judgment and confusion, problems with short-term memory, dizziness and unsteady gait, loss of consciousness, seizure, death.
- *Behavioral signs and symptoms:* irritability, erratic behavior, nightmares, inconsolable crying.
- *Non-specific symptoms:* hunger, headache, nausea, tiredness.

Early warning signs and symptoms of hypoglycemia are much more difficult to identify in young children.

Treatment

In mild or moderate symptomatic hypoglycemia, after documenting a blood glucose of ≤70 mg/dL (3.9 mmol/L):

- Provide immediate oral, rapidly absorbed 5–15 g glucose or sucrose: glucose tablets, "Smarties" or 4 oz (100 mL) of sweet drink (juice, soda).
- Retest blood glucose in 10–15 min, if no response or inadequate response—repeat as above.

As symptoms improve and euglycemia is restored, ingest solid snack or meal (e.g. fruit, bread, cereal) to prevent recurrence.

- Retest blood glucose in 20–30 min to confirm that target glucose has been maintained.

In severe hypoglycemia, where the child has an altered mental status and is unable to assist in their care, may be unconscious and/or seizing, urgent treatment with parenteral glucagon or dextrose is required.

Glucagon

Glucagon is given intramuscularly or subcutaneously (10–30 μg/kg body weight):

- 0.5 mg for those <12 years
- 1 mg for those older than 12 years or heavier than 100 lb (45 kg).

Glucagon injection may be repeated in 5–10 min, if response was inadequate; however, it is likely to be ineffective after prolonged fasting. Side effects include vomiting and tachycardia.

Dextrose

Dextrose can be given intravenously by trained medical staff if glucagon is unavailable or recovery is inadequate in a hospital setting or by paramedics:

- Intravenous dextrose should be administered slowly over several minutes (e.g. dextrose 10% at 2–3 mL/kg).
- Rapid administration or higher concentration may result in an excessive rate of osmotic change, phlebitis and extensive tissue damage, if extravasated.

Close observation and monitoring of blood glucose is essential because vomiting is common and hypoglycemia may recur. Severe headache and transient paresis lasting up to 24 hours are not uncommon but generally do not require radiologic work-up.

Hypoglycemia unawareness

Hypoglycemia unawareness occurs when there is reduced awareness of the onset of hypoglycemia. A single hypoglycemic episode can lead to hypoglycemia unawareness secondary to a decrease in counter-regulatory responses, but it is usually seen in children who have multiple periods of blood glucose <70 mg/dL. Avoiding subsequent hypoglycemia for 2–3 weeks may reverse this loss of awareness.

Prevention

Hypoglycemia occurs more frequently

- when the treatment regimen or lifestyle is altered (increased insulin, less food, more exercise);
- in younger children;
- with lower HbA_{1c} levels;
- with previous severe hypoglycemia;
- when there is hypoglycemia unawareness;
- during sleep; or
- after alcohol ingestion.

Children and families should be aware of the above risk factors so that glucose monitoring and insulin regimens can be changed accordingly. There is an increased risk for hypoglycemia during,

immediately after, and up to 24 hours after exercise. Untreated celiac disease and Addison disease may also increase the risk of hypoglycemia.

Nocturnal hypoglycemia is often asymptomatic and should be suspected if the morning blood glucose is low and/or there are episodes of confusion, nightmares, or seizures during the night, or if there is impaired thinking, altered mood or headaches upon awakening. Nocturnal hypoglycemia can be confirmed with blood glucose monitoring during the night and may be prevented by including more protein and fat in the bedtime snack. Care should be taken that this does not occur at the expense of high overnight blood glucose levels.

Studies have shown an association between hypoglycemia and decrease in cognitive functioning in children with T1DM, particularly in children diagnosed before the age of 5–6 years. Recurrent severe hypoglycemia has been associated with worsened long-term memory, attention, and verbal IQ, but studies have been inconsistent. Severe hypoglycemia can increase parental and patient's worry, poor sleep, emergency room visits, hospitalizations, excessive lowering of insulin doses and subsequent worsening of glycemic control. Long-term follow-up of the Diabetes Control and Complications Trial (DCCT) participants has been reassuring that there was no evidence for permanent neurocognitive changes related to hypoglycemia in adolescent and young adult individuals, suggesting that the effect of severe hypoglycemia on long-term neuropsychological functioning may be age-dependent [26].

Ultimately, hypoglycemia is frequently predictable and should be prevented. Children and their caregivers must be taught to recognize the symptoms of hypoglycemia and treat this immediately and appropriately. Children with diabetes should always carry around a source of rapid-acting glucose and should wear identification noting that they have diabetes. The diabetes care provider should be notified if a child is having recurrent episodes of symptomatic hypoglycemia or if there is hypoglycemia unawareness. This will facilitate discussions to adjust insulin regimens, food intake patterns, blood glucose goals and monitoring. Continuous glucose monitoring helps to detect and to avoid hypoglycemia.

Sick-day management

Children with diabetes in good metabolic control should not experience more illness or infections than children without diabetes; however, they will go through their share of routine infections, which can be challenging for their caregivers. The influenza vaccine and other routine childhood immunizations are recommended for all children with diabetes. When children with diabetes become ill, the underlying precipitating illness should be treated promptly.

Healthcare providers should equip families soon after diagnosis with the tools necessary to avoid dehydration, uncontrolled hyperglycemia or ketoacidosis, and hypoglycemia. Face to face education and written instructions are important, but most parents require telephone advice when first facing sickness in their child and some may need repeated support. Over time, most parents should be able to manage sick days independently as well as identify appropriate times when to seek help from their diabetes provider or emergency services. Children and their families should immediately seek medical attention if:

- blood glucose concentrations continue to rise despite extra insulin;
- blood glucose concentrations remain persistently below 70 mg/dL (3.5 mmol/L);
- blood ketones are higher than 1.5 mmol/L or ketonuria is severe and persistent; or
- the child becomes exhausted, confused, dehydrated, or develops difficulty in breathing, severe abdominal pain, or a severe hypoglycemic reaction.

Missed insulin injection, inactivated insulin or interruption of insulin delivery from pump may lead to "sick days" as well, especially in older children. While treatment is essentially the same as for hyperglycemia in the course of an infection, the differential diagnosis is important for prevention of recurrent events.

Hyperglycemia is seen in many illnesses, particularly those associated with fever, as a result of elevated levels of stress hormones, which promote gluconeogenesis and insulin resistance. Severe illness increases ketone body production secondary to inadequate insulin action or insufficient oral intake of carbohydrates. By contrast, illnesses associated with vomiting and diarrhea can lead to hypoglycemia secondary to decreased food intake, poor absorption, and slower gastric emptying.

In general, during illness, blood glucose concentrations must be monitored more frequently—at least every 3–4 hours and more often when blood glucose concentrations are outside the target range (e.g. 80–200 mg/dL). Urinary or blood ketones must be checked at least twice daily and always when blood glucose concentration exceeds 300 mg/dL (17.6 mmol/L). If available, the authors recommend testing blood ketones (β-hydroxybutyrate, using, for example, Precision Xtra/Exceed meter) over urine ketone testing as a more specific and timely marker of ketosis:

- The presence of ketones when blood glucose concentrations are persistently elevated above 200 mg/dL (11.1 mmol/L) indicates the need for supplemental insulin and fluids.
- The presence of ketones when blood glucose concentrations are low or normal, especially during gastrointestinal illness, indicates insufficient oral intake of carbohydrates (starvation ketones). In this case, ketones do not reflect insulin deficiency, but rather a physiologic response and may protect the child patient from severe hypoglycemia as β-hydroxybutyrate is the only alternative fuel to glucose for the brain. Supplemental insulin is contraindicated as it will likely cause hypoglycemia; the correct treatment includes fluids with glucose.

Insulin therapy must never be stopped during a sick day, although the dose may need to be decreased if the child is vomiting or eating less than usual. A fasting child still requires approximately 40% of the usual daily insulin dose, as long-acting

basal insulin, to cover basic metabolic needs and prevent ketoacidosis; however, infections associated with normal food intake often require an increase of basal insulin by 10–15%. In addition, extra doses of rapid-acting insulin are usually needed to correct hyperglycemia, prevent ketoacidosis and avoid hospital admission. These doses may be repeated every 2–4 hours as needed based on the results of blood glucose and ketone monitoring.

With blood glucose concentrations greater than 200 mg/dL (11.1 mmol/L), the authors recommend:

- Usual high blood glucose correction (e.g. 1 unit of rapid-acting insulin for each 50 mg/dL above 100 mg/dL, if blood ketones <0.6 mmol/L or urine ketones negative/small;
- Injection of rapid-acting insulin in the amount of 10% of the total daily dose, if blood ketones 0.6–1.5 mmol/L or urine ketones are moderate or large;
- Injection of rapid-acting insulin in the amount of 10–20% of the total daily dose if blood ketones >1.5 mmol/L or urine ketones are moderate or large;
- As acidosis is present in most children with hyperglycemia and blood ketones >3.0 mmol/L, this warrants referral to an emergency department.

Children using insulin pumps who develop hyperglycemia and moderate or large urine ketones (or ≥1.0 mmol/L blood ketones) must always take into consideration the possibility of an interruption in insulin delivery. If blood glucose levels do not decrease appropriately after an insulin bolus from the pump, the correction bolus of short-acting insulin should be given as injection by pen or syringe and the pump infusion set should be changed. A temporary increase in the basal rate by 20% or more may be required until blood glucose concentrations begin to normalize and ketones clear.

If hypoglycemia <70 mg/dL (<3.9 mmol/L) persists and the child is unable to tolerate any oral intake, an injection of low-dose glucagon may reverse the hypoglycemia and enable oral fluid intake to resume. Glucagon is mixed as usual but given using an insulin syringe with the dose being one unit per year of age up to 15 years [27]. Upon mixing with water, glucagon remains stable for at least 48 hours at 4 °C. The small dose of glucagon can be repeated every 2–4 hours; however, it is likely to be less effective with prolonged fasting. This dose of glucagon is not to be used for the emergency treatment of severe hypoglycemia.

Hydration status must be followed closely. Fever, hyperglycemia with osmotic diuresis, and ketonuria all increase fluid losses. Households should maintain a supply of sugar and electrolyte-containing fluids:

- Oral water is sufficient to prevent dehydration in uncomplicated cases of hyperglycemia.
- If there is an ongoing fluid loss from diarrhea or vomiting, hydration liquids should contain salt in addition to water (e.g. Pedialyte, Rehydralate). These preparations contain 25–30 g/L glucose, 45–90 mEq/L sodium, 30 mEq/L bicarbonate, and 20–25 mEq/L potassium. Oral rehydration fluid can be made at home by mixing half of a flat teaspoon of salt (~3 g of NaCl = ~50 mEq sodium), 7 teaspoons of sugar (28 g), and (optionally) 100 mL (4 oz) of orange juice into 1 L water.
- If there is difficulty eating or keeping food down and the blood glucose is falling below 200 mg/dL (11.1 mmol/L), sports drinks should be administered. They contain less electrolytes but higher amounts of glucose (e.g. Gatorade contains 255 g/L glucose, 20 mEq/L sodium, 3 mEq/L bicarbonate, and 3 mEq/L potassium).
- If the blood glucose is falling below 100 mg/dL (5.6 mmol/L), fluids with higher concentration of sugar are recommended (e.g. juice or non-carbonated regular soda containing approximately 70 g glucose per 100 mL). These fluids contain almost no sodium and are not appropriate in large amounts for children with diarrhea.

The required volume of oral fluid replacement is the sum of maintenance volume, deficit and ongoing losses. In practical terms, infants and toddlers with diabetes who vomited more than twice or have multiple loose stools should be referred to an emergency department for evaluation and intravenous fluids. Those with milder symptoms can be given oral fluid therapy at home using small amounts (5 mL) of cold fluids every 5 minutes. Most children with vomiting can be successfully orally rehydrated with persistent gentle encouragement of parents.

Antiemetic medication at home is generally contraindicated, especially in young children, as it may mask acute abdominal processes such as appendicitis, volvulus or intussusception and may have significant adverse effects. Ondansetron can be used to contain vomiting in children properly evaluated by a physician and selected older children presenting without abdominal pain.

Monitoring and goals of diabetes management

Glycated hemoglobin (HbA_{1c}) is the only measure of mid- to long-term glycemic control for which robust outcome data are available (see Chapter 27). Elevated HbA_{1c} predicts long-term microvascular and macrovascular complications but has its limitations. In the DCCT, an HbA_{1c} of 53 mmol/mol (7.0%) corresponded to a higher average blood glucose concentration (measured seven times a day) of 192 mg/dL in the conventionally treated participants compared with 163 mg/dL in those in the intensively treated group. Consequently, the same HbA_{1c} level conferred significantly higher risk of microvascular complications and hypoglycemia in the conventionally treated group compared with the intensively treated group [19]. HbA_{1c} is only one of the measures of optimal glycemic control, with other measures including documented hypoglycemia, type of treatment, patient's age, and quality of life. Ideally, there should be four to six measurements per year in younger children and three to four measurements per year in older children.

Self-monitoring of blood glucose (SMBG) provides immediate and daily documentation of hyperglycemia and hypoglycemia, helps to determine immediate and daily insulin requirements and detects hypoglycemia and assists in its management. Blood

glucose is best measured during the night, after the overnight fast, before meals, 2 hours after a meal—typically 4–6 times a day. Blood glucose should also be measured in association with illness, exercise, and prior to driving a car. The frequency of SMBG is associated with improved HbA_{1c} in people with T1DM [19]. Patient acceptance of SMBG may be enhanced by including the opportunity for testing alternative sites in addition to the fingertips (e.g. the palm of the hand or the forearm); however, as alternative sites may be slower to reflect falling blood glucose, the fingertips should be used if there is concern for hypoglycemia based on symptoms or its presence using alternative sites for measurement.

A logbook or some type of electronic memory device has to be used to record patterns of glycemic control and adjustments to treatment. The record book is useful at the time of consultation and should contain time and date of blood glucose reading, insulin dosage, together with a note of special events (e.g. illness, parties, exercise, menses, hypoglycemic episodes, and episodes of elevated blood or urine ketones).

At present, the safest recommendation for glycemic control in children is to achieve the lowest HbA_{1c} that can be sustained without severe hypoglycemia, frequent moderate hypoglycemia, or prolonged periods of significant hyperglycemia where blood glucose levels exceed 250 mg/dL (14 mmol/L). Each child should have targets individually determined. Targets for HbA_{1c} and SMBG recently proposed by the International Society for Pediatric and Adolescent Diabetes (ISPAD) [19] are summarized in Table 59.4.

Table 59.4 Biochemical targets of glycemic control. These targets are intended as guidelines, each child should have their targets individually determined.

Level of control	Optimal	Suboptimal	High risk
HbA_{1c}			
DCCT standardized (%)	<7.5	7.5–8.9	≥9.0*
IFCC (mmol/mol)	<58	58–74	≥75
SMBG mmol/L (mg/dL)			
Fasting or pre-prandial blood glucose	4–8 (70–145)	>8 (>145)	>9 (>162)
Postprandial blood glucose	5–10 (90–180)	10–14 (180–250)	>14 (>250)
Bedtime blood glucose	6.7–10 (120–180)	<6.7 (<120) or >9 (>162)	<4.4 (<80) or >11.1 (>200)
Nocturnal blood glucose	4.5–9 (80–162)	<4.2 (<75) or >9 (>162)	<4.0 (<70) or >11.1 (>200)

DCCT, Diabetes Control and Complications Trial; IFCC, International Federation of Clinical Chemistry; SMBG, self-monitoring of blood glucose.
* DCCT conventional adult cohort had a mean HbA_{1c} value of 8.9% (74 mmol/mol), both DCCT and Epidemiology of Diabetes Interventions and Complications (EDIC) have shown poor outcomes with this level.

Continuous glucose monitoring

Sensors are available and in development that measure interstitial fluid glucose every 1–5 min (i.e. "continuously"). Currently, these devices are expensive, may not be available in many countries, and insurance coverage is limited. Over time, it is anticipated that these devices will become the standard of care in children with T1DM. The continuous glucose results are available to the user in real-time and are stored in the receiver device or pump for downloading to a computer at a later time. The download allows the child and healthcare professional to review the results and make appropriate and educated insulin dosage adjustments. This much more sophisticated approach to SMBG may allow targets to be determined so that an alarm will alert the wearer to a glucose value projected to fall below or above the preset target and inform insulin delivery from a pump. As continuous glucose monitoring becomes more widely used, decreased blood glucose targets may be more safely achieved in children with diabetes.

The average HbA_{1c} is lowest in the youngest age group, perhaps reflecting the more complete caregiver involvement at younger ages. Of all age groups, adolescents are currently the farthest from achieving HbA_{1c} <58 mmol/mol (<7.5%), reflecting the diabetes mismanagement that frequently accompanies the increased independence in diabetes care during the adolescent years, as well as the effect of psychological and hormonal challenges of adolescence. Goals that are too ambitious may lead to an unwarranted sense of failure and alienation of the teenager with diabetes. As diabetes technology improves, especially continuous glucose monitoring, recommended target indicators for glycemic control will likely decrease to reflect a new balance of benefits and risks.

Healthcare providers should be aware that achieving an HbA_{1c} consistently below the target range without extensive personal and national healthcare resources and outside of a clinical trial structure may be very difficult. As a benchmark, intensively treated adolescents in the DCCT achieved a mean HbA_{1c} of 65 mmol/mol (8.1%), compared to 54 mmol/mol (7.1%) in adults. Older well-educated DCCT participants with excellent access to the newest diabetes technology maintained HbA_{1c} of 62–66 mmol/mol (7.8–8.2%) during 12 years of follow-up in the Epidemiology of Diabetes Interventions and Complications (EDIC) study [28].

Psychological care

The diagnosis of T1DM changes the lives of affected families and poses lifelong challenges. Children with T1DM are at risk for adjustment disorder during the initial period after diagnosis (Chapter 56). Those with adjustment disorder are also at increased risk for continued psychological concerns. Young people with T1DM are more frequently diagnosed with and treated for psychiatric disorders, disordered eating, neurocognitive and learning problems, family dysfunction and poor coping skills than the

Table 59.5 Psychologic care recommendations for families of children with T1DM.

1	Resources should be made available to include professionals with expertise in the mental and behavioral health of children and adolescents within the interdisciplinary diabetes healthcare team. Mental health specialists include psychologists, social workers, and psychiatrists.
2	Mental health professionals should be available to interact not only with children and families at clinic visits to conduct screening and more complete assessments of psychosocial functioning, but also to support the diabetes team in the recognition and management of mental health and behavior problems.
3	There should be easy access to consult psychiatrists for cases involving severe psychopathology and the potential need for psychotropic medications.
4	All mental and behavioral health specialists should have training in diabetes and its management.
5	The interdisciplinary diabetes healthcare team should maintain regular, consistent and uninterrupted contact with children and their families. When clinic visits are missed or not frequent, other modes of contact such as phone, texting, or e-mail should be made available
6	Assessment of developmental progress in all domains of quality of life (i.e. physical, intellectual, academic, emotional and social development) should be monitored routinely.
7	Routine assessment should be made of developmental adjustment to and understanding of diabetes management, including diabetes-related knowledge, insulin adjustment skills, goal-setting, problem-solving abilities, regimen adherence, and self-care autonomy and competence. This is especially important during late childhood and prior to adolescence when in many families the child may take on diabetes management responsibilities without adequate maturity for effective self-care.
8	Identification of psychosocial adjustment problems, depression, eating disorders and other psychiatric disorders should be performed at planned intervals and by appropriately trained mental health professionals. These assessments are particularly important in young people not achieving treatment goals or who exhibit chronically poor metabolic control.
9	The interdisciplinary team should assess general family functioning needs (conflict, cohesion, adaptability, and parental psychopathology) and diabetes-related functioning (communication, parental involvement and support, and roles and responsibilities for self-care behaviors) especially when there is evidence of cultural, language, or family problems.
10	The interdisciplinary team should aim to provide preventative interventions for patients and families (including training parents in effective behavior management skills) at key developmental times, particularly after diagnosis and prior to adolescence. These interventions should emphasize appropriate family involvement and support (i.e. teamwork) in diabetes management, effective problem-solving and self-management skills, and realistic expectations about glycemic control.
11	Evidence-based psychosocial, behavioral, or psychiatric interventions should be made available for patients or families exhibiting conflict, disordered communication, behavioral or psychiatric difficulties, or adherence problems affecting glycemic control. Developmental needs of children and adolescents should be considered while planning interventions incorporating social, emotional, and tangible support.
12	In counselling young people and parents regarding advances in diabetes management, and encouraging the intensification of insulin regimens, motivational interviewing may be useful. This may help in clarifying patient and parental goals and resolve ambivalence about regimen intensification. Patients should not be denied access to regimen intensification based on perceptions of limited competence, as even youth with low self-management competence have been shown to improve with intensive insulin therapy.
13	Adolescents should assume increasing responsibility for diabetes management tasks but with continuing, mutually agreed parental involvement and support. The transition to adult diabetes care should be discussed, negotiated, and carefully planned with adolescents, their parents, and the adult diabetes team well in advance of the actual transfer to adult care.

general population. The psychological care recommendations of the ISPAD [29] are summarized in Table 59.5.

Screening and early treatment of risk factors for complications and associated conditions

Dyslipidemia

Cardiovascular disease (CVD) is a leading cause of morbidity and mortality in adults with T1DM. Preclinical atherosclerosis often starts in childhood. While children with T1DM generally have a favorable lipid profile, this remains a major modifiable CVD risk factor in this population. Screening for dyslipidemia in children with T1DM should commence after diagnosis, once glycemic control has been established, in those older than 10 years of age. Screening should start at the age of 2 years if there is a family history of hypercholesterolemia or CVD or if family history is unknown. Lipids should be repeated every 5 years thereafter if normal [30].

Approved therapies for children include bile acid sequestrants and statins [31]. Bile acid sequestrants are not well tolerated and therefore adherence is poor. Several short-term trials of statins have confirmed their safety and efficacy in children and adolescents with familial hypercholesterolemia. Per ISPAD guidelines [32], children with low density lipoprotein (LDL) levels >100 mg/dL ($\geq$2.6 mmol) should obtain glucose control, and dietary and lifestyle interventions. If LDL is 130 mg/dL ($\geq$3.4 mmol/L) and has one or more CVD risk factors, then statin therapy is recommended for children greater than 10 years of age. Target LDL level is 100 mg/dL (<2.6 mmol/L). Target high density lipoprotein (HDL) is >35 mg/dL (>1.1 mmol/L) and triglycerides 150 mg/dL (<1.7 mmol/L). ADA guidelines state that after 10 years of age, if LDL is >160 mg/dL and does not respond to lifestyle therapy or if the child has additional risk factors (i.e. family history of early CVD) and LDL >130 mg/dL that has not responded to lifestyle therapy, statin therapy should be considered. If therapy with statins is undertaken, regular monitoring of liver function and screening for symptoms of

rhabdomyolysis should occur. Appropriate contraceptive advice should be given to girls receiving statins.

Microalbuminuria

Microalbuminuria is the first clinical manifestation of diabetic nephropathy and may be reversible with diligent glycemic and blood pressure control. Microalbuminuria is defined as any of the following:

- Albumin excretion rate 20–200 μg/min, or 30–300 mg/24 h in 24-hour urine collections.
- Albumin concentration 30–300 mg/L (in early morning urine sample).
- Albumin : creatinine ratio 2.5–25 mg/mmol or 30–300 mg/g (spot urine) in males and 3.5–25 mg/mmol in females (because of lower creatinine excretion).

Screening for microalbuminuria with a random spot urine sample should occur annually in children once they are 10 years of age and have had diabetes for more than 5 years. If values are increasing or borderline, more frequent screening should occur. Abnormal results should be repeated. The diagnosis of microalbuminuria requires documentation of two abnormal samples out of three samples over a period of 3–6 months. Once persistent microalbuminuria is confirmed, non-diabetes-related causes of renal disease should be excluded and treatment started. Persistent microalbuminuria is associated with end-stage renal disease and increased risk of macrovascular disease. Treatment with an angiotensin-converting enzyme (ACE) inhibitor should be started in the setting of persistent microalbuminuria, even if the blood pressure is normal. Children and their families should be counselled about the importance of glycemic control and smoking cessation if applicable, and appropriate contraceptive advice should be given to girls receiving ACE inhibitors [32]. Angiotensin receptor blockers are not approved for use in children but are occasionally used off-label.

Elevated blood pressure

Hypertension in adults with diabetes is associated with the development of both micro- and macrovascular disease. Treatment of blood pressure is critical in reducing these complications in adults and presumably in children and adolescents as well. Blood pressure should be checked and reviewed at each clinic visit. Hypertension is defined as systolic or diastolic blood pressure (measured on at least three separate days) above the 95th percentile for the child's age, sex and height and target blood pressure is <90th percentile. Care should be taken to ensure use of the appropriate-sized cuff in children to avoid inaccurate readings. If elevated blood pressure is confirmed, non-diabetes causes of hypertension should first be excluded. Treatment includes lifestyle interventions and ACE inhibitors if lifestyle fails [32].

Retinopathy

Adolescents have a higher risk of progression to severe non-proliferative or proliferative retinopathy compared to adults with diabetes [33]. The first dilated ophthalmologic examination should be obtained by an ophthalmologist, optometrist, or other healthcare professional trained in diabetes-specific retinal examination once the child is ≥10 years old or puberty (if this is earlier) and has had diabetes for 2–5 years [34]. The frequency of subsequent examination is generally every 1–2 years, depending on the individual risk profile and advice of an eye care provider [32].

Celiac disease

The prevalence of biopsy-confirmed celiac disease in children with T1DM ranges from 1–10%, compared to <1% in the general population [35]. The risk is greatest in children diagnosed before age 5 years. Many children with diabetes are asymptomatic but are positive for specific serologic markers of celiac disease such as autoantibodies to tissue transglutaminase. Most of the children with diabetes and celiac disease still remain undiagnosed, despite intestinal symptoms and/or short stature in about half of the cases.

Clinical manifestations of celiac disease are diverse, vary with age and may overlap with functional disorders. Some of the manifestations, such as delayed growth and puberty, decreased bone mineralization, abdominal pain and abnormal liver function tests, may overlap with those of poorly controlled diabetes. Therefore, physicians and other healthcare providers need to consider celiac disease in the differential diagnosis and many have argued for a routine transglutaminase screening in children with T1DM.

T1DM and celiac disease share HLA and non-HLA susceptibility genes. The prevalence of transglutaminase autoimmunity is highest in those with the HLA-DR3, DQB1∗0201 haplotype. One in four children with diabetes homozygous for this haplotype and 12% of the heterozygotes are positive for transglutaminase autoantibodies.

Most children with T1DM with celiac disease are transglutaminase-autoantibody-positive at the initial screening, although new cases develop during follow-up. All children should be screened for immunoglobulin A (IgA) transglutaminase-autoantibodies at onset of diabetes and, if negative and asymptomatic, rescreened every other year. If the transglutaminase-autoantibodies are negative, but the child has symptoms and/or signs consistent with celiac disease, other causes (e.g. poor glycemic control, or intolerance of milk, soy or salicylates) should be explored. HLA-DQB1 typing and total IgA level measurement may be helpful; if DQB1*0201 is present, IgA <10 mg/dL and, if symptoms persist, biopsy is recommended. Celiac disease is unlikely if both HLA-DQ2 and HLA-DQ8 are negative. Positive transglutaminase autoantibody findings have to be confirmed on another occasion, because transglutaminase autoantibody levels can fluctuate. If transglutaminase autoantibodies are strongly and persistently positive (radioimmunoassay index >0.5 or ELISA >60), biopsy is recommended even in a completely asymptomatic child. By contrast, children with low to moderately positive transglutaminase autoantibody levels may have false-negative biopsy and may be falsely reassured that they do not have celiac disease and forego further follow-up. The authors recommend repeating transglutaminase autoantibody testing every 3–6 months as

long as the levels are positive. Recent guidelines suggest that celiac disease can be diagnosed without biopsy in symptomatic children with elevated transglutaminase autoantibodies provided the endomysial IgA is also positive and either HLA-DQ2 or HLA-DQ8 is present.

Untreated celiac disease may pose problems with diabetes management, including increased risk of hypoglycemia and chronic diarrhea that is difficult to differentiate from that caused by autonomic neuropathy in adults. It is an open issue whether treating silent celiac disease improves diabetes-related outcomes. To date, results suggest small benefit in growth and bone mineralization, excess weight gain but no diabetes control benefit, or a slight decrease in HbA_{1c}. Gluten-free diets may prevent some of the episodes of hypoglycemia. The benefit of early detection and treatment remains unproven, but is the subject of ongoing investigation.

Thyroid disease

Hypothyroidism is present in 3–8% of children with T1DM. Long-term follow-up suggests that as many as 30% of people with T1DM develop autoimmune thyroiditis [36, 37]. The presence of hypothyroidism has been associated with thyroid autoantibodies, which are observed more frequently with increasing age and diabetes duration and female gender. With follow-up of 20 years, 80% of people with T1DM and thyroid peroxidase (TPO) autoantibodies develop hypothyroidism. Hyperthyroidism is less common than hypothyroidism in people with T1DM, but still more common (3–6%) than in the general population.

The presence of autoimmune thyroiditis in the population with T1DM has the potential to affect growth, weight gain, diabetes control, menstrual regularity, and overall well-being. All children with T1DM should be screened for elevated levels of the thyroid-stimulating hormone (TSH) after stabilization at onset of diabetes and every 1–2 years thereafter, or sooner if symptoms of hypothyroidism or hyperthyroidism are present. We also recommend measuring TPO and free T4 at the time of TSH screening. Those with positive TPO autoantibodies and normal thyroid function should be screened on a more frequent basis (every 6–12 months). Treatment of thyroid disease in children with T1DM is the same as that for the general population.

Addison disease

Addison disease affects approximately 1 in 10,000 of the general population and in 1% of people with T1DM [36]. The autoimmune process resulting in Addison disease can be identified by the detection of autoantibodies reacting to 21 hydroxylase (21-OH). The presence of this autoantibody in the general population is very rare, in contrast to 1–2% in people with T1DM. Of those with positive antibodies but as yet free of Addison disease, 15% develop Addison disease within a few years. Progression to adrenal insufficiency begins with elevated plasma renin activity and then progresses to increased adrenocorticotropic hormone, decreased stimulated cortisol, and eventually abnormalities of basal cortisol. The authors' current practice is to screen all children with T1DM for the presence of 21-OH autoantibodies. Those positive are followed for adrenal insufficiency by plasma renin activity and adrenocorticotropic hormone stimulation testing. Most children who develop disease are mildly symptomatic with decreasing insulin doses and HbA_{1c}.

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60 Adolescence and Emerging Adulthood: Diabetes in Transition

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Key points

- The time period of adolescence and young adulthood involves significant physical, social, and emotional growth, and presents unique challenges to those with diabetes.
- The intensive treatment required for consistent and effective diabetes care, especially for type 1 diabetes, can be time-consuming and challenging for young adults with diabetes, but it can be especially challenging as adolescents move toward adulthood. The degree of independence and responsibility adolescents accept for their diabetes care ideally increases as they enter older adolescence and young adulthood.
- Empowering emerging adults with a sense of self-efficacy with respect to their capacity to care for diabetes effectively is crucial to ensuring success during this transition phase and in establishing consistent self-care habits for life.
- As the emerging adult is likely to leave the home, the supportive role originally assumed by parents and family members can be taken on by close friends and significant others.
- The process of transition followed by the actual transfer from pediatric diabetes care to an adult practice can be challenging for emerging adults with diabetes. It is imperative that parents and the pediatric diabetes team members provide the necessary training and preparation for self-care to support the transfer to an adult practice. It is recommended that parents continue to support their teenager's diabetes care during this tumultuous developmental stage.
- Parents of teenagers and their healthcare professionals should monitor and attempt to prevent teenage burnout from diabetes care. Inclusion of diabetes educators and mental health clinicians on the teenager's and emerging young adult's diabetes team can help reduce the likelihood of burnout and help overcome barriers to self-care acquisition.

Introduction

Although this chapter focuses on the adolescent and young adult with type 1 diabetes (T1DM), the commonest type of diabetes affecting this age group, many of the issues also apply to young persons with type 2 diabetes (T2DM). Thus, this chapter will describe the process of transition that begins during adolescence and culminates in the transfer from a pediatric care team to an adult diabetes or endocrinology practice for young persons with diabetes, either T1DM or T2DM. This period of transition is impacted by multiple developmental changes that teenagers undergo between the ages of 13–18 years with additional developmental issues arising during the stage of emerging adulthood, between the ages of 18–25 and 25–30 years. The chapter will examine the psychosocial and physical changes experienced by adolescents as well as the special challenges teenagers and emerging young adults with diabetes encounter as they transition from adolescence into early adulthood.

The process of transition requires the growing and developing adolescent to take on the responsibilities for diabetes self-care previously managed by the youth's parents. This process should be gradual with sharing of diabetes management between parents and teenagers initially, followed by the ultimate transfer to self-care that should precede the time when the older adolescent or emerging young adult leaves the pediatric diabetes team and receives care from a medical team that specializes in adult diabetology or endocrinology.

There is no exact age at which the young person with diabetes should perform all self-care; rather this is a process that needs to be individualized, depending on development stage, maturity, family support, family expectation, education from the healthcare team, as well as other factors. Acquisition of self-care can begin for some youngsters in the higher primary grades or during the middle school years while the youths are under the supervision of adults for diabetes management tasks, such as checking blood glucose levels, assessing the carbohydrate content of meals or

Textbook of Diabetes, Fifth Edition. Edited by R. Holt, C. Cockram, A. Flyvbjerg and B. Goldstein.

snacks or reading the values on food packages, and participating in calculating insulin doses. Participation in these management tasks are generally encouraged by parents and the pediatric diabetes team with decreasing supervision by parents and other adults from around the ages of 12 or 13 years [1]. Direction and support provided by members of the pediatric diabetes medical team is imperative to promote the gradual transfer of these self-care tasks to the teenager with the goal to maintain treatment adherence in order to maximize the opportunities to achieve target HbA_{1c} values and reduce the likelihood of acute and chronic diabetic complications [2]. As youth differ in their cognitive capacity to perform diabetes tasks with increasing independence, it is imperative that healthcare professionals, parents, and the young person with diabetes work together to establish realistic goals. Helping the growing and developing teenager to develop a sense of self-efficacy in performing diabetes self-management tasks with increasing independence is critical, certainly prior to the transfer to adult diabetes clinics, where healthcare providers expect independence in diabetes care. The eventual goal is for the adult with diabetes to have the capacity and to possess the skills to engage in full and effective diabetes self-care, having traversed adolescence without diabetes burnout [3].

Demographic information about diabetes

There appears to be a significant increase in the occurrence of T1DM and T2DM in youth between the ages of 13 and 18 years. According to the SEARCH for Diabetes in Youth study in the United States, more than 190,000 youth were estimated to have physician-diagnosed diabetes in 2009 [4]. The US Centers for Disease Control and Prevention and the American Diabetes Association (ADA) report that an estimated 208,000 Americans under the age of 20 years have been diagnosed with diabetes, which represents approximately 0.25% of that population. Although this statistic does not differentiate between T1DM and T2DM, the report notes that between 2008 and 2009, the annual numbers of diagnosed diabetes in youth was estimated at 18,436 for T1DM and 5089 for T2DM [5]. The SEARCH study indicated that there has been an overall increase by 21.1% and 30.5% in the number of estimated cases of diabetes of T1DM and T2DM, respectively, between 2001 and 2009 [4].

Physical changes during adolescence

At the same time that there is an expectation for the teenager to take on increasing responsibility for diabetes self-management, the young teenager undergoes substantial physical, developmental, behavioral, and emotional changes, many of which substantially impact insulin needs. The major change in diabetes management results from the recognized insulin resistance associated with pubertal growth and development [2, 6] (See Chapter 59). Regardless of the age at diagnosis of diabetes, this period of adolescence requires great vigilance to assess diabetes needs and direct management due to physical and lifestyle changes. This vigilance entails frequent blood glucose monitoring, attention to carbohydrate intake, physical activity that becomes as much therapeutic as recreational in nature, and, of course, careful attention to insulin delivery both in terms of amount and timing. Shortly after diagnosis, persons with T1DM generally experience a time-limited phase known as "the honeymoon" stage during which the pancreatic β cells continue to produce a small amount of insulin. As time progresses, the pancreas produces less insulin and persons with T1DM experience increasing needs for exogenous insulin as the honeymoon wanes. This intensification of T1DM can be particularly apparent for the growing and developing adolescent whose insulin needs usually increase rapidly during puberty by up to 50% or even more [2].

In order to manage insulin effectively for an adolescent, parents and the pediatric diabetes team need to pay close attention to changes related to puberty, weight gain, and linear growth. Insulin doses need to be increased to help ensure that the HbA_{1c} remains within the target range of <7.5% (<58 mmol/mol). Thus, while teenagers with diabetes experience increasing independence in many aspects of their lives related to school and social life, the period of pubertal growth and development requires ongoing parental involvement in diabetes management to ensure that glycemic control does not deteriorate. Indeed, teamwork in diabetes management between the parents and the teenagers is recommended at this stage. Furthermore, frequent consultation with members of the pediatric diabetes team regarding insulin adjustments, appropriate nutrition, stress management, and exercise also reduces the likelihood of uncontrolled diabetes and the development of acute complications [2, 6].

Developmental stages

This section of the chapter will describe the normal developmental stages of adolescence and emerging adulthood with a focus on various transitions and recommendations for optimal family management of diabetes (Table 60.1). Key developmental changes that may impact the ability of the youth with diabetes to engage in self-care tasks independently will be reviewed (Figure 60.1). There will also be a section on empiric evidence for specific intervention and care strategies for adolescents and emerging adults with diabetes. Lastly, novel technology platforms to support optimal diabetes management will be discussed.

Adolescence (ages 13–18 years)

Along with rapid physical growth, cognitive development, and pubertal maturation, adolescence is a time of increased attention to body image and sexuality. Youth within this age range are also forming their identities, a process that can lead to increases and decreases in taking on and accepting greater responsibility for a variety of school and home-related tasks. Furthermore, relationships with same-age peers have a powerful influence on an adolescent's behavior [7–9].

Table 60.1 Developmental stages and major developmental tasks during adolescence and emerging adulthood.

	Typical development	Diabetes-specific development	Psychosocial challenges
Early adolescence (ages 13–15 years)	• Rapid growth • Sexual maturation • Body image concerns • Changing physical activity level • Social / friend interactions • Interest in technologies • Ongoing cognitive development • Emerging alcohol and drug experimentation	• Frequent alterations in glucose levels • Expanding needs for self-care and sharing diabetes responsibilities between teens and parent • Body image concerns related to wearing diabetes devices • Concerns regarding peer awareness and comments about diabetes • Understanding exercise and diabetes needs	• Diabetes family conflict • Disordered eating • Depressive symptomatology • Fear of hypoglycemia / hyperglycemia • School staff knowing what to do in an emergency • Family planning
Later adolescence (ages 16–18 years)	• Identity formation • Sexual activity • Body image concerns • Changing physical activity level • Social / friend interactions • Interest in technologies • Ongoing cognitive development • Emerging alcohol and drug experimentation	• Balancing T1DM care with schoolwork and social interests • Greater independence / need of adult support related to diabetes care • Body image concerns related to wearing diabetes devices • Concerns regarding peer awareness and comments about diabetes • Understanding exercise and diabetes needs	• Diabetes family conflict • Disordered eating • Depressive symptomatology • Fear of hypoglycemia / hyperglycemia • School staff knowing what to do in an emergency • Family planning • Driving a motor vehicle
Early phase emerging adulthood (ages 19–24 years)	• Education and career training • Moving away from family home • Dormitory / apartment roommates • Changes in emotional and financial ties with parents • Wider friendship group	• Possible gaps in medical insurance • Making time for T1DM when with friends • Negotiating performing diabetes tasks at first job or while at college • Remembering to re-fill / re-order prescriptions • Recreational substance use • Negotiating self-advocacy	• Diabetes family conflict • Disordered eating • Depressive symptomatology • Fear of hypoglycemia / hyperglycemia • Professors / co-workers knowing what to do in an emergency • Family planning
Later phase emerging adulthood (ages 25–30)	• Interest in marriage, starting a family • Further career advancement • Expanding social, emotional, and financial independence	• Increasing awareness of the impact of diabetes care on significant others, family planning, and career development • Recreational substance use • Negotiating self-advocacy • Remembering to re-fill / re-order prescriptions	• Diabetes family conflict • Health roles of close friends / significant others • Professors/ co-workers knowing what to do in an emergency • Family planning

A tremendous number of physical, social, and emotional changes occur during the period of adolescent growth and development, often challenging the management of diabetes for youth, their parents, and healthcare providers. The ADA and the International Society of Pediatric and Adolescent Diabetes (ISPAD) along with other organizations recommend a glycated hemoglobin goal of <7.5% (<58 mmol/mol) for persons under 18 years old and <7% (53 mmol/mol) for persons 18 and older [10–12]. However, the maintenance of HbA_{1c} within this range is an elusive goal for most adolescents [13]. Along with the impact of pubertal development, physical growth, and emotional stress that most adolescents experience, diabetes, and especially T1DM, when compared to other chronic illnesses of childhood, requires the teenager to perform management tasks multiple times each day, day in and day out without any break. In addition to checking blood glucose levels, attending to food intake, administering insulin, understanding the impact of exercise on glucose levels, youth with diabetes and their families also must navigate the impact of acute

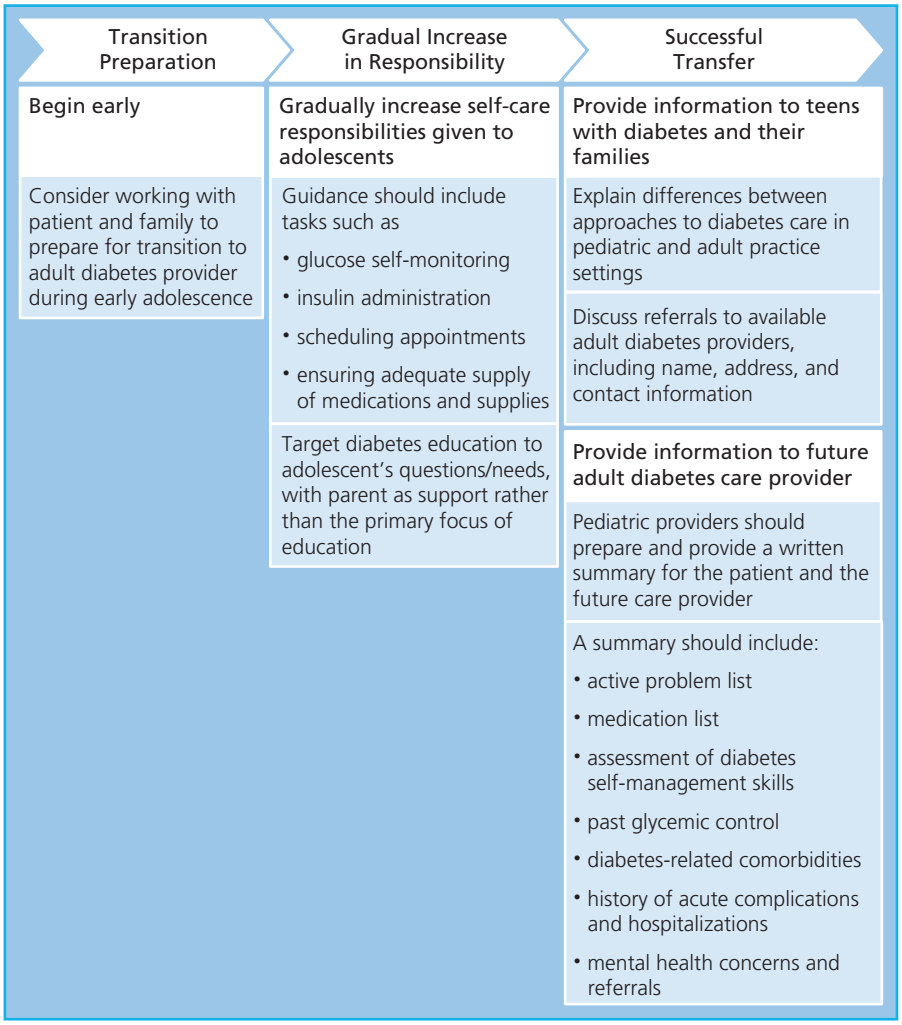

Figure 60.1 Trajectory of transition preparation, self-care acquisition, and transfer to adult care.

illness on their diabetes management needs [1]. Teenagers develop emotional maturity and the ability to take on diabetes responsibilities with independence at varying rates and at various ages. However, some teenagers do not possess the emotional maturity to sustain tasks of daily self-care and some may experience gaps in medical care, which can lead to adverse health outcomes [14].

Family support, family involvement in diabetes management, and low levels of diabetes-specific family conflict are associated with smoother transitions for adolescents as they acquire and accept more responsibilities of T1DM self-care [15–17]. While adolescents with diabetes learn to adapt to fewer adult prompts to engage in and perform self-care tasks accurately and consistently, parents are encouraged to remain involved in sharing management responsibilities. The roles and responsibilities that parents keep versus those that they pass on to the adolescent will differ depending on the adolescent's cognitive capacity and willingness to engage in care activities. As these factors are rarely static due to ongoing maturation and situational stressors experienced by the adolescent and/or family, the roles parents and teenagers fill during this transition will frequently need to be re-negotiated. Members of the adolescent's diabetes team can serve as an excellent resource in problem-solving the division of responsibilities and ensuring teenagers with diabetes are provided with a realistic amount of self-care tasks. The ultimate goal is for the adolescent to possess a sense of self-efficacy and the capacity to accept and treat diabetes optimally [1].

Additional important factors for an optimal transition of diabetes management from parents to the adolescent include the establishment of self-efficacy and self-advocacy for the teenager, especially in the context of developmental and social needs. Teenagers with a strong belief and confidence that they can perform self-care and advocate for themselves in particular situations are more likely to overcome barriers to diabetes self-care. Teenagers should be empowered to speak up for their diabetes self-management needs in public settings, such as school or athletics, and have confidence in doing so. Setting alarms on a smartphone can help increase the likelihood that teenagers will check blood glucose levels and respond in a timely manner. There are improved outcomes when there is acceptance of self-care leading to improved glycemic control [18–20]. In a study conducted

by Wiebe et al. (2014), the investigators found that youth who reported a decrease in parental involvement for T1DM care and a high sense of self-efficacy were better able to maintain treatment adherence than those with a lower sense of self-efficacy [21]. Youth who possessed a lower sense of self-efficacy had better glycemic control only when a parent played a greater role in establishing self-care skills [22]. These findings support the need for the adolescent's diabetes team to consider the level of self-efficacy an adolescent possesses when increasing their self-care independence.

In addition to the impact of pubertal insulin resistance, other factors can lead to deterioration in glycemic control. Target glycemic control can be challenging when teenagers have competing preoccupations, for example, with athletics, academic studies, and social distractions, which can detract from self-management, leading to lower adherence and poorer glycemic control [6,17,23–25]. Only 23% of more than 6000 adolescents with T1DM (ages 13–<18 years) in the T1D Exchange Clinic Registry had HbA_{1c} levels in the target range of <7.5% [24,26]. Hilliard et al. (2013) analyzed predictors of deterioration in glycemic control in 150 adolescents with T1DM over a period of 18 to 24 months [27]. Approximately two-thirds of participants did not meet the requirement to check blood glucose values ≥4 times daily and did not achieve the target HbA_{1c} of <7.5%. There were a variety of modifiable and non-modifiable factors related to the suboptimal management and glycemic outcome. Non-modifiable factors included ethnic minority status and unmarried care-giver status. The authors highlighted that diabetes healthcare professionals should identify these non-modifiable factors in order to assess a patient's risk and provide timely support. The modifiable factors associated with deteriorating T1DM care and glycemic control included injection-based insulin regimens as well as diabetes-specific family conflict [27]. This latter finding emphasizes the importance of including behavioral and mental health assessments as part of adolescent diabetes care visits in order to assess and intervene for stressful parent–teenager interactions around diabetes management and transitions in self-care to the teenager.

As mentioned earlier, social context can have an important impact on an adolescent's diabetes self-management. Borus et al. (2013) conducted a study where, over a 14-day period, adolescents with T1DM, aged 14–18 years, carried handheld devices that prompted them to report social context variables related to self-monitoring of blood glucose. Despite concern that many adolescents with T1DM do not check their blood glucose as often as recommended, the study demonstrated an increased likelihood of the youth checking blood glucose levels when the teenagers expressed a strong desire to blend in with peers and a lower likelihood of checking blood glucose levels when the teenagers wanted to impress others. The authors suggested that these findings could help providers to encourage teenagers to check their glucose levels more frequently as monitoring allows teenagers to identify out-of-range glucose values in a timely manner, thereby allowing them to avoid possible embarrassment as a result of sudden unexpected hypoglycemia or symptomatic hyperglycemia [28].

There have been a variety of family-based behavioral interventions aimed at optimizing glycemic control during adolescence. Ellis et al. (2012) performed a 6-month behavioral intervention using multi-systemic family therapy in youth with poor glycemic control. This group was compared to a second group of participants who only received telephone support. Results indicated that teenagers in the multi-systemic family therapy group experienced a significant reduction in HbA_{1c} at the post-treatment time point and 12 months after the intervention [29]. Wysocki et al. (2006) conducted a 6-month behavior intervention using Behavioral Family Systems Therapy for Diabetes (BFST-D). Participants exposed to this intervention were compared with two comparison groups (educational support and standard care); teenagers in the BFST-D group demonstrated greater treatment adherence at follow-up compared to the comparison groups [30].

Another series of studies focused on cost-effective, clinic-based interventions utilizing "care ambassadors" [31–33]. The "care ambassadors" do not possess medical training but they provide support to patients and families between medical visits, ensuring timely follow-up, which is particularly important when the competing needs of adolescence may impede routine diabetes visits. Those with T1DM receiving care ambassador support compared to standard care demonstrated increased outpatient visits, reduced hospitalizations and emergency room visits, and reduced occurrence of severe hypoglycemia. Furthermore, those youth with T1DM with poor control at study entry who were assigned to receive care ambassador support compared with standard care demonstrated a decrease in HbA_{1c} [31–33].

Motivational interviewing has also demonstrated usefulness in regard to bolstering an adolescent's willingness to increase self-management. Motivation interviewing involves collaborative communication between a member of the pediatric diabetes team and the adolescent in an effort to strengthen the teenager's personal motivation for change and commitment toward achieving a specific goal [34]. Channon et al. (2011) designed and implemented a randomized controlled trial that studied the impact of motivational interviewing during clinic visits in 66 teenagers with T1DM, aged 14 and 17 years [35]. Findings of the 12-month study showed that, compared to control participants, those who received the motivational interviewing intervention had lower mean HbA_{1c}. Furthermore, this improvement was maintained a year after the intervention ended. Motivational interviewing may serve a role during transition as a means to motivate support for the acquisition of self-care tasks among teenagers with diabetes.

A number of studies have examined the use of mobile technologies to assist adolescents in their transition to diabetes self-care. Text-messaging has been studied as means to offer reminders to adolescents for self-care when they are away from their parents and other adult care providers. Markowitz et al. (2014) conducted a study where adolescents and young adults with diabetes received text-messages that promoted a general healthy lifestyle and diabetes self-care [36]. Messages were tailored to assisting study participants attain personal goals regarding diabetes adherence. While self-efficacy and glycemic control did not change during the 3-month pilot study, results indicated that text-messaging was highly acceptable to participants and could be expanded in future studies [36]. A Scottish study entitled, "Sweet Talk," sent

daily automated text-messages that reinforced goals that adolescent study participants had set during their diabetes clinic visit [37]. The intervention did not demonstrate consistent improvement in participants' HbA_{1c}. However, results suggested that the adolescent participants developed a stronger sense of self-efficacy related to their ability to care for T1DM. Considering the popularity and ubiquitous nature of cell-phone text-messaging among adolescents, text-messaging may prove to be a useful and cost-effective means to support and promote adolescent self-care during transition.

Emerging adulthood

To add to the challenges of transition to self-care during adolescence, another development stage, termed emerging adulthood, demands the attention of both pediatric and adult diabetes care providers in their efforts to support the young person with diabetes. This developmental stage of young adulthood has been popularized over the past 20 years in the United States and other high-income countries [38]. The period of emerging adulthood is marked by the observation that many individuals in their late teens and early 20s are delaying tasks that had been traditionally associated with this age, such as marriage, parenthood, and work. These life events now occur for many in their late 20s and early 30s. The period between ages 18 and 30 years is now referred to as "Emerging Adulthood" by some developmental theorists and psychologists [38]. This post-adolescent period can be separated into an early phase and later phase. Notably, health insurance coverage for young adults with diabetes has generally not been a problem in countries with universal coverage but young adults in the United States had been at risk for gaps in health insurance coverage until reforms such as the Patient Protection and Accountable Care Act in the USA mandated coverage under parents' policies until the age of 26 years [13].

The early phase of emerging adulthood corresponds to the years immediately after high school, ages 18 through 24 years. During this phase, the emerging adult may be moving physically away from home and beginning to change the degree and nature of emotional and financial ties with parents, although the emerging adult is not yet fully independent. During this phase, the young adult experiences tremendous pressures related to academic studies, occupational choices, and social commitments, while separating from the family [13]. Thus, it is not surprising that these competing needs for time, energy, and effort often detract from diabetes self-care, leading to further deterioration in adherence and glycemic control. Indeed, data from the Type 1 Diabetes Exchange Clinic Registry in the United States indicate that HbA_{1c} reaches its highest level of 9.2% (77 mmol/mol) during this phase of development [3,24]. Thus, pediatric and adult healthcare professionals working with these emerging young adults must be aware of these competing demands and help to ensure that young adults with diabetes receive reinforcement for self-care behaviors, along with ongoing education and training in self-management, including how to fill prescriptions and make diabetes follow-up appointments [39].

During the later phase of emerging adulthood, usually occurring between the ages of 25 to 30 years, the young adult starts to assume more traditional adult roles [38]. An increasing sense of maturity leads many emerging young adults in the second phase to realize the importance of monitoring their health. Interest in getting married, raising children, and establishing a career lead many individuals to invest more effort to improving self-care and achieving better glycemic control [13]. Considering the young person's increased awareness of self-care needs and health outcomes, this period is an ideal time for the diabetes healthcare professional team to bolster diabetes management habits. As transfer from pediatric to adult providers likely occurs during this developmental stage, both pediatric and adult healthcare professionals should be well versed in these issues [13].

Changes in family involvement

Family involvement is a critical component of diabetes management during childhood and adolescence. Additionally, parents and family members as well as members of the pediatric diabetes team play significant roles in helping adolescents and young adults transition to taking on the primary role of managing their diabetes. Interestingly, the perceptions of parents may contrast at times with that of the pediatric diabetes team with respect to a youth's capacity to engage independently and effectively in self-care and to sustain adherence to tasks. Wysocki et al. (1992) had parents and members of pediatric medical diabetes teams complete surveys that measured their estimates of the self-care independence of youth with T1DM [40]. This study, which was conducted across multiple T1DM centers, found that compared to parents, healthcare professionals characterized young children and those in elementary school as being less capable of independently monitoring and treating T1DM without the supervision of an adult care-taker. Parents of these children, however, reported earlier mastery of skills by their children related to motor activities (e.g. self blood glucose monitoring) and the capacity to take care of T1DM events with immediate consequences (e.g. preventing or treating hypoglycemia). Additional results indicated that many parents of adolescents, however, reported lower levels of self-care and competence for critical skills involving executive functions. These self-care activities included planning, anticipation, and self-regulation (e.g. preventing hyperglycemia or adjusting insulin doses) [40].

Prior to 1986, no guidelines existed for the family sharing of T1DM management activities or what tasks were appropriate at different ages and stages of development of youth. Research conducted by Ingersoll et al. (1986) found that as youth grew older, responsibility for T1DM tasks shifted from the parent to the growing teenager [41]. This finding matches the general developmental expectation that adolescents will require less guidance, in general, from teachers, for example, to write down homework assignments and fewer prompts from parents to complete homework. However, when parental involvement in diabetes management tasks decreased, specifically regarding adjusting insulin, Ingersol

et al. (1986) reported that adolescents did not increase their independence and effectiveness in the self-care management of T1DM. However, youth who took over more responsibility for insulin adjustments were at "advanced levels of cognitive maturity and had a stronger personal sense of control over diabetes" [41]. These findings launched a critical body of research related to family teamwork during adolescence, which has changed the paradigm of care during this stage of development, and continues to highlight the need to individualize approaches based upon the individual's cognitive, emotional, and social development.

As parent involvement in T1DM care declines over time, roles of the child or teenager and family in diabetes management rarely remain static; the growing and developing youth goes from a stage of dependence upon parents or other adults, to sharing tasks or a state of interdependence, prior to emerging with full independence in self-care during later adolescence and young adulthood. In order to provide optimal care, pediatric diabetes providers are encouraged to be well-versed in the ebb and flow of the roles of the youth and family members during the course of adolescent development. Normal developmental tasks of childhood and adolescence call for slowly increasing the youth's acquisition of responsibilities, personal decision-making, and self-care (Figure 60.1) [10]. Division of T1DM management roles within the family is often directed by the multi-disciplinary diabetes care team, which ideally provides ongoing education and psychological support for youth with T1DM and their families, with a need to direct diabetes education and support from the parent to both the youth and parent. Healthcare team members can provide anticipatory guidance and realistic expectations related to the roles of the youth and family members [2].

It is also important to recognize that adolescents and emerging adults will likely differ in their capacity to perform diabetes self-management independently. The ability to manage diabetes responsibilities can be impacted by executive functioning challenges, such as attention-deficit/hyperactivity disorder (ADHD) as well as short-term and working memory difficulties [42]. A number of recent studies have focused on the impact that hypoglycemia and hyperglycemia may have on a cognitive ability and executive functioning skills [43, 44]. The findings have been mixed, and deeper examination of these studies is beyond the scope of this chapter. Nonetheless, it is important to consider the impact ADHD, short-term/working memory, executive functioning, and organizational skills on an adolescent's or emerging adult's capacity to perform diabetes self-care independently, consistently, and effectively. The individual may benefit from carrying a discrete, step-by-step checklist or by utilizing mobile phone alarms as reminders or aides to perform diabetes tasks as the young person acquires increasing independence in self-care. Depending on the skill level of the teenager or young adult, the checklist or reminder can include instructions for what to do when blood glucose levels are out of range, either low or high.

To increase the likelihood that adolescents and young adults with diabetes will experience success in self-care, it is imperative that parents and members of the pediatric diabetes team monitor and take action to prevent or intervene on diabetes burnout. Research has suggested that a variety of factors, including low self-efficacy, low self-esteem, complex treatment regimens, and longer duration of the disease contribute to burnout [45, 46]. Burnout in adolescents becomes evident when teenagers reduce their frequency of blood glucose monitoring and glycemic control subsequently deteriorates [47]. Members of the adolescent's diabetes team, specifically diabetes educators and mental health counselors, can help parents and teenagers identify and manage diabetes burnout and ensure parents remain in supportive roles when the adolescent experiences this challenge during transition to greater self-care.

Diabetes technologies

Despite the burgeoning of new technologies to assist in managing diabetes, especially T1DM, over the past 20+ years, consistent and effective use of devices, such as insulin pumps and continuous glucose monitors (CGM), can be challenging for persons with diabetes across the age range. Insulin pumps can simplify insulin delivery throughout the day and night and CGM devices can enable persons with diabetes to monitor trends in glucose levels and to receive alerts and alarms when glucose values fall out of range [48, 49]. However, none of these devices is fully automated and all require input and vigilance to ensure proper functioning. Thus, the additional effort needed to use these advanced diabetes technologies may impede uptake or lead teenagers and emerging adults to stop using them. The healthcare team can help by providing families, adolescents, and emerging adults with realistic expectations and ongoing education and support regarding the use of these technologies to maximize their uptake and durability of use. This support should include discussions regarding optimal timing of initiation of these devices. It is likely that similar approaches will be needed for soon-to-be-available "closed-loop" systems that will provide automated or semi-automated insulin delivery in an "artificial pancreas" as human input will remain critical for proper functioning and surveillance of such systems.

Type 2 diabetes in adolescence and transition

Unlike T1DM, where pancreatic β cells cease to produce insulin, the pancreas of individuals with T2DM still produces insulin but there is peripheral resistance to insulin action [50]. T2DM is generally considered a disorder associated with middle or older age. However, the increased occurrence of childhood obesity over the past few decades has led to an increase in the number of youth diagnosed with T2DM [51]. This is particularly problematic in minority populations, including Afro-Caribbean, Hispanic, Asian/Pacific Islander and Native American youth, between the ages of 10 and 19 years, where T2DM can represent more than half of the newly diagnosed cases of diabetes [52]. Furthermore, youth diagnosed with T2DM are at increased risk for developing

comorbid complications, such as hypertension, hyperlipidemia, and diabetes complications at an early age [53]. Although obesity is the hallmark of T2DM, in North America there are increasing rates of childhood overweight and obesity in the general population, and, as a result, more children with T1DM are overweight or obese today. This can make it challenging, at times, to distinguish between the two types of diabetes [54].

The Treatment Options for Type 2 Diabetes in Adolescents and Youth (TODAY) Study is the largest clinical trial examining the management of youth with T2DM [55]. This study enrolled 699 participants, age 10–17 years old, with recent-onset T2DM. After a run-in period during which metformin was used to attain an HbA_{1c} of <8%, participants were randomized to treatment with metformin alone, metformin with a lifestyle intervention, or metformin with rosiglitazone. About half of the participants experienced the primary outcome of loss of glycemic control (defined as $HbA_{1c} \geq 8\%$ for 6 months or metabolic decompensation requiring treatment with insulin) over an average follow-up of about 4 years. Loss of glycemic control occurred at approximately equivalent rates in the metformin alone and metformin plus lifestyle groups while the group receiving rosiglitazone in addition to metformin had superior outcomes, with an approximately 25% reduction in the proportion of participants randomized to that group reaching the primary outcome. This highly important finding underscores the need for treatment of young persons with T2DM with more than one antidiabetes agent; however, rosiglitazone and other thiazolidinedione drugs are not FDA-approved for use in children. The transfer of older teenagers and emerging adults to adult diabetes care may offer a unique opportunity to overcome clinical inertia and to re-visit a young adult's diabetes treatment regimen by adding a second medication to the care plan. Similar to the young person with T1DM, this transition period can also be a time full of multiple changes in the young adult's life, and the provider must take special care to continue to integrate the needs of the young adult with diabetes and their family into the holistic model of care.

Studies of T2DM medical care have focused on including a short-term diabetes educational component. The TODAY study provided "standardized diabetes education" during which teenagers with T2DM received education not only about pathophysiology, how medications work, and lifestyle guidelines, but also about how to improve their diabetes self-care with focused goal setting. Participants were closely monitored with regard to dosages of injected medication and/or oral medication(s) for diabetes. As this chapter is about ensuring the transition from pediatric diabetes care to adult care and increasing the likelihood that adolescents and emerging adults will establish consistent self-care practices, it is important to acknowledge that all participants in the TODAY study had to complete a 2–6 month run-in period successfully prior to randomization. During this period, which could include a minimum of 6 to a maximum of 12 clinic visits, participants were required to demonstrate ≥80% medication adherence for at least 6 weeks, miss no more than two run-in visits and maintain an HbA_{1c} of <8% for at least 2 months [52]. In order to fulfill these requirements, participants were provided with a significant amount of support, including appointment reminders and follow-up phone calls or text messages from study staff. Despite this support, 24% of the young adults who were screened for the study failed to fulfill the requirements of the run-in period and thus were excluded from randomization into the main trial.

It is also important to consider inclusion of a family-based behavioral lifestyle intervention with the focus on weight loss or prevention of continued weight gain during the transition process and even upon transfer from pediatric to an adult diabetes medical practice. Hannon and Arslanian (2015) reviewed the importance of a multidisciplinary team that could include the patient, family, physician, nurse educator, dietician, behavioral specialist, and personnel from the adolescent's school [50]. Although the authors did not go into detail regarding the emerging adults' transition from pediatric to adult diabetes care, they emphasized that the focus should be geared toward individualized therapy, family-based interventions, and pharmacotherapy with the objective of weight loss or prevention of continued weight gain while optimizing diabetes management and glycemic control [50, 56].

Van Walleghem and colleagues from Canada consider transitions in care for children with T2DM [57]. The Diabetes Education Resource for Children and Adolescents (DER-CA) in Winnipeg, Manitoba, Canada, follows children from diagnosis to age 18 years in a "… coordinated, family centered integrated program of care" [57]. The numbers of youth with T2DM referred to the service increased from four new cases in 1986 to 67 in 2010 and T2DM was cited as accounting for more than 50% of the children with new-onset diabetes. As of 2012, DER-CA was following 207 youth with T2DM, leading to their interest and focus on T2DM transition [57].

The number of children at the DER-CA transitioning from pediatric to adult care has also increased from 8 in 2001 to 42 in 2009. While Van Walleghem and colleagues acknowledged that youth with T2DM and T1DM experience similar challenges during the transition process and with transfer from pediatric to adult care, the authors emphasized differences due to "… the clinical complexity, the different cultural and social characteristics, and the aggressive progression of life-threatening complications in emerging adult life for T2DM" that "require[s] a different approach to transition" [57]. The authors proposed a "life-cycle approach" to care, education, and support along with further research related to T2DM. The authors have examined a model of care similar to the "care ambassador" approach described earlier for T1DM, by utilizing a patient navigator in the "Maestro Project" [57]. The Maestro Project aims to increase the rate of medical follow-up and reduce morbidity and mortality from acute and chronic complications of diabetes. The authors emphasized that medical systems must respond quickly and creatively to meet the needs of adolescents and young adults with T2DM who are transitioning from pediatric to adult care [57].

Many studies in youth and adults with T2DM have found a high prevalence of other cardiovascular risk factors, encapsulated in the metabolic syndrome. The TODAY study found a very

high prevalence of metabolic syndrome (75.8%) at baseline, and this did not differ in those with excellent glycemic control ($HbA_{1c} < 6\%$) or improve with treatment [58].

Family planning and the possibility of pregnancy are also of major importance in women with diabetes, and the transition and transfer to adult care presents a unique opportunity for exploration of this topic. As part of the TODAY study of youth with T2DM, all female participants received counseling on birth control, and in fact were required to use some form of contraception (including abstinence) in order to participate in the study. Despite that, 10% of female participants became pregnant during the study. Of the pregnancies that were not electively terminated, 26.4% ended in miscarriage, stillbirth, or intrauterine demise, and 21.5% of the live-born infants had major congenital anomalies [59].

Acute and chronic complications in young adults diagnosed with diabetes in childhood

Youth with T2DM are at risk of acute complications, such as diabetic ketoacidosis and hyperosmolar hyperglycemia [53]. Youth with T2DM are also at increased risk for a variety of chronic complications and comorbidities including hypertension, dyslipidemia, nephropathy, retinopathy, non-alcoholic fatty liver disease, polycystic ovary syndrome, depression, and binge eating [53]. The TODAY study found that hypertension, dyslipidemia, and microalbuminuria were present at baseline, and increased by the end of the study [60].

The commonest acute complication for adolescents and young adults with T1DM are hypoglycemia and diabetic ketoacidosis. The ADA recommends assessment of the history of acute complications, along with continued education on prevention of recurrence of acute complications [10]. Adolescents and young adults with T1DM are also at risk for various psychiatric disorders, including depression and eating disorders, and providers should attempt to identify and intervene for such problems to avoid worsening, particularly at the sensitive time of transition. Finally, chronic vascular complications, such as retinopathy, nephropathy, neuropathy, and cardiovascular disease, can begin in childhood and continue or worsen in young adulthood. The ADA and other national and international organizations regularly publish guidelines regarding the screening for such complications and the most recent ADA screening recommendations can be found in the 2016 Standards of Medical Care in Diabetes [12].

What is transition?

Transition is the re-orientation that people experience in response to a change. While change is situational, such as moving to a new town or changing jobs, transition is the way in which people respond to the changes they encounter in their lives [61]. Transition is the movement people make through such a disruptive life event in order to continue to live with a coherent, albeit evolving, sense of themselves [62]. Transfer refers to the physical change in the ministration of responsibilities from one individual to another; in this case, the pediatric endocrinologists or diabetologists end their relationships with youth diagnosed with diabetes and the person with diabetes begins meeting with an adult physician. As noted, transition is a process in which the adolescent or young adult with diabetes prepares for self-care and the future change in providers, while transfer is the actual transfer event. If these activities are managed poorly, failure to engage with adult services decreases the likelihood of regular attendance at diabetes medical centers [63].

Within pediatric healthcare, transition has often been defined as the time when an adolescent or young adult makes a purposeful, planned movement from pediatric to adult care services. The goal is to optimize health and well-being. To accomplish this, a number of factors need to be met. These include:

- transition preparation,
- engagement in chronic disease management, and
- the actual transfer of healthcare from pediatric to adult systems [63].

The moment of transfer requires a hands-off approach between providers. Successful transition from pediatric to adult services involves the family, is impacted by demographic characteristics, diabetes history, glycemic control, self-management, and a sense of self-efficacy and transition preparation [64]. Transition is considered to be successful when an emerging adult demonstrates the ability to self-manage diabetes, meet with members of the diabetes healthcare team at recommended intervals, maintain glycemic control, and avoid acute complications [63]. See Figure 60.1 for a schematic of tasks during the period of transition and for the ultimate transfer between providers.

Problems with transition

Emerging adults with diabetes and their healthcare providers encounter a variety of issues during the transition from a specialized pediatric diabetes clinic to an adult endocrinology, diabetology, or primary care practice (Box 60.1). Notably, the topic of transition has recently garnered substantial interest from the diabetes clinical and research communities for a number of reasons; first, there are more young persons with T1DM and T2DM who need to undergo transition and, second, there is a deficiency of intervention research aimed at guiding the transition process and optimizing health outcomes of emerging adults with diabetes [13, 63, 65].

One difficulty with transition is that the emerging adult must part with a long-term, familiar relationship with a group of pediatric healthcare providers. In addition, there are some fundamental differences in healthcare delivery between pediatric and adult settings [13]. The relationship with the pediatrician is family-centered and holistic with respect to pediatric and adolescent developmental needs. Adult visits tend to be shorter in duration and tend to focus more on medical treatment [13]. Adult medical providers tend to focus the visit almost exclusively on the young

Box 60.1 Challenges for older teenagers and young adults with diabetes during the transitional period.

- Diabetes self-care often loses priority to competing demands related to social, emotional, educational, and occupation interests and needs.
- Emerging adults with diabetes are at high risk for poor glycemic control.
- Mental health issues (i.e. depression, anxiety, disordered eating behaviors) are common at this age.
- Issues around sexual and reproductive health become paramount.
- Risk-taking behaviors around alcohol, smoking, and drug abuse often increase in this age group.
- There is increased risk of acute complications (i.e. DKA and severe hypoglycemia) for transitioning youth.
- There is a risk of missing screening opportunities for eye and kidney complications and CVD risk factor identification.
- Pediatrics and adult providers employ different approaches to diabetes care.
- Loss to follow-up is a common problem at time of transition / transfer.
- Developing chronic complications of diabetes may present in older adolescence and young adulthood and may go under-detected and untreated.

DKA, diabetic ketoacidosis; CVD, cardiovascular

adult, rather than the family, with the belief that the individual is capable of making independent decisions regarding care and treatment [13]. Adult care providers often assume that the person with diabetes possesses the skills and capacity to perform diabetes care independently, which could be problematic if the emerging adults were ill-prepared by the pediatric team to assume the necessary responsibilities for their diabetes self-care. In turn, the emerging adult may feel unsupported and vulnerable following the transfer [64]. In some instances, young adults may choose to reject adult care, limiting their openness to the medical provider's recommendations. These factors contribute to the frequent loss to follow-up care experienced by many emerging adults [13]. Furthermore, more than one third of older teenagers and emerging adults transferring care between pediatric and adult providers experience gaps in care exceeding 6 months [13]. These gaps in care and loss to follow-up can lead to acute complications and the emergence of chronic complications that go undetected and untreated.

Unsuccessful transition is more likely to occur when emerging young adults lack skills for independent decision-making, especially when they do not feel ready to handle such responsibilities [3, 13]. Furthermore, there are many age-appropriate social, emotional, educational, and work-related activities that compete for the attention of older teenagers and emerging adults, often superseding self-care and attendance at healthcare visits [64]. Many older teenagers and young adults may also feel uncomfortable disclosing their chronic medical condition to others, especially when entering a new school or work environment, making it challenging for those with diabetes to perform management tasks consistently. The successful balance of diabetes self-care demands with these competing needs requires self-efficacy and self-advocacy. Transition preparation should include attention to these areas.

Gaps in care or loss to follow-up care results in poor glycemic control and places the emerging adult at increased risk for medical complications in both the short and long term [66]. The short-term complications are related to extreme glucose fluctuations (i.e. severe hypoglycemia or hyperglycemia) and can lead to emergency room hospitalizations, especially in the absence of routine care. Further, persistent hyperglycemia with uncontrolled diabetes increases the risk for long-term microvascular and macrovascular complications [67]. Transition preparation from the pediatric team should include discussion of chronic diabetes complications, pregnancy planning, and routine screening for clinical evidence of early kidney and eye changes as well as risk factors for macrovascular complications. Otherwise, some emerging young adults may opt to avoid follow-up adult care rather than be suddenly faced with discussions regarding complications when they have been ill-prepared [3].

There are a number of behavioral, psychosocial, and psychiatric challenges that can confront the older teen and emerging adult with diabetes during the transition; these include diabetes distress, fear of hypoglycemia, fear of hyperglycemia, burnout, depressive symptoms, depression, anxiety, and disordered eating behaviors, among others. These challenges can interfere with effective self-care and consistent diabetes follow-up, leading to a vicious cycle of discouragement and burnout, which, in turn, may further diminish attention to diabetes self-care. Data in teenagers and emerging adults with T1DM identify psychosocial and socioeconomic risk factors associated with reduced diabetes self-management and burnout [25, 68–70].

The coexistence of psychiatric conditions (Chapter 57), specifically depression and anxiety, brings considerable challenges to the management of diabetes during adolescence and emerging adulthood, substantially impacting self-care and consistent follow-up with medical providers [3]. Although such conditions are common in the general population, rates of depression and anxiety are higher in those with diabetes especially during these developmental stages [71]. Collaborative care from professionals, including psychologists, social workers, and psychiatrists, versed in depression and anxiety disorders, including their impact on diabetes, is necessary to aid in the management of these conditions. Depressive symptoms and frank depression, associated with reduced motivation, often lead to reduced attention to diabetes self-care, yielding hyperglycemia. Further, the symptoms of depression and persistent hyperglycemia can overlap with intensification of fatigue. Anxiety disorders also complicate living with and managing diabetes, in particular, related to fear of needles/injections or fear of extremes of glucose levels. Fear of hypoglycemia is more common than fear of hyperglycemia but some may fear the latter

due to extreme concerns about the development of diabetes complications. Extreme anxiety can trigger panic attacks. Additionally, symptoms of hypoglycemia and anxiety can also overlap, at times, further complicating management and generally leading to poor control [13].

Disordered eating behaviors and eating disorders, especially common in females, also complicate diabetes management, especially during the period of transition [13]. A unique manifestation of eating disorders in diabetes is the purposeful restriction or omission of insulin. The deliberate under-dosing of insulin serves as a very potent but dangerous weight-loss strategy [72]. Many specific elements of T1DM and its treatment have been linked to the development of disordered eating behaviors. Specifically, the following have been linked to the occurrence of disordered eating and eating disorders:

- the initial loss of weight at the onset of the disease followed by weight gain upon initiating insulin replacement;
- occasional weight gain associated with intensive insulin therapy;
- a focus on diet as part of the diabetes treatment plan; and
- the need to eat often without hunger due either to peaking insulin action or hypoglycemia [73, 74].

Furthermore, disordered eating and eating disorders, particularly with insulin restriction or omission, lead to deterioration in glycemic control and subsequent complications, and even premature mortality [75–77]. It is crucial that teenagers and emerging adults with disordered eating behaviors or eating disorders receive specialized care, often coordinated by the diabetes treatment team; however, this can be problematic if care for the affected person falls between the pediatric and adult healthcare systems [13].

In addition to the challenges enumerated above, there is a lack of empirically validated programs to promote transition readiness, well-defined criteria to determine transition readiness, and methods to ensure a smooth transfer between pediatric and adult healthcare systems. Thus, it is not surprising that many older teenagers and young adults with diabetes experience gaps in care upon transfer, deterioration of glycemic control, and increased risk for acute complications and the unrecognized emergence of chronic complications. Finally, there may be a component of reticence and even ambivalence regarding transition and transfer on the part of pediatric providers. Many pediatric diabetes providers have known their patients for years and may have difficulty discharging their patients to adult providers, as they worry about how their patients will adjust to different models of care. Thus, there is a need for coordinated efforts between pediatric and adult providers to ease the transition and transfer for patients and families as well as for the providers.

Existing transition programs and interventions

Currently, some transition programs exist in the USA and in other countries. However, there is no documented "gold standard" approach that has been empirically proven to yield optimal outcomes with respect to engagement, follow-up, medical outcomes, and psychosocial outcomes. The literature includes descriptions of structured and unstructured transition programs, with structured programs generally reporting better outcomes. The following section will describe published approaches to transition programs along with suggestions for future directions.

There are three main approaches to developing transition programs: clinics dedicated solely to emerging young adults, clinics focused on transition planning, and clinics that incorporate care coordinators (care ambassadors or patient navigators) to ensure timely follow-up. In dedicated young adult clinics, there are generally specific days and times reserved for the care of young adults within diabetes clinics. These focused clinics tend to be staffed by adult providers who possess particular interests in the care of emerging young adults.

Outcomes resulting from care in young adult clinics have been variable, with some studies yielding no effect on glycemic control [78], while others have demonstrated superior outcomes with lower HbA_{1c} levels and reductions in hospital admissions [79, 80]. The different results may reflect variations in design and features of each of the programs.

The second kind of transition program relates to transition preparation, which provides pediatric diabetes teams, patients, and families with a more structured and purposeful approach to transition planning aimed at creating a successful transfer. In 2009, Cadario and colleagues [81] retrospectively examined two groups who were transferred from pediatric to adult diabetes care in different ways. The first group received a letter with information about their medical history and a scheduled appointment with an adult provider. The second group participated in a structured transition program, which included transition planning during the last year of pediatric care and discussions about what to expect following the transfer. Additionally, both pediatric and adult physicians participated in the last pediatric clinic appointment and first adult clinic appointment, with the pediatrician providing a medical summary to the patient and adult doctor at the last pediatric appointment. The second group had more optimal outcomes, with a shorter time between last pediatric and first adult clinic appointments, better clinic attendance in the first year post-transfer, and improved HbA_{1c}. Furthermore, the second group reported satisfaction with the transition process [81]. More rigorous, prospective studies are needed.

The third type of transition program utilizes a care coordinator who works closely with the older teenagers or young adults as they transition from pediatric to adult diabetes care. Van Walleghem and colleagues [82] evaluated an intervention called the Maestro Project, which assigns a care coordinator to maintain consistent contact and ensure access to diabetes care for patients during the transition process. In addition to the care coordination, this program provided a website, newsletter, group meetings, and educational events. The authors reported that patients in the program had greater retention in care. Further, the coordinator helped recapture patients who had been previously lost to

follow-up care. Other studies of care coordination have shown varied results; one demonstrated improved glycemic control and reduced hospitalizations [79] while another study comparing usual care with outreach by phone revealed no difference in outcomes [83]. Again, varying results may reflect differences in program features or implementation.

British researchers performed a systematic review of care transition among many chronic diseases of childhood and compared the effectiveness of different transition programs by evaluating the reported health outcomes [84]. The evaluation of outcomes varied according to the study design and included comparisons of transition programs with control conditions as well as pre- and post-intervention designs. Three categories of intervention were studied. The first was directed toward the patient and consisted of educational programs and skills training. The second focused on staff and involved care coordinators and joint pediatric and adult clinics. The third involved healthcare service delivery and after-hours phone support with intensive follow-up specifically directed at the young adults. Results indicated the most successful programs included patient education and transition clinics directed either to young adults within adult healthcare settings or including both pediatric and adult providers, all of which included people with diabetes [84]. From this report, it remains clear that there is a need for more prospective, longitudinal research.

In addition to the transition programs housed within either pediatric or adult diabetes clinics described above, there may be opportunities to support older teenagers and young adults within a support group setting. Our team at the Joslin Diabetes Center in Boston recently examined the utility of monthly support groups for young adults with T1DM and found that after 5 months of participation, self-reported diabetes burden decreased, two-thirds of participants had improved HbA_{1c}, and there was a trend for improved self-care [85]. Another report described a program that combined aspects of many of the clinical centers listed earlier [86]. Vidal and colleagues implemented a program that included transition planning, coordinated transfer visits, an extended intake appointment with adult diabetes staff, and support group sessions [86]. They found that those who participated in this program had improved HbA_{1c}, decreased hypoglycemic episodes, and greater diabetes-specific knowledge compared to those who received standard care. A number of investigations are ongoing worldwide to design, implement, and evaluate transition programs, given the increasing numbers of older teen and emerging adults with diabetes in need of improved systems of care and improved health outcomes.

Summary

Significant physical, social, and emotional growth occurs during the adolescent years. The extra burden of diabetes adds further challenges at this time. Teenagers with diabetes have often developed a strong relationship with their pediatric diabetes care team, and the transfer to a new adult diabetes care team disrupts an established bond. Adolescents and young adults must develop increasing independence and responsibility for their diabetes care. This could be a time of crisis or a time of opportunity. By approaching this transition equipped with information about normal developmental stages and the unique challenges of diabetes self-care at this time, parents and diabetes healthcare providers can help older adolescents and emerging adults make this transition, and empower them to negotiate the transition and transfer as seamlessly as possible to preserve health and prevent the emergence of diabetes complications.

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61 Diabetes in Pregnancy

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Key points

- The main risks to pregnancy in women with diabetes are an increased rate of congenital malformations, an increased risk of intrauterine death in late pregnancy, and complications during delivery and in the postnatal period resulting from fetal overgrowth (macrosomia).
- By improving glycemic control in late pregnancy, remarkable reductions in perinatal mortality in women with diabetes were achieved in the middle of the 20th century, but rates of late intrauterine death remain 3–5-fold higher than in non-diabetic pregnancies.
- Less progress has been made in reducing the rate of congenital malformations, which are the consequence of exposure of the fetus to hyperglycemia in the first 6–8 weeks of pregnancy. A wide range of congenital malformations are associated with diabetes, but complex conotruncal cardiac anomalies are the most common.
- Metabolic changes in pregnancy facilitate nutrient transfer to the fetus. Maternal insulin resistance, which increases significantly from about 24 weeks' gestation, helps divert glucose to the fetus. Women with pregestational diabetes require increasing insulin doses during pregnancy. Women without diabetes before pregnancy become glucose intolerant in pregnancy if they have insufficient insulin reserve.
- Fetal insulin is an important fetal growth factor. Accelerated fetal growth occurs in many diabetic pregnancies as a consequence of maternal hyperglycemia causing fetal hyperinsulinemia. In later pregnancy, this metabolic environment may render the fetus susceptible to hypoxia and acidosis and ultimately stillbirth. It also increases the risk of neonatal hypoglycemia.
- The outcome of pregnancy can be improved by good prepregnancy care, the main components of which are folic acid supplementation, achieving good glycemic control, avoiding potentially embryotoxic drugs, and optimal control of diabetic complications before discontinuing contraception and attempting pregnancy.
- The proportion of women with diabetes who receive good prepregnancy care is disappointingly low, and it remains a major challenge to ensure that more women with diabetes are properly prepared for pregnancy.
- Diabetic retinopathy may deteriorate in pregnancy and in the months following birth, sometimes to the point where laser treatment is required. Those at greatest risk are women with pre-existing retinopathy who come into pregnancy with poor glycemic control that then rapidly improves.
- Diabetic nephropathy is a risk factor for pre-eclampsia, intrauterine growth retardation, and preterm birth, but pregnancy does not seem to affect the long-term outlook of renal disease.
- Antenatal management should focus on achieving maternal glucose levels as near normal as is safely achievable, and close maternal and fetal surveillance for medical and obstetric complications. A number of national evidence-based clinical guidelines for diabetes in pregnancy have been published.
- Secular trends towards having fewer children later in life and increasing levels of obesity impact on fertility and obstetric management.
- The increasing prevalence of obesity has seen a marked rise in the prevalence of type 2 diabetes in pregnancy. Obesity itself has a significant impact on maternal and fetal pregnancy outcomes, and is associated with stillbirth, macrosomia, and hypertension in pregnancy. Rising obesity levels are also contributing to the increasing number of women developing glucose intolerance during pregnancy.
- Excessive gestational weight gain is an important cause of macrosomia, hypertension in pregnancy and fetal morbidity in women with established and gestational diabetes.
- Testing for gestational diabetes is undertaken at 24–28 weeks' gestation when maternal insulin resistance is increasing. There is continued debate on how gestational diabetes is best diagnosed, the thresholds for treatment, and the risks, costs, and benefits of intervention.
- Dietary modification, physical activity, and limiting gestational weight gain are the mainstays of treatment of gestational diabetes, with insulin or oral antidiabetes therapy added if glucose values cannot be normalized.
- Intervention trials in mild gestational diabetes have shown that treatment makes babies 2–3% lighter (so lowering the incidence of macrosomia), and reduces the incidence of shoulder dystocia and hypertensive disorders of pregnancy. It is not clear if these effects are primarily due to lower maternal blood glucose values or to less maternal weight gain.
- Both metformin and glibenclamide are effective in reducing maternal glycemia, but fetal outcomes appear to be poorer with glibenclamide.

Textbook of Diabetes, Fifth Edition. Edited by R. Holt, C. Cockram, A. Flyvbjerg and B. Goldstein.

- A proportion of women diagnosed with gestational diabetes actually have previously unrecognized diabetes. These pregnancies have the same risks as those of women with known diabetes, and there is increased interest in diagnosing such cases early in pregnancy, by either screening or risk factor-based testing.
- The majority of newly recognized diabetes cases will have type 2 diabetes, but the onset of type 1 diabetes in pregnancy is not uncommon.
- Women with pregestational and pharmacologically treated gestational diabetes should be offered induction of labor at 38 completed weeks to reduce the risk of a late stillbirth and the risk of birth injury from a large for gestational age infant.
- Insulin requirements fall to prepregnancy values in the immediate postpartum period.
- Early breastfeeding reduces the risk of neonatal hypoglycemia. All mothers with diabetes should be encouraged to breastfeed within 30 min of birth and then every 3–4 h, until a regular feeding pattern is established.
- Women who have had gestational diabetes should be screened for diabetes postpartum and then annually and receive lifestyle advice to lessen their long-term risk of future diabetes.

Introduction

The dramatic improvement in the outcome of pregnancy for women with diabetes that occurred in the middle decades of the last century was one of the outstanding medical achievements of the age. Before the discovery of insulin, the chances of a woman with diabetes dying in pregnancy were very high and those of delivering a live, healthy baby were negligible. The discovery of insulin transformed the life expectancy of women of child-bearing age, and its use also restored fertility, previously affected by the disease and its treatment [1]. Maternal mortality dropped very sharply, but the prognosis for the fetus remained dismal. As late as 1953, even centers specializing in diabetes pregnancy were recording perinatal mortality rates of 20–25% [2]. The major cause of perinatal mortality was the late intrauterine death of overgrown or "macrosomic" fetuses, but birth trauma, early neonatal death (particularly from severe hypoglycemia), and major congenital anomalies also took their toll. Over the following two decades, advances pioneered at centers such as the Joslin Clinic in Boston, King's College Hospital in London, and the Rigshospitalet in Copenhagen established that good glycemic control in mid- and late pregnancy, coupled with early delivery, could substantially reduce perinatal mortality and morbidity [2]. These results were soon replicated around the world as the need for intensive integrated care was recognized, and units specializing in diabetes pregnancy were established. It is worth remembering that these remarkable improvements in pregnancy outcome were achieved well before the development of technologies such as glycated hemoglobin measurement, insulin pens and pumps, self-blood glucose monitoring, and obstetric ultrasound on which much of current practice relies.

Until the 1980s, type 2 diabetes mellitus (T2DM) was largely confined to middle-aged and older people and so its occurrence in pregnancy was rare, but the epidemic of obesity has seen not only a great increase in the number of people with T2DM, but also a reduction in age at its onset. The UK National Diabetes Pregnancy Audit of 2013 reported that the proportion of women with established diabetes who have T2DM increased from 27 to 45% in 10 years [3], and in many countries the number of women with T2DM in pregnancy now exceeds that of women with type 1 diabetes mellitus (T1DM). This change has brought its own set of problems and challenges, as the majority of women with T2DM are overweight, and obesity is itself strongly associated with adverse obstetric outcomes [4–8].

Maternal overweight and obesity are also central to the issue of gestational diabetes. Observations in the 1930s and 1940s suggested that women who later developed what we now call T2DM had reproductive histories with a high incidence of large babies and fetal loss, raising the possibility that a prediabetic state existed that was harmful to the fetus [9]. The concept of gestational diabetes was developed in the 1960s, but the diagnostic criteria initially proposed were based on the ability of the glucose tolerance test in pregnancy to predict future diabetes in the mother, rather than fetal outcomes [10]. As discussed later, the diagnostic criteria and the value of treatment remain the subject of much current debate.

Changes in glucose metabolism in pregnancy

Maternal metabolism changes significantly during pregnancy. From about 8 weeks' gestation fasting glucose concentrations decrease, and reach a nadir by the end of the first trimester. The sensitivity of muscle and adipose tissue to insulin changes little in early pregnancy, but decreases significantly after about 22 weeks' gestation, by 33–78%, depending on the method by which it is assessed. The degree of insulin resistance may be even greater than this, as the methods of assessment do not capture (the non-insulin-requiring) glucose utilization by the placenta and fetus. As a consequence of increased insulin resistance, postprandial glucose levels are increased. There is a concomitant increase in fasting insulin, but hepatic glucose production, which would normally be suppressed by the increase in insulin, is also increased, indicating decreased hepatic insulin sensitivity.

The precise mechanism underlying the insulin resistance of late pregnancy is uncertain, but it appears to be related to a combination of increased hormone concentrations (human placental lactogen, progesterone, estrogen, prolactin, and cortisol), increased free fatty acid concentrations, and changes in various cytokines secreted by the placenta, such as tumor necrosis factor-alpha (TNF-α), adipocyte fatty acid-binding protein, and leptin [11]. The degree to which insulin resistance is increased is also related to maternal weight gain. Non-obese women gain 3.5 kg of

fat on average during a normal pregnancy; subcutaneous deposits increase and provide a ready source of calories for the fetus and mother, but increased visceral deposits contribute to insulin resistance.

For glucose tolerance to be maintained, maternal β cells compensate for the fall in insulin sensitivity by increasing first- and second-phase insulin responses approximately threefold by the last trimester [12]. Increased insulin secretion is associated with morphological changes in the pancreas, including marked β-cell hypertrophy and hyperplasia [13].

In teleological terms, pregnancy-related maternal insulin resistance benefits fetal growth, since a rise in postprandial glucose concentration aids glucose transfer to the fetus ("facilitated anabolism") [14]. Maternal to fetal glucose transfer in the fasting state is also enhanced by maternal lipolysis, which occurs in late pregnancy, with free fatty acids becoming the main maternal fuel substrate with diversion of glucose to the fetus. The ability of insulin to suppress lipolysis via inhibition of hormone-sensitive lipase in adipose tissue is impaired in late pregnancy, when maternal free fatty acid release and fatty acid oxidation are increased in parallel with reduced carbohydrate oxidation [15–17]. This process of enhanced lipolysis [18] is attributed to the actions of human placental growth hormone and other placental hormones [19–24]. All of these metabolic changes facilitate the transfer of glucose and amino acids to the fetus. The increase in hepatic glucose output in late pregnancy resulting from hepatic insulin resistance ensures that maternal glucose is available to the fetus between meals [25]. The main changes in glucose and lipid metabolism in pregnancy are summarized in Table 61.1. Increased insulin resistance induced by the fetoplacental unit reverses within a few hours of delivery, although of course any increase related to excessive maternal weight gain in pregnancy persists.

Table 61.1 Changes in glucose metabolism and lipids in normal pregnancy.

	Early pregnancy	Late pregnancy
Basal metabolism		
Fasting glucose	Decreased	Decreased (×0.9)
Fasting insulin	Unchanged	Increased (×1.6)
Hepatic metabolism		
Hepatic glucose production	Unchanged	Increased (×1.3)
Hepatic insulin sensitivity	Unchanged	Decreased
Insulin metabolism		
First-phase insulin response	Increased (×2)	Increased (×3)
Second-phase insulin response	Increased (×1.5)	Increased (×3)
Peripheral insulin sensitivity	Decreased (×0.7)	Decreased (×0.4)
Plasma lipids		
Triglycerides	Unchanged	Increased (×3)
Total cholesterol	Unchanged	Increased (×1.5)
HDL cholesterol	Unchanged	Increased (×1.2)
LDL cholesterol	Unchanged	Increased (×1.7)
Free fatty acids	Unchanged	Increased (×1.6)

HDL, high-density lipoprotein; LDL, low-density lipoprotein.
Source: Data summarized from Catalano et al. 1999 [12], Sivan et al. 1999 [15], Homko et al. 1999 [16], and Sivan et al. 1997 [17].

Gestational diabetes mellitus (GDM) is defined by the presence of glucose concentrations that are at the upper end of the population distribution and first detected in pregnancy. In most cases it arises from a relative failure to increase insulin secretion in the face of chronic insulin resistance (primarily related to obesity) that worsens in pregnancy and is often compounded by excessive gestational weight gain. Most studies of women who have had GDM reveal decreased β-cell function compared with women maintaining normal glucose tolerance in pregnancy [26–28]. The mechanism is therefore essentially the same as that occurring in T2DM, and so from this perspective GDM can be considered as simply a specific subtype of prediabetes.

Glycated hemoglobin (HbA_{1c}) values are lower in normal pregnancy than in the non-pregnant state, probably because of reduced fasting blood glucose levels and shortened erythrocyte survival [29]. Suggested upper limits of the reference range are 36 mmol/mol in the first and second trimesters and 40 mmol/mol in the final trimester [30, 31]. The small increase in HbA_{1c} in late pregnancy could be the consequence of developing iron deficiency [32].

Classification of diabetes in pregnancy

Diabetes in pregnancy encompasses those women known to have diabetes before pregnancy (sometimes called "pregestational diabetes") of various types, and those with hyperglycemia first detected in pregnancy ("gestational diabetes"). The latter category includes some women who have diabetes that was undetected before pregnancy, in whom pregnancy outcomes may be particularly poor [33–35]. Recent classifications have attempted to distinguish this group by glucose tolerance test or glycated hemoglobin-based criteria [36, 37]. A rather confusing terminology has resulted, the group with suspected undetected diabetes being termed "diabetes in pregnancy" (World Health Organization [WHO]) or "overt diabetes in pregnancy" (International Association of Diabetes and Pregnancy Study Groups [IADPSG] and American Diabetes Association [ADA]). The WHO further suggested that the label "gestational diabetes" be restricted to women with hyperglycemia first detected in pregnancy who do not have "diabetes in pregnancy" (Table 61.2).

New-onset T1DM in pregnancy

Most women diagnosed with "overt diabetes in pregnancy" will have previously unrecognized T2DM. The onset or detection of T1DM in pregnancy is, however, not uncommon. The finding of unusually high blood glucose results with or without ketonuria in a woman who is not obese should prompt consideration of the diagnosis. Serological tests for islet cell autoimmunity are usually strongly positive. Between 3 and 10% of women with newly recognized diabetes in pregnancy prove to have T1DM [38, 39].

It has been suggested that the incidence of T1DM in pregnancy exceeds the expected rate [40]. This at first seems unusual, given

Table 61.2 Recent proposals for the classification of diabetes in pregnancy.

Type of diabetes	Also called
Known diabetes	*Pregestational diabetes*
Type 1 (T1DM)	
Type 2 (T2DM)	
Genetic diabetes (*GCK, HNF1A*, etc.)	
Other types (cystic fibrosis, etc.)	
Hyperglycemia first detected in pregnancy	*Gestational diabetes*
Diabetes in pregnancy[a] *(WHO classification)*	Overt diabetes in pregnancy[a] *(ADA–IADPSG classification)*
Gestational diabetes	

[a]Diabetes first detected in pregnancy but with an HbA_{1c} or fasting glucose that suggests undetected diabetes antedating the pregnancy.
Source: International Association of Diabetes and Pregnancy Study Groups 2010 [36] and World Health Organization 2013 [37].

that with most other autoimmune disorders disease activity is suppressed in pregnancy. However, it is likely that the increased insulin resistance of pregnancy in the context of declining β-cell function overcomes any such effect (70% of such women are diagnosed in the third trimester). Most of these women have modest hyperglycemia detected by screening for GDM, but presentation with diabetic ketoacidosis can occur: the latter presentation is associated with a high perinatal mortality rate [41]. After delivery, a high proportion of women in this category can stop insulin and may even lose their diabetes, but with time relapse occurs in almost all cases [41].

Fulminant-onset T1DM

This entity was first described in Japan in 1987, but has since been observed in women in or originating from other East and South-East Asian countries. Women present abruptly with severe diabetic ketoacidosis, often preceded by flu-like symptoms and abdominal symptoms. Serum pancreatic enzymes are commonly elevated and whereas blood glucose levels are very high, glycated hemoglobin levels are normal, emphasizing the acuteness of onset [42]. The disease seems to have a particular predilection for late pregnancy (or immediately postpartum): 21% of cases in women in the 13–49-year-old age group occurred in pregnancy [43] and again, emphasizing its acute nature, many cases had tested negative for GDM just a few weeks beforehand. The perinatal mortality rate with this condition is very high [44].

New-onset T2DM in pregnancy

The majority of cases of diabetes detected for the first time in pregnancy have T2DM. A proportion of these women will have had GDM in earlier pregnancies or be known to have had prediabetes, and almost all will have some other features of the metabolic syndrome, such as truncal obesity, acanthosis nigricans, hypertension, dyslipidemia, and fatty liver. The frequency with which this condition is seen depends largely on the prevalence of obesity in the community. In Auckland, New Zealand, where obesity is prevalent amongst Māori and Pasifika communities, for every three cases of known T2DM in pregnancy a further two were detected for the first time in pregnancy; 13% of cases of GDM had previously undetected T2DM (as defined by early postpartum glucose tolerance testing) [35]. Women with previously unrecognized T2DM have higher rates of perinatal mortality and congenital malformation than those with lesser degrees of GDM, and the same as those with known T2DM [33–35]. The recognition that this is a high-risk condition has prompted the interest in detecting it by early pregnancy screening.

Cystic fibrosis-related diabetes and pregnancy

Survival into adulthood is now common amongst people with cystic fibrosis, so that pregnancy is becoming an issue for these women. The incidence of cystic fibrosis-related diabetes increases with prolonged survival; in the 20–30-year-old age group about one-third will have developed diabetes (see Chapter 21). Women with cystic fibrosis who become pregnant actually have better survival than those who do not, but this is because the ones who have children are less ill: they have better pulmonary function, higher body mass index (BMI), and a lower prevalence of diabetes [45]. Women with cystic fibrosis-related diabetes have a higher incidence of premature delivery than those without diabetes, but this is likely in part to be iatrogenic [46].

Monogenic diabetes

Diabetes is a heterogeneous condition and although most women with pre-gestational diabetes will have T1DM or T2DM, a few will have genetic diabetes (most commonly due to *GCK* or *HNF1A* mutations, or mitochondrial diabetes). Pregnant women are younger than the average adult with diabetes and so the pregnant population has a relatively high proportion of women with genetic forms (with diabetes presenting from birth in the case of *GCK* mutations, or from the teenage years to the 20s in the case of *HNF1A* mutations). The same considerations apply to women with "overt diabetes in pregnancy" discovered as result of screening for GDM. Pregnancy may thus be the first time that asymptomatic forms of monogenic diabetes are diagnosed. The clues to identifying such women lie in attaining accurate family histories and phenotyping (see Chapter 18). Recognition is important because of the impact of certain forms of monogenic diabetes on fetal growth.

Effects of diabetes on pregnancy

Fertility and conception

Fertility is usually normal in women with T1DM, although delayed menarche in girls diagnosed before puberty is common, especially if diabetic control is poor [47, 48]. Although the age at menopause in women with T1DM is normal [49], fertility declines

with age and, in common with the general population, women with T1DM now often choose to delay having children. Other potential causes of infertility in women with T1DM are eating disorders (prevalent among young women with T1DM; see Chapter 57) that are commonly associated with anovular cycles and amenorrhea [50]. Rarely, autoimmune premature ovarian failure can be associated with T1DM [51].

The degree to which polycystic ovarian syndrome is expressed clinically is strongly related to obesity and, indeed, polycystic ovaries may be regarded as a component of the metabolic syndrome. Women with T2DM are usually overweight and there is a strong association between glucose intolerance and polycystic disease [52]. Subfertility due to polycystic disease responds to weight loss and metformin treatment. Other insulin sensitizers may also improve fertility but should be avoided because of their potential adverse effects on the developing fetus.

Miscarriage

Spontaneous miscarriage rates among women with diabetes are broadly similar to those in the general population (12–15%), although the risk is increased when diabetic control is poor [53–55].

Early fetal loss in non-diabetic pregnancies is often attributable to lethal chromosomal abnormalities. Fetal trisomy is more common with advancing maternal age, hence the association of the latter with an increased miscarriage rate. Diabetic pregnancies are not at increased risk of chromosomal abnormalities, but nonviable congenital malformations are more common than in nondiabetic pregnancies and probably contribute to the increased early miscarriage rate in women with poorly controlled diabetes.

Maternal obesity is associated with poorer success with *in vitro* fertilization and may also be a risk factor for first-trimester miscarriage. Not all studies concur, but a threefold increase in recurrent early miscarriage (defined as more than three successive miscarriages before 12 weeks) was found in a United Kingdom study of pregnant obese women (BMI >30 kg/m^2) compared with age-matched women of normal weight [56]. As more older and obese women with T2DM are now becoming pregnant, miscarriage rates may well rise.

Congenital anomalies

The risk of major fetal congenital anomalies is increased in women with diabetes, irrespective of the type of diabetes. Abnormally high glucose levels in maternal blood, transported to the embryo, are responsible for the teratogenic effect. To have such an effect, fetal exposure to hyperglycemia must occur at the earliest stages of pregnancy (6–8 weeks), during which organogenesis occurs. Major fetal anomalies (detected by ultrasound in early pregnancy) are common reasons for elective termination of pregnancy and an important cause of perinatal morbidity and mortality. As many women do not present for care until after the critical first 8 weeks, it is unsurprising that it has been difficult to reduce the proportion of diabetic pregnancies complicated by major congenital anomalies.

The most prevalent abnormalities are neural tube defects (including anencephaly and encephalocele), which are increased fourfold, and congenital heart disease, which is increased threefold [57]. Although no cardiac anomaly is specific to diabetes, severe conotruncal anomalies are more common than simple anomalies. Transposition of the great arteries, tricuspid atresia, and truncus arteriosus are at least 15 times more prevalent in infants of mothers with diabetes [58].

A wide variety of other defects are commonly seen either singly or in combination (Figure 61.1, Table 61.3). Again none are exclusive to diabetes, although caudal dysgenesis (sacral agenesis) is relatively specific to diabetic pregnancy [59]. Many anomalies are components of the VACTERL association (vertebral defects, anal atresia, cardiac defects, tracheo-esophageal fistula, renal anomalies, and limb abnormalities). One model for the clustering of these features is the idea of the "developmental field defect," in which malformations that occur in blastogenesis tend to result in polytopic anomalies, affecting multiple organ systems [60]. It has been suggested that tissue-specific developmental control genes are regulated at specific times in embryonic development by glucose metabolism or that maternal diabetes, possibly through epigenetic changes, reduces the precision of gene regulation [61, 62].

The risk of a fetus having a major congenital anomaly is clearly related to maternal glycemia around the time of conception [63, 64]. The absolute risk is ~3% when the periconceptional HbA_{1c} is 50 mmol/mol, and 10% when it is 100 mmol/mol. However, the 95% confidence intervals (CIs) around these estimates are very wide (Figure 61.2), so there is no certainty of prediction, suggesting that whether or not a fetus is affected is a stochastic event.

Fetal morbidity

Macrosomia

Maternal hyperglycemia increases placental fetal transfer of glucose. In response to this, fetal insulin secretion is increased; immunoreactive insulin is detectable in the human fetal pancreas by the seventh week after conception, with evidence of functional fetal β cells by the end of the first trimester [65]. The diabetic intrauterine metabolic environment promotes abdominal fat disposition and visceral growth, notably in the liver and heart. The infant of a mother with diabetes is thus "growth promoted" [66]. Maternal diabetes, particularly when it is poorly controlled, is therefore a potent cause of accelerated growth. In women with T1DM, birth weights are typically 1.3–1.4 standard deviations above the population norm, with twice as many babies with birth weights >90th centile as normal [67, 68]. There is increasing recognition that maternal obesity and gestational weight gain are also important causes of fetal overnutrition and macrosomia. Along with rest of the population, there is a secular trend to increasing BMI in women with T1DM, which may contribute to persistently high rates of macrosomia [69].

Macrosomia has variously been defined as a birth weight >90th or >95th centile, for general or population-specific norms; or a birth weight of >4 or >4.5 kg. Higher maternal age, height, parity,

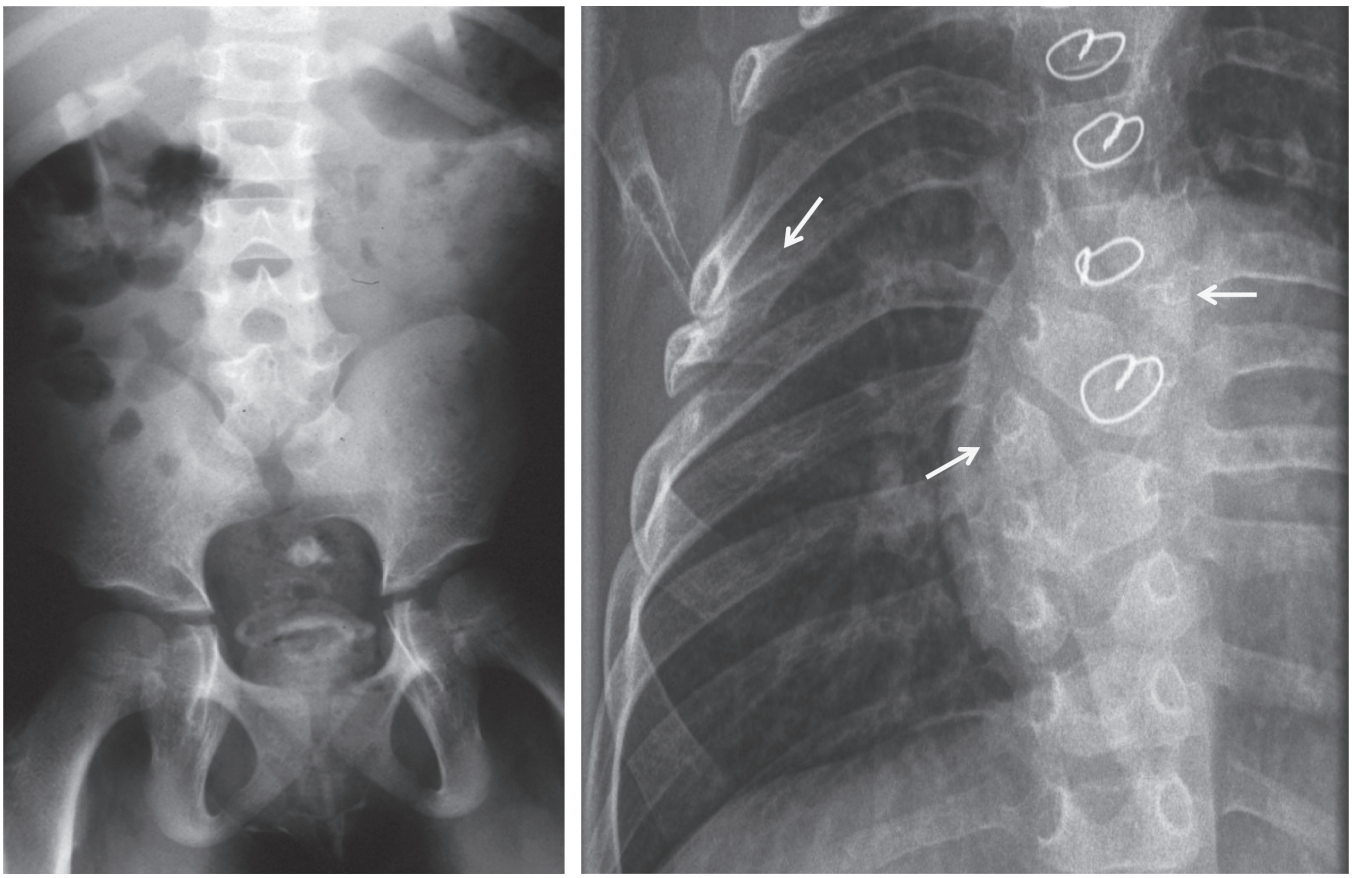


Figure 61.1 Examples of diabetic embryopathy. Left: sacral agenesis in a child whose mother had poorly controlled T2DM at conception. Affected children can have spina bifida-like features with difficulties walking and bowel and bladder dysfunction. Right: chest radiograph from an infant of a mother with T1DM. The child had cardiac surgery at age 7 months for double outlet right ventricle. Note also the two hemivertebrae and the fused ribs (arrowed).

BMI, presence of diabetes, gestational age at delivery, and male fetal sex are all significantly related to macrosomia [70]. Although simple to measure and almost universally recorded, birth weight is a fairly crude measure; a long, thin newborn can weigh the same as a short, fat child, but the *in utero* exposures and neonatal risks are not necessarily the same.

Accelerated growth can be detected on routine clinical ultrasound as a relative increase in the abdominal circumference

Table 61.3 Absolute and relative frequencies of congenital malformations in diabetic pregnancy.

Type of defect	Approximate frequency (%)	Relative frequency
Congenital heart disease	21	3×
Central nervous system	18	3×
Renal and urinary defects	12	4×
Lower spine defects	12	39×
Upper spine/rib defects	11	26×
Caudal dysgenesis	5	53×

Source: Martinez-Frias 1994 [59]. Reproduced with permission of John Wiley & Sons.

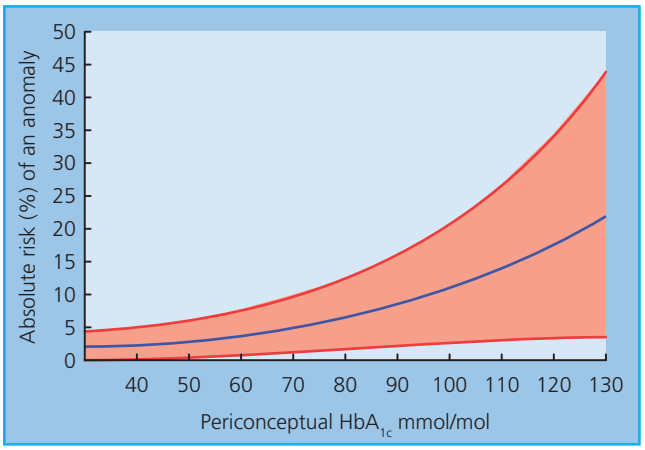


Figure 61.2 The risk of major or minor congenital anomalies according to periconceptual HbA_{1c} in women with diabetes. The data are presented as the absolute risk with upper and lower 95% CIs (shaded area). Note that the CIs are very wide, making prediction difficult in an individual case. Source: Data from Guerin et al. 2007 [63].

Table 61.4 Differential effects on fetal growth of mutations in genes causing monogenic diabetes according to whether the mother or the fetus carries the wild-type (–) or the mutated form (+) of the gene.

Gene	Mother+/fetus–	Mother+/fetus+	Mother–/fetus+
GCK	Increased birth weight[a]	Normal birth weight (decreased if maternal hyperglycemia is treated)	Decreased birth weight
HNF1B	Increased birth weight[a]	Low birth weight	Normal birth weight
HNF4A	Increased birth weight[a]	Increased birth weight – neonatal hypoglycemia	Increased birth weight – neonatal hypoglycemia

[a] Birth weight can be normalized by treating maternal hyperglycemia.
Source: Hattersley et al. 1998 [73], Spyer et al. 2009 [74], Edghill et al. 2006 [75], and Pearson et al. 2007 [76].

measurement after about 28 weeks' gestation (Figure 61.3) [71]. Although characteristic of the diabetic pregnancy, this finding again is not specific, as it can result from maternal obesity and excess gestational weight gain. Fetal liver length measurements may be more specific to hyperglycemia [72], but are technically challenging.

Many other factors influence fetal growth, including placental size and function, uterine blood flow, hypertension, and smoking. Genetic factors are also important. This is most graphically illustrated by the effects of *GCK* and *HNF4A* mutations (Table 61.4), which can differ according to whether the mother and fetus have the same or are mismatched for the disease-associated mutation [73–77]. Genome-wide association studies have identified mutations and polymorphisms in other genes that are associated with fetal growth patterns [78].

The potential consequences of accelerated growth *in utero* include an increased risk of shoulder dystocia, birth trauma and birth asphyxia. Emergency cesarean section and some neonatal morbidities are also linked to fetal overgrowth. The increase in subcutaneous fat distribution in these infants combined with their high hematocrit gives them a typical "macrosomic" appearance with plethoric features and an obese body (Figure 61.3).

Shoulder dystocia and brachial plexus injury

Shoulder dystocia occurs when, after delivery of the fetal head, the baby's anterior shoulder becomes stuck behind the mother's pubic bone. If this happens, the remainder of the baby does not follow the head out of the vagina as easily as during normal delivery. There is no agreed definition; some suggest that shoulder dystocia should be diagnosed only when there is some time delay (1 min is often quoted) between the delivery of a baby's head and shoulders. Others suggest that shoulder dystocia is present any time that the midwife or obstetrician finds that the shoulders cannot be delivered with the normal amount of downward traction on the fetal head. Still others have suggested that the definition of true shoulder dystocia requires that special maneuvers have to be employed in order to deliver the shoulders. Hence there is always some degree of subjectivity in the reports of its incidence.

The Confidential Enquiry into Maternal and Child Health (CEMACH) study reported that 8% of babies of mothers with established diabetes had shoulder dystocia, compared with 3% in a general maternity population. The risk of shoulder dystocia was clearly related to birth weight, increasing from <1% in babies weighing <2.5 kg to 43% of babies weighing >4.5 kg [79]. The incidence of brachial plexus injury (Erb palsy) was increased 10-fold but remained an infrequent event (<0.5%). Another study of women with T1DM reported an incidence or Erb palsy of 2% [80]. Although most babies suffering brachial plexus injuries recover without long-term sequelae, the most serious damage tends to occur in the largest babies [81, 82].

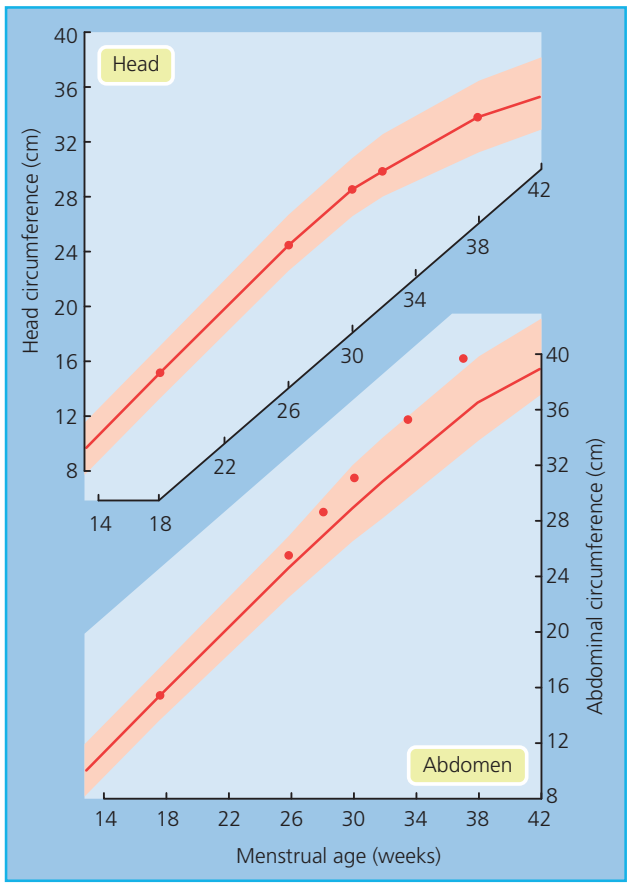
Shoulder dystocia also affects maternal morbidity, in particular increasing the risk of postpartum hemorrhage and third- and fourth-degree perineal tears [83].

Stillbirth

Stillbirth is defined as fetal loss occurring after 24 completed weeks of gestation. In women both with and without diabetes, identifiable causes of stillbirth include congenital malformations, chromosomal abnormalities, infection, and intrauterine growth restriction. Approximately one-quarter of all cases are unexplained [84]. The risk of stillbirth in diabetic pregnancies is approximately fivefold higher than for non-diabetic pregnancies [85–87]. In the CEMACH audit, there were 63 stillbirths in 2536 births in one calendar year, representing a 4.7-fold greater risk than that of the general UK antenatal population (5.7 per 1000 births). There was no difference in the stillbirth rate between T1DM (25.8/1000) and T2DM (29.2/1000). A similar stillbirth rate of 25 per 1000 births was seen in an audit of T1DM pregnancies in northeast England between 1990 and 1994 [88]. The CEMACH audit and other studies have identified poor glycemic control throughout pregnancy as a risk factor for stillbirth [79, 89]. Other identifiable risk factors include diabetic nephropathy, smoking, and lower socioeconomic status [90].

It is important to recognize that obesity and increasing maternal age are also risk factors for stillbirth in women both with and without diabetes. This may explain why, in obstetric units that serve extremely obese women with T2DM, the stillbirth risk may be higher for T2DM than T1DM [35, 91].

A proportion of stillbirths in diabetic pregnancies cannot be explained by congenital malformations or other identifiable causes. The etiology remains uncertain, although chronic fetal hypoxia and acidosis may be contributory factors [92]. Fetal



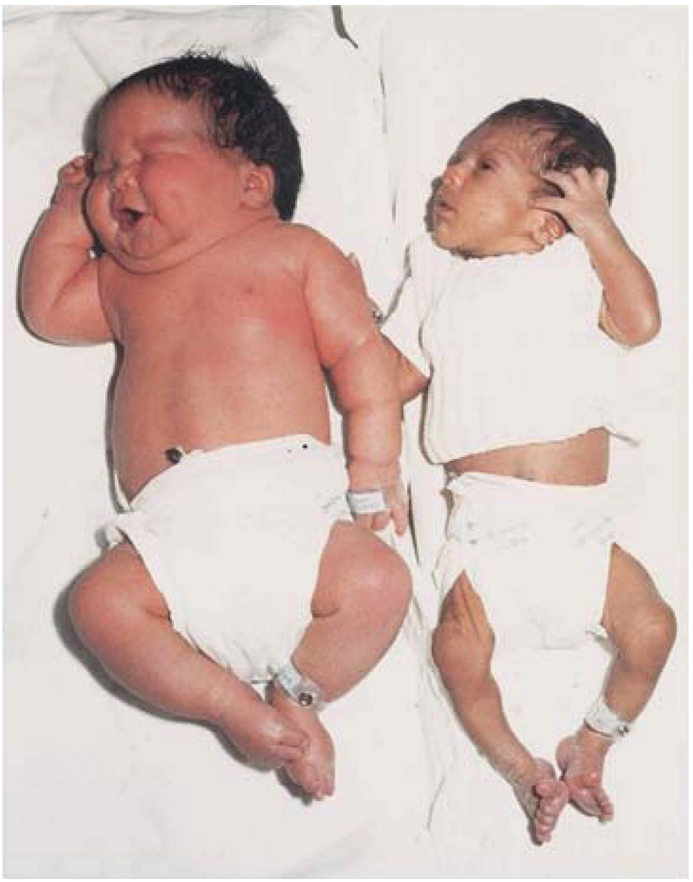


Figure 61.3 Macrosomia. Left: accelerated fetal growth, manifested as a progressive increase in abdominal circumference (lower panel), while head circumference remains on the 50th centile (upper panel). The red line represents the 50th centile and the shaded area represents the 3rd to 97th centile. The accelerated growth in abdominal circumference is not specific to maternal diabetes. It can also result from maternal obesity and excessive gestational weight gain. Right: a macrosomic baby born to a mother with diabetes, with a normal-weight baby born to a mother without diabetes for comparison.

hyperinsulinemia combined with the availability of excessive fuel substrate increases oxygen demand in insulin-sensitive tissues and it is postulated that this may eventually exceed placental oxygen supply [93]. Human and large animal studies suggest that the fetuses of diabetic pregnancies may be more susceptible to acidosis than those of a non-diabetic pregnancy [94, 95]. Amniotic erythropoietin, a marker of chronic fetal hypoxia in late pregnancy, is higher in diabetic than non-diabetic pregnancies. In one study of women with T1DM, amniotic erythropoietin levels correlated inversely with cord blood pH and pO_2 at birth [92].

Hypoglycemia

Neonatal hypoglycemia is important because if prolonged and severe it can cause brain injury and poor neurodevelopmental outcome. Although there is debate about the definition, thresholds for treatment (typically <2.2 or <2.6 mmol/L) have been established and are used in clinical practice [96]. Neonatal hypoglycemia affects as many as 5–15% of otherwise healthy babies [96, 97] and is widespread in resource-poor countries [98].

Capillary blood glucose readings are often unreliable as they commonly have poor precision at low values, and so when neonatal hypoglycemia is suspected, the plasma or blood glucose concentration should be determined immediately by using one of the laboratory enzymatic methods (e.g. glucose oxidase, hexokinase, or dehydrogenase method) [99].

Hypoglycemia is common, albeit usually transient, in infants of women with diabetes and occurs in approximately half of all diabetic pregnancies. However, it is also common after preterm birth, in small-for-gestational-age and large-for-gestational-age babies [100]. The macrosomic infants of mothers with diabetes are at risk for hypoglycemia because of postpartum hyperinsulinemia secondary to fetal β-cell hyperplasia and the inhibition of hepatic glucose production by hyperinsulinemia.

Most cases of neonatal hypoglycemia occur in the first 24 h after delivery [100]. The risk is greater if the maternal blood glucose concentration is high during labor, and can be minimized by maintaining the maternal blood glucose at <8 mmol/L during labor [101].

Early feeding reduces the risk for hypoglycemia, and so it is recommended that all mothers with diabetes be encouraged to breastfeed within 30 min of birth and then every 3–4 h, until a regular feeding pattern is established. The current National

Institute for Health and Care Excellence (NICE) guideline recommends the use of intravenous glucose to treat neonatal hypoglycemia only when there are clinical signs or a persistent blood glucose <2.0 mmol/L that cannot be raised by oral or tube feeding, or when the blood glucose is very low (1.1–1.4 mmol/L). If intravenous glucose is required, this should be continued until the glucose level is >2.5 mmol/L [102]. The prophylactic use of a glucose gel applied to the buccal mucosa of at-risk babies can reduce the incidence of neonatal hypoglycemia by half [98].

Other neonatal complications

Neonatal erythrocytosis

The infants of mothers with diabetes commonly have an elevated hematocrit. This finding (often erroneously termed "polycythemia") has been attributed to fetal hyperinsulinemia and chronic fetal tissue hypoxia [103, 104]. However, hematocrit is not strongly related to birth weight, and the relationship with late-pregnancy maternal glycated hemoglobin is fairly weak [105]. The mode of delivery has a pronounced effect: the hematocrit is lower in babies delivered by cesarean section.

Jaundice

Jaundice is more common in macrosomic babies. The cause of hyperbilirubinemia is probably multifactorial, including birth trauma, erythrocytosis, hemolysis, and immature hepatic uptake and conjugation of bilirubin.

Respiratory distress syndrome

This was considered to be common in diabetic pregnancies [106] but is likely to result from preterm birth and high rate of cesarean section rather than any underlying metabolic effect [107, 108]. Delivery before term is common in women with diabetes, and an increased incidence of respiratory distress syndrome may reflect some clinical reluctance to administer glucocorticoids to hasten fetal lung maturation, because of their effects on maternal glycemia.

Transient hypertrophic cardiomyopathy

Transient hypertrophic cardiomyopathy, characterized by ventricular septal hypertrophy and sometimes subaortic stenosis, occurs in up to 30–80% of all babies of mothers with diabetes (the more sensitive the echocardiogram the higher is the proportion apparently affected) [109–111]. Very severe cases may present with congestive cardiac failure, but this usually has a benign course, resolving within 1 month without any clinical sequelae. Echocardiograms in older children of mothers with T1DM do not show persistence of ventricular hypertrophy [112].

Other metabolic abnormalities

Both hypocalcemia and hypomagnesemia occur more frequently in the infant of a mother with diabetes, usually as a consequence of prematurity or birth asphyxia.

Effects of maternal diabetic ketoacidosis and hypoglycemia on the fetus

Diabetic ketoacidosis

Diabetic ketoacidosis is fortunately uncommon in pregnancy, but it can have serious consequences. Most cases occur in women with T1DM, but it may also occur in "atypical" T2DM. The fetus and the placenta use large quantities of maternal glucose as a major source of energy, and so with relative insulin deficiency this leads to an increase in maternal free fatty acids, which are then converted to ketones in the liver. Ketoacidosis therefore tends to develop at lower levels of blood glucose than in the non-pregnant state [113].

Ketoacidosis may be precipitated by a number of factors, including protracted vomiting and starvation, infections, poor glycemic control, poor adherence to treatment, insulin pump failure, the use of β-sympathomimetic agents for tocolysis or steroid use for fetal lung maturation (or for other medical disorders), or new-onset T1DM. Women with diabetes are particularly sensitive to the effects of vomiting and starvation, which may arise through hyperemesis, gastroparesis, eating disorders, or gastroenteritis (or other infections).

The exact mechanism by which maternal diabetic ketoacidosis affects the fetus is unknown Keto acids readily cross the placenta, but whether it is the acidosis, hyperglycemia, severe volume depletion, or electrolyte imbalance that is the most malign for the fetus is uncertain [113, 114]. Cardiotocography during diabetic ketoacidosis has shown an absence of baseline heart rate variability, persistent late deceleration, and non-reassuring biophysical profile—all indicating fetal distress. Fetal mortality rates are high, ranging from 10 to 30%, although these seem to have improved in recent years [115]. The mortality rate is particularly high in fulminant-onset T1DM (see above).

Treatment should follow standard guidelines for the management of diabetic ketoacidosis.

Maternal hypoglycemia

One of the main aims of managing diabetes in pregnancy is to try to maintain maternal blood glucose values as close to normal as possible. An inevitable consequence, particularly in women with T1DM, is more frequent hypoglycemia including asymptomatic nocturnal hypoglycemia [116, 117], and with that comes reduced hypoglycemic awareness and an increased risk of severe hypoglycemia (requiring the assistance of others to recognize and/or treat it). Those at greatest risk are women known to have hypoglycemic unawareness and to have suffered severe hypoglycemia before pregnancy [118, 119]. The risk is greatest in the first trimester [119, 120]. A recent study has suggested that this risk can be reduced by a focused intervention, including education of caregivers and women [121].

The CEMACH study documented that 61% of women with T1DM had recurrent hypoglycemic episodes during pregnancy and 25% had severe hypoglycemia [122]. Severe hypoglycemia has been implicated in maternal deaths [120]. Although women with T2DM had a lower risk for severe hypoglycemia in the CEMACH

study, 21% of the women with T2DM had recurrent episodes of hypoglycemia [122].

In the CEMACH study, neither recurrent nor severe hypoglycemia was associated with poor pregnancy outcome (odds ratio [OR] 1.1; 95% CI: 0.7–1.7 and OR 1.3; 95% CI: 0.7–2.3, respectively) [122]. It is therefore the mother who is at greatest risk from severe hypoglycemia, raising the question of exactly how tight maternal glucose needs to be in order to maximize the benefits to the fetus and minimize the risks to the mother.

Effects of pregnancy on diabetes complications

Diabetic retinopathy

Diabetic retinal disease commonly progresses during pregnancy, sometimes to the point where laser treatment becomes necessary. Two main factors determine the severity of such deterioration: the degree of pre-existing retinopathy and the degree to which glycemic control improves. The risk of progression to sight-threatening retinopathy is of the order of 20–30% for those with moderate to severe retinopathy before pregnancy but ≤2% for those with minimal disease or no retinopathy. The phenomenon of a rapid tightening of glycemic control causing an acute deterioration in retinopathy is not restricted to pregnancy [123, 124]. In the Diabetes Control and Complications Trial (DCCT), if the fall in HbA_{1c} during pregnancy was ≤17 mmol/mol (1.6%) then a similar proportion (20–30%) of women had some deterioration as had some improvement in retinopathy. If, however, the fall in HbA_{1c} during pregnancy was ≥35 mmol/mol (3.2%) then >80% had some deterioration [125].

The women at greatest risk are therefore those with pre-existing moderate to severe retinopathy who enter pregnancy with high glycated hemoglobin levels and then have very rapid improvement in glycemia. This should not preclude efforts to improve glycemic control as the benefits to the fetus outweigh the risks to the mother. Conversely, women who come into pregnancy with no retinopathy and glycated hemoglobin levels that are already low are at minimal risk. Diabetic retinopathy is commonly associated with nephropathy, and hypertension in early pregnancy is associated with an increased risk of progression, although it is not clear that intensive treatment of hypertension reduces the risk [126].

Pregnancy is associated with increased circulating concentrations of many growth factors, angiopoietic factors, and proinflammatory molecules. Current evidence points toward a critical role of placental growth factor (PGF) in increasing the susceptibility of the retina in pregnancy. PGF is a member of the vascular endothelial growth factor subfamily and is a key molecule in angiogenesis and vasculogenesis, particularly during embryogenesis. Its main source during pregnancy is the placental trophoblast, and maternal plasma concentrations of PGF increase 15–20-fold between 8 and 32 weeks' gestation. Increasing PGF concentrations in the vitreous alters the permeability of the retinal pigment epithelial cells, permitting the development of retinal and macular edema [127], and overexpression of *Pgf* in rat eyes produces a diabetic retinopathy phenotype [128]. The *Pgf*-knockout mouse is resistant to oxygen-induced retinopathy, and knockout of the *Pgf* gene in the Akita diabetic mouse model prevents diabetes-induced retinal cell death, capillary degeneration, pericyte loss, and breakdown of the blood–retinal barrier [129]. In addition, the constriction of the retinal arteries and reduction in retinal blood flow that occur in the third trimester of pregnancy are more pronounced in diabetic pregnancies [130]. This could lower the threshold for retinal ischemia and hypoxia and hence progression of retinopathy.

Retinopathy can develop *de novo* in pregnancy, although this is unlikely to progress to proliferative retinopathy [126, 131]. A characteristic feature of marked pregnancy-associated deterioration in retinopathy is the appearance of cotton-wool spots (Figure 61.4). These lesions, which are related to microinfarction in the retinal nerve fiber layer, develop in up to half of those with progression to sight-threatening retinopathy. Cotton-wool spots usually regress postpartum and may not require immediate treatment, but the overall risk of deterioration in retinopathy status may persist for up to 1 year after delivery [125], and some women may require laser treatment in the postpartum period [132]. However, the pregnancy effect does not seem to change the long-term natural history or progression of diabetic retinopathy [125]. An analysis of 59 women with T1DM before pregnancy who had annual follow-up for up to 10 years after delivery showed that baseline retinopathy status was the only independent risk factor predicting later progression of retinopathy [133].

Diabetic nephropathy

Diabetic nephropathy can have a major influence on pregnancy outcome for both mother and baby. Maternal hazards include worsening of renal failure and pre-eclampsia; fetal complications include intrauterine growth restriction, prematurity, and death. Nephropathy is a progressive disorder and the pregnancy risk increases the more advanced the disease.

During normal pregnancy, the glomerular filtration rate (GFR) increases by 50–100% compared with non-pregnant values, driven by an increase in effective renal plasma flow (ERPF), which increases by ~80% during early pregnancy but falls significantly from this new level during the third trimester. The GFR remains ~50% above the non-pregnant level throughout pregnancy. The filtration fraction (GFR/ERPF) is significantly reduced during early pregnancy but rises to a value equivalent to the non-pregnant level during the third trimester [134]. In women with nephropathy, the GFR may increase only slightly during pregnancy [135] and there can be dramatic increases in protein excretion, particularly in late pregnancy. After delivery, albumin excretion may remain high for a few weeks, but usually then falls to prepregnancy levels. For most women with nephropathy, pregnancy is not associated with any reduction in GFR, but for those with stage 3 or 4 chronic kidney disease there may be some deterioration; however, this usually reverts to prepregnancy levels in the postpartum period [136].

The development of pre-eclampsia superimposed upon the renal disease is the greatest hazard. In a prospective study of 203 women with T1DM, pre-eclampsia developed in 6%

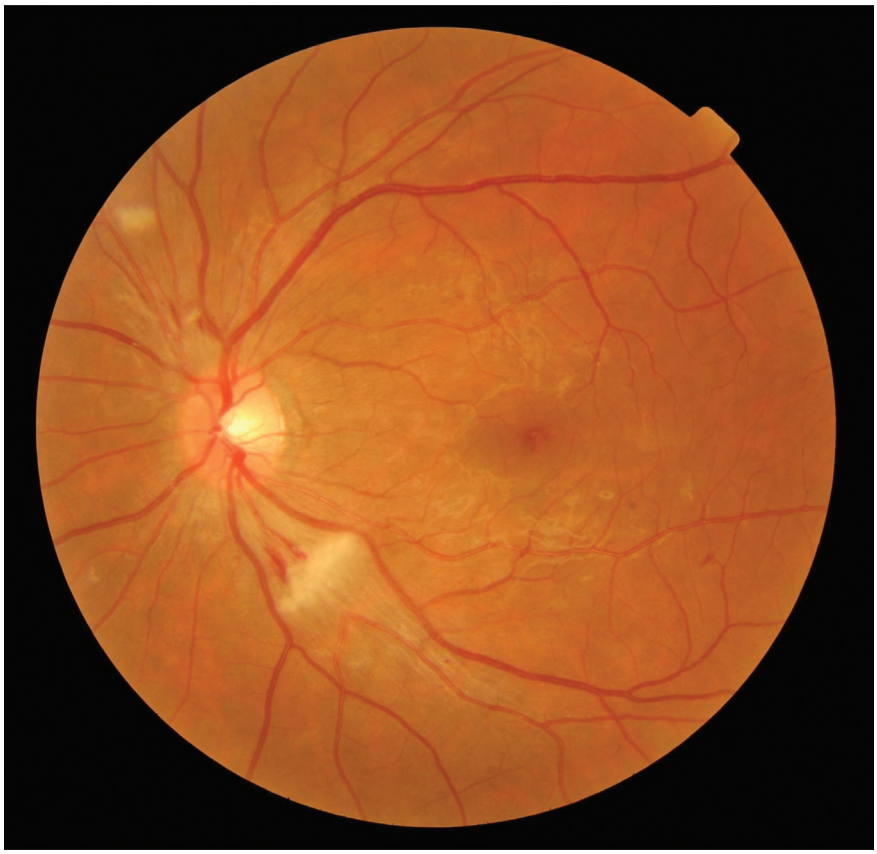


Figure 61.4 Acute retinal changes in pregnancy. Retinal photograph from a woman with T2DM recognized for the first time in pregnancy who presented with an HbA_{1c} of 89 mmol/mol at 9 weeks' gestation. She started insulin and metformin treatment, with a rapid reduction in her blood glucose levels (by 27 weeks the HbA_{1c} was 25 mmol/mol). At 14 weeks' gestation she developed blurred vision: the retinal photograph shows numerous cotton-wool spots, which result from microinfarcts in the retinal nerve fiber layer caused by occlusion of small retinal arterioles.

of women without microalbuminuria, in 42% of those with microalbuminuria, and 64% of those with heavy proteinuria [137]. Pre-eclampsia is usually defined by the new appearance of hypertension and proteinuria in pregnancy, but this definition is problematic in women with nephropathy who have renal disease antedating the pregnancy. In this circumstance, pre-eclampsia may be defined by worsening hypertension and a doubling of proteinuria (or albuminuria), along with the other defining features (increasing plasma creatinine, platelet count $<150 \times 10^3/mm^3$, or plasma aspartate aminotransferase >40 U/L).

Early intensive hypertensive management before and during pregnancy may reduce the risks of pregnancy-induced hypertension, pre-eclampsia, and preterm birth [138–140], as may good glycemic control [141]. The antihypertensive agents of first choice for people with diabetic nephropathy are angiotensin-converting enzyme inhibitors (ACEi) or angiotensin receptor blockers (ARB). However, both are contraindicated in the second and third trimesters because they cause the fetal renin–angiotensin system blockade syndrome, characterized by renal failure and complications that include oligohydramnios, arterial hypotension, intrauterine growth retardation, respiratory distress syndrome, pulmonary hypoplasia, hypocalvaria, limb defects, persistent ductus arteriosus, cerebral complications, or death [142].

There is controversy as to whether these agents are teratogenic in early pregnancy. One study reported that infants exposed to ACEi were at increased risk of malformations of the cardiovascular system (risk ratio [RR] 3.72; 95% CI: 1.89–7.30) and the central nervous system (RR 4.39; 95% CI: 1.37–14.02), and the authors concluded that exposure to ACEi during the first trimester cannot be considered safe [143]. However, there were a number of potential confounders in this study (notably maternal diabetes) that were not accounted for, and more recent analyses suggest that exposure during the first trimester may not be hazardous. It is common practice to discontinue ACEi and ARB when pregnancy is confirmed, rather than when pregnancy is planned, as it may be more hazardous to change therapy and risk losing control of blood pressure and albuminuria. Although the fetal renin–angiotensin system blockade syndrome appears to be more common with ARB than ACEi [142], the risk of congenital malformations related to early pregnancy exposure does not seem to be increased with ARB [144].

Diabetic nephropathy, especially when the serum creatinine is raised, carries a significant risk of birth before 32 weeks' gestation, very low birth weight, and neonatal hypoglycemia [145]. The increased rate of preterm births may well explain the mild disturbances in growth and development in early childhood seen in offspring of these pregnancies [146].

Renal transplantation

The first report of successful pregnancy following a renal transplant in women with diabetic nephropathy was in 1986 [147]. Successful pregnancies are now common in the general renal

transplantation population [148, 149], with a number of national and international registries providing pregnancy outcome data. These all show some increased risk of miscarriage, stillbirth, ectopic pregnancy, preterm birth, low birth weight, and neonatal death. However, most of these registries do not document outcome according to the mother's original renal disease, and as women with diabetic nephropathy have more advanced microvascular and macrovascular disease it is probable that their outcomes are worse. In the Australian and New Zealand Dialysis and Transplant Registry report of pregnancies in renal transplant recipients, only 4% had diabetes/hypertension as the primary renal disease, suggesting that many such women choose not to become pregnant [150].

Combined renal–pancreatic transplantation

The United States National Transplantation Pregnancy Register reported outcomes in pregnancies in 38 women a mean 3.7 years after combined renal–pancreatic transplantation [151]. Although the live birth rate was 79%, problems with hypertension (75%), pre-eclampsia (34%), infection (55%), prematurity (78%), and low birth weight (63%) were common. In pregnancy, 6% had a rejection episode affecting one or both organs and 16% experienced graft loss in the 2 years after delivery, although it is not clear whether this was any higher than in the population that did not have a pregnancy.

Neuropathy

Pregnancy has no long-term impact on the progression of peripheral or autonomic neuropathy, but given their relatively poor prognosis, women who have already suffered neuropathic foot ulceration are generally advised not to become pregnant. Severe gastroparesis due to autonomic neuropathy can cause pregnancy loss and maternal malnutrition and is likewise a contraindication to pregnancy [110, 114, 152]. Gastroparesis can be a factor in hyperemesis gravidarum and a precipitant of ketoacidosis in women with T1DM [153, 154]. However, there is no evidence that hyperemesis is more prevalent in women with long-standing diabetes than in the general population.

Ischemic heart disease

Maternal diabetes, obesity, and increasing age are all known risk factors for ischemic heart disease in pregnancy [155], hence as the general antenatal population becomes more obese and more women give birth in their late reproductive years, ischemic heart disease in pregnancy is likely to become more prevalent.

Outside pregnancy, women with T1DM aged 35–45 years have a 15-fold higher risk of a major cardiovascular event and women with T2DM aged 35–54 years have a fivefold higher risk of a myocardial infarction than women without diabetes of a similar age [156, 157]. Pregnancy increases the risk of an acute myocardial infarction 3–4-fold, with the risk being greatest in the peripartum period [155]. The number of pregnant women with ischemic heart disease and maternal deaths from ischemic heart disease have both increased in recent years. Ischemic heart disease is now the most common cause of cardiac death associated with pregnancy in the UK [158]. Nevertheless, the overall mortality rates from acute myocardial infarction in pregnancy have declined [159].

Acute myocardial infarction during pregnancy in women with diabetes has a poor prognosis, but pregnancy outcomes seem to be better in women who have survived a myocardial infarction before pregnancy [160]. Women who suffer acute coronary syndromes in pregnancy should receive the same urgent and intensive management as those in the non-pregnant state and interventions should not be withheld for fear of causing fetal harm [161].

Hypertensive disorders of pregnancy

Hypertensive disorders of pregnancy are common in women with diabetes of all types, and the combination of hypertension with diabetes has a greater impact on adverse maternal and fetal outcomes than either alone [162]. There is a wide spectrum of hypertension in pregnancy defined by severity, time of onset, and associated features (Table 61.5). The impact on pregnancy is greatest with early-onset pre-eclampsia and least with gestational hypertension.

The risk factors for pre-eclampsia in the general population include chronic hypertension (adjusted OR 2.72; 95% CI: 1.78–4.13), pregestational diabetes (adjusted OR 3.88; 95% CI: 2.08–7.26), multiple gestation (adjusted OR 2.96; 95% CI: 1.74–5.03), pre-eclampsia in a previous pregnancy (adjusted OR 3.63; 95% CI: 2.29–5.73), nulliparity (adjusted OR 1.73; 95% CI: 1.26–2.38), assisted reproductive techniques (adjusted OR 1.72; 95% CI: 1.10–2.68), and being overweight or obese [163].

The majority of studies in women with diabetes have been in those with T1DM in whom hypertensive disorders of pregnancy are reported to be 2–4-fold more prevalent than in women without diabetes [163, 164]. In women with T1DM, additional risk factors for hypertensive disorders of pregnancy include a long duration of diabetes, poor glycemic control, and the presence of nephropathy or early or prepregnancy proteinuria [165–171]. Many of these characteristics are incorporated in the White classification of diabetes in pregnancy that is commonly used in North America (Table 61.6), hence there is a strong relationship between White class and the risk of hypertension in pregnancy [172].

The worst outcomes (fetal death, impaired fetal growth, premature delivery, need for cesarean section, and neonatal intensive care) are seen with severe early-onset pre-eclampsia [173], which in the context of diabetes most often arises in women with pre-existing hypertension and proteinuria due to nephropathy [168, 172, 174]. Diabetes per se is more strongly associated with late- than early-onset pre-eclampsia [173].

In many parts of the world, pregnancy in women with T2DM is now more common than in women with T1DM. Relatively few studies have examined hypertensive disorders of pregnancy in women with T2DM, but compared with women with T1DM they tend to be older and more obese, hence there is more chronic (essential) hypertension; however, their duration of diabetes tends to be shorter and they are less frequently nulliparous, and so

Table 61.5 Classification of hypertension in pregnancy and its severity.

Severity of hypertension	a. *Hypertension* Hypertension in pregnancy is defined as a systolic blood pressure ≥140 mmHg or diastolic blood pressure ≥90 mmHg, or both b. *Severe hypertension* Severe hypertension in pregnancy is defined as systolic blood pressure ≥160 mmHg or diastolic blood pressure ≥110 mmHg, or both. Severe hypertension in pregnancy is considered to be a hypertensive emergency that requires urgent intervention
Classification of hypertension	a. *Chronic (pre-existing) hypertension* Chronic hypertension is defined as hypertension (systolic blood pressure ≥140 mmHg or diastolic blood pressure ≥90 mmHg, or both) that is present before 20 weeks' gestation or prior to pregnancy b. *Gestational hypertension* Gestational hypertension is defined as new hypertension (systolic blood pressure ≥140 mmHg or diastolic blood pressure ≥90 mmHg, or both) presenting at or after 20 weeks' gestation without proteinuria or other features of pre-eclampsia c. *Pre-eclampsia and chronic hypertension with superimposed pre-eclampsia* Pre-eclampsia is defined as hypertension plus significant proteinuria (urine protein excretion ≥300 mg/day or a spot urine protein : creatinine ratio of ≥30 mg protein/mmol creatinine). Rarely, pre-eclampsia can occur without proteinuria, but with hepatic, hematopoietic, or other manifestations. Edema is not a specific diagnostic criterion. This category includes: *Gestational hypertension plus new onset proteinuria* *Chronic hypertension with superimposed pre-eclampsia with new or worsening proteinuria* (defined as a rapid 2–3-fold increase in proteinuria) Pre-eclampsia may be further classified into *early-onset* (<34 weeks' gestation) and *late-onset* pre-eclampsia (≥34 weeks' gestation) d. *Severe pre-eclampsia* The criteria for severe pre-eclampsia include the presence of any one of severe hypertension (systolic blood pressure ≥160 mmHg or diastolic blood pressure ≥110 mmHg, or both), cerebral or visual disturbance, epigastric or right upper quadrant pain, oliguria, pulmonary edema, cyanosis, impaired liver function, thrombocytopenia, or intrauterine growth restriction e. *Eclampsia* Eclampsia is defined as new-onset grand mal seizures in women with pre-eclampsia. Some women presenting with eclampsia do not have diagnosed pre-eclampsia, and some may present with eclampsia in the post-partum period

there is generally less pre-eclampsia. As a consequence, the overall impact of hypertensive disorders of pregnancy on pregnancy outcomes may be less for women with T2DM than those with T1DM [175]. Proteinuria is more prevalent in women with T2DM, but may reflect pathologies other than diabetic nephropathy. The predictive power for low-level proteinuria detected in early pregnancy appears to be poorer for T2DM than T1DM [175, 176].

Table 61.6 The modified White classification of diabetes in pregnancy.

Class	Onset age (years)	Duration (years)	Insulin treated	Criteria
A_1	Any	Any	No	Gestational diabetes
A_2	Any	Any	Yes	Gestational diabetes
B	>20	<10	Yes	Benign retinal and renal findings
C	10–19	10–19	Yes	Age of onset 10–19 years *or* duration 10–19 years
D	<10	>20	Yes	Age of onset <10 years *or* duration >20 years
F	Any	Any	Yes	Nephropathy (>500 mg/day protein)
R	Any	Any	Yes	Proliferative retinopathy
RF	Any	Any	Yes	Retinopathy and nephropathy
T	Any	Any	Yes	Renal transplant patient
H	Any	Any	Yes	Cardiovascular disease

The White classification performs relatively poorly at predicting hypertensive disorders of pregnancy in women with T2DM because a high proportion of women fall into a single category (B) [175].

Of relevance particularly to women with T2DM or GDM is that obesity is also a significant risk factor for pre-eclampsia (including severe pre-eclampsia). In a large community study, the adjusted OR (compared with a BMI of <25 kg/m^2) was 1.65 for BMI 25–30 kg/m^2, 2.34 for BMI 30–35 kg/m^2, 3.59 for BMI of 35–40 kg/m^2, and 6.03 for BMI >40 kg/m^2 [163]. Increasing levels of obesity in the community may help explain why blood pressure levels in pregnancy have increased in recent decades, including in women with T1DM [177].

Despite a knowledge of the risk factors that predispose to pre-eclampsia, it remains a difficult condition to predict, as there are no reliable biomarkers in early pregnancy. Nevertheless, the accurate identification of women at risk, early diagnosis, and prompt and appropriate management (e.g. antenatal corticosteroids for fetal lung maturation, treatment of severe hypertension, early delivery) may improve maternal and perinatal outcome.

Aspirin therapy

A number of studies have examined whether aspirin can prevent hypertensive disorders of pregnancy. In a Cochrane review (34 studies, 20,701 participants) [178], no statistically significant difference was found in the incidence of gestational hypertension in women receiving antiplatelet agents compared with women

receiving placebo or no antiplatelet agents (RR 0.95; 95% CI: 0.88–1.03). Pre-eclampsia was evaluated in 43 studies (32,590 participants) and the pooled analysis showed that antiplatelet agents were associated with a statistically significant reduction in the risk of pre-eclampsia (RR 0.83; 95% CI: 0.77–0.89). On this basis, NICE has recommended that women at high risk for pre-eclampsia should take 75 mg of aspirin daily from 12 weeks until the birth of the baby. "High risk" in this definition includes hypertensive disease during a previous pregnancy, chronic kidney disease, T1DM or T2DM, and chronic hypertension [179]. In addition, NICE recommends that women with more than one moderate risk factor for pre-eclampsia should to take 75 mg of aspirin daily from 12 weeks until the birth of the baby. Moderate risk factors are first pregnancy, age 40 years or older, pregnancy interval of more than 10 years, a BMI of 35 kg/m^2 or more at first visit, a family history of pre-eclampsia, or multiple pregnancy [179].

This very broad recommendation of aspirin therapy—for all women with established diabetes and some women with GDM—is somewhat at odds with the evidence concerning women with diabetes in the major clinical trials, in whom no benefit was seen [180], which may explain why this recommendation is generally not promulgated by diabetes societies.

Calcium therapy

Randomized controlled trials suggest that calcium supplementation can reduce the risk of gestational hypertension and pre-eclampsia, particularly in those women with a low calcium intake, although current guidelines stop short of recommending it [179].

Management of diabetes in pregnancy

Managing pregnancy successfully in women with established diabetes is demanding and complex, requiring the full support and commitment of a multidisciplinary team. Numerous agencies have issued management guidelines that are updated periodically. Overall there is good agreement between the various guidelines. The recommendations below are largely drawn from the NICE Guidelines that were updated in 2015 [102], with comment on where there are significant omissions or differences from other recent guidelines issued by the American Diabetes Association (ADA), the Endocrine Society (ES), and the Canadian Diabetes Association (CDA) [181–183].

Prepregnancy counseling

All the guidelines emphasize the importance of planning pregnancy and there is good evidence that prepregnancy counseling can improve outcomes. The risk of fetal or infant death is increased with higher periconception HbA_{1c}, lack of folate use, and the presence of diabetes complications [184]. A recent meta-analysis suggested that prepregnancy care is effective in reducing both congenital malformation (RR 0.25; 95% CI: 0.16–0.37); number needed to treat [NNT] 19; 95% CI: 14–24) and perinatal mortality (RR 0.34; 95% CI: 0.15–0.75; NNT 46; 95% CI: 28–115) [185]. The important elements are obtaining good glycemic control, folate administration, the management of diabetic complications, smoking cessation, withdrawal of potentially teratogenic medication, and making sure that women are well informed about the likely changes through pregnancy.

Glycemic control

The purpose of achieving good glycemic control before embarking on pregnancy is to minimize the risk of major congenital anomaly and miscarriage. NICE recommends that women with established diabetes maintain their blood glucose level at >4 mmol/L and below the following target levels, if these are achievable without causing problematic hypoglycemia: fasting, 5.3 mmol/L; 1-h postprandial, 7.8 mmol/L; and 2-h postprandial: 6.4 mmol/L. The recommended HbA_{1c} target is <48 mmol/mol (6.5%) and women with an HbA_{1c} >86 mmol/mol (10%) should be "strongly advised" not to get pregnant. The ADA recommendations differ somewhat, with a target HbA_{1c} of <53 mmol/mol (7.0%) or "as close to normal as possible" while avoiding significant hypoglycemia. For most women, achieving such targets means either starting insulin (in T2DM) or intensifying the insulin regimen, using a basal/bolus regimen or a continuous subcutaneous infusion pump, with frequent self-monitoring of blood glucose. A meta-analysis of the effectiveness of prepregnancy counseling found that an average reduction in HbA_{1c} of 13 mmol/mol (1.2%) was achieved, but at the expense of an increased risk of hypoglycemia during the first trimester (RR 1.51; 95% CI: 1.15–1.99) [185].

Folate supplementation

Folate supplementation is recommended in a daily dose of 5 mg (NICE and ES) or 0.6 mg (ADA) in order to reduce the risk of neural tube defects.

Assessment of diabetic complications

This is important for the reasons discussed above in order to identify those at risk of deterioration in retinopathy in pregnancy and the association of nephropathy with pre-eclampsia and fetal growth retardation. All guidelines recommend that any necessary treatment for retinopathy is completed and the clinical condition is stable before embarking on pregnancy.

NICE recommends that if the serum creatinine is ≥120 μmol/L, the urinary albumin : creatinine ratio is >30 g/mol, or the estimated glomerular filtration rate (eGFR) is <45 mL/min/1.73 m^2, review by a nephrologist should be considered before discontinuing contraception.

The ADA also recommends ultrasound screening for fatty liver in women with elevated serum gamma-glutamyltransferase and/or alanine transaminase enzymes, and an electrocardiogram in asymptomatic women >35 years of age (and more intensive cardiovascular investigation of symptomatic women).

Drug cessation

NICE recommends that ACEi and ARB should be discontinued before conception, or as soon as pregnancy is confirmed.

Alternative antihypertensive agents suitable for use during pregnancy should be substituted. Statins should be discontinued before pregnancy or as soon as pregnancy is confirmed. NICE makes no specific comment about smoking cessation, but the benefits for women with diabetes women are the same as those for women without diabetes.

Obesity

NICE recommends that women with diabetes with a BMI >27 kg/m^2 who are planning to become pregnant should be advised to lose weight.

Autoimmune disease

Up to one-third of women with T1DM have serological evidence of autoimmune hypothyroidism, and up to half of these develop postpartum thyroiditis [186]. The ES and ADA recommend pre- or early pregnancy screening of women with T1DM with thyroid-stimulating hormone and thyroid antibody tests, with consideration also of testing for vitamin B_{12} deficiency. NICE makes no specific recommendation.

Achieving preconception recommendations

The recommendations for prepregnancy care—particularly the glycemic targets—are demanding to fulfill, and so it is perhaps not surprising that many women do not achieve the ideal. The sociological dimension should not be ignored. The studies that have demonstrated benefit from prepregnancy counseling have all been observational, and so the groups with and without counseling are self-selected. It is difficult to control for confounding factors such as social class, level of education, patient motivation, smoking, maternal age, obesity, parity, and complications of diabetes. Risky behaviors cluster together, and so women with poorly controlled diabetes tend also to be those who are irregular in the use of contraception, have unplanned pregnancies, are smokers, present late to diabetes pregnancy clinics, and have more diabetes complications [79, 187–190]. Thus the paradox of Tudor Hart's "inverse care law" prevails: those who would probably benefit most from rigorous prepregnancy counseling may be the least likely to receive it [191]. From this perspective, the problem is less of what to do (which is largely known), but rather how to reach those women who would benefit most.

Management of T1DM in pregnancy

Glycemic targets

All the guidelines recommend tight glycemic control. The ADA suggests that the target for preprandial, bedtime, and overnight blood glucose values should be 3.3–5.5 mmol/L; peak postprandial values (1 h after eating) should be 5.6–7.2 mmol/L, the mean daily glucose <6.1 mmol/L, and a target HbA_{1c} 42 mmol/mol (6.0%). The ES recommends a fasting blood glucose of ≤5.0 mmol/L, a preprandial target of ≤5.3 mmol/L, 1-h postprandial blood glucose ≤7.8 mmol/L, and 2-h postprandial blood glucose ≤6.7 mmol/L, with a target HbA_{1c} of 42 mmol/mol (6.0%). NICE suggests that fasting blood glucose be kept between 3.5 and 5.9 mmol/L and 1-h postprandial blood glucose <7.8 mmol/L. NICE advises that HbA_{1c} should not be used routinely for assessing glycemic control in the second and third trimesters but (somewhat ambiguously) also advises that its use should be considered to assess the level of risk (Table 61.7).

For a majority of women, particularly those with T1DM, achieving such low glycemic targets is very demanding, and there is no doubt that their pursuit can induce hypoglycemic unawareness with a significantly increased risk of hypoglycemia. In one study, the rate of severe hypoglycemia episodes increased threefold in the first trimester compared with the 4 months before conception [192]. First-trimester severe hypoglycemia is independently related to a history of severe hypoglycemia before gestation, a long duration of diabetes (>10 years), and an HbA_{1c} ≤48 mmol/mol (6.5%) [193]. All the guidelines add the caveat that these targets should be relaxed if there is "undue" hypoglycemia or hypoglycemia unawareness. Reassuringly, the limited evidence from clinical trials suggests that the outcomes of moderately tight glycemic control (fasting blood sugar 5.0–6.5 mmol/L) are not inferior to those of "tight" glycemic control [194]. In a large observational study, the risk of some adverse outcomes (macrosomia, pre-eclampsia, early delivery, and neonatal hypoglycemia) were elevated only when the 26-week HbA_{1c} was ≥48 mmol/mol (6.5%) [195] (cf. ≤42 mmol/mol, 6.0%, recommended by ES and ADA).

Ketone testing is recommended by the ADA and NICE for women with T1DM who become ill or and/or hyperglycemic. Urine ketone (acetoacetate) estimation has been the traditional method of testing for ketosis, but some blood glucose meters can (with the use of special strips) also quantitate β-hydroxybutyrate in the blood. Although more expensive, these have the advantage of providing more immediate information than urine tests.

Choice of insulin

The introduction of each new insulin formulation has been followed by a period of uncertainty as to whether it is safe in pregnancy. Relatively small non-inferiority trials were undertaken for insulin detemir and aspart, but often acceptance of the use of a new insulin in pregnancy follows when observational studies of women who were using it before conception and continue it through pregnancy do not indicate harm [196]. All the guidelines now suggest that quick-acting insulin analogs such as lispro or aspart are preferred for mealtime coverage. There is less agreement about the choice of basal insulin. NICE still suggests that isophane insulin should be the first choice. The ADA suggests that women already taking insulin or glargine should be transitioned to isophane, but the ES recommends that women already using insulin detemir or glargine continue these agents through pregnancy. The so-far unproven theoretical risks of the newer long-acting insulins (which are centered on transplacental transfer and potential mitogenicity) [197] have to be balanced against the risks of losing good glycemic control during the transfer process.

Table 61.7 Comparison of guidelines on management of diabetes in pregnancy.

	Issuing group			
Parameter	**NICE 2015**	**ADA 2014**	**CDA 2013**	**Endocrine Society 2013**
Glycemic targets prepregnancy				
Preprandial (mmol/L)	<5.3	NS	NS	≤5.3
Postprandial (mmol/L)	<7.8 (1 h) <6.4 (2 h)	NS	NS	≤ 7.8 (1 h) ≤ 6.7 (2 h)
HbA_{1c} (mmol/mol)	<48 (6.5%)	<53 (7.0%)	<53 (7.0%)	<48 (6.5%)
Glycemic targets in pregnancy				
Preprandial (mmol/L)	3.5–5.9	3.3–5.5	≤5.3	
Postprandial (mmol/L)	<7.8 (1 h)	5.6–7.2 (1 h)	<7.8 (1 h) <6.7 (2 h)	<7.8 (1 h] <6.7 (2 h)
HbA_{1c} (mmol/mol)	"Consider" use—not routine	≤42	NS	≤42
Long-acting insulin	Switch glargine/detemir to NPH insulin	NPH or detemir—stop glargine	Continue detemir or glargine	
Retinal screening intervals	Booking and 28 weeks (all)	Booking and 3rd trimester (all)	Booking and as indicated	Booking and as indicated
Weight gain in pregnancy	NS	IOM guidelines[a]	NS	IOM guidelines[a]

[a]See Table 61.8.
NS, not stated.
Source: NICE 2015 [102], Kitzmiller et al. 2008 [181], Blumer et al. 2013 [182], and Thompson et al. 2013 [183].

Continuous subcutaneous insulin infusion (CSII) therapy

CSII therapy has been widely used in the management of pregnancy in women with T1DM, and to a lesser extent in women with T2DM. There may be particular women, for example with recurrent hypoglycemia, a pronounced "dawn phenomenon" or labile glycemia who benefit from the insulin delivery by CSII, but there is no evidence that in general the outcomes are any better than with the use of multiple daily injection regimens [198]. There are also some risks — of hyperglycemia or ketoacidosis in the event of pump failure — and also increased costs. However, women whose diabetes is well managed with CSII preconception usually choose to continue it through pregnancy.

Continuous glucose monitoring (CGM)

CGM has been explored in a small number of trials in women with (mainly) T1DM. One small randomized controlled trial (RCT) [199] found that HbA_{1c} in late pregnancy and mean birth weight were lower than in women using CGM (although the latter may have been influenced by the high number of twin pregnancies in the CGM group), but a larger RCT [200, 201] found no evidence that CGM was more effective than frequent self-monitoring of blood glucose. An analysis of data from both of these trials showed that women who developed large-for-gestational-age infants had higher glucose values in the early morning and afternoon in the second trimester and in the evening in the third trimester [202]. A larger study of CGM in women with T1DM (CONCEPTT) is nearing completion. One small study has suggested a possible role in managing hyperglycemia induced by steroid treatment in women at risk of preterm birth [203].

The ADA suggests that continuous blood glucose monitoring would be helpful for selected women if there are problems with hypoglycemia unawareness. NICE suggests that CGM should be considered in pregnant women on insulin therapy who have problematic severe hypoglycemia (with or without impaired awareness of hypoglycemia) or who have unstable blood glucose levels (to minimize variability), or to gain information about variability in blood glucose levels.

Insulin requirements during pregnancy

The dose of insulin required to maintain good glycemic control varies substantially through pregnancy. In the early weeks of pregnancy, insulin doses may increase (particularly if glycemic control was poor coming into pregnancy), or decrease (particularly if there is marked pregnancy-associated sickness), or remain similar to prepregnancy levels. At ~20–24 weeks' gestation, insulin requirements typically start to rise in response to increasing insulin resistance. The degree of change is very variable, averaging ~100%, but ranging from very little to a >200% increment. The degree of change is closely related to maternal weight gain,

particularly between weeks 20 and 29 [204]. On a weight-adjusted basis (U/kg), the typical increment in women with T1DM is of the order of 60–65% [205]. Insulin requirements may be higher in twin pregnancies; in one study, the weekly increase in insulin dose between 14 and 27 weeks was doubled compared with singleton pregnancies [206]. In women using continuous insulin infusion pumps, both basal and bolus doses increase, but the proportionate change is greater for the latter [207, 208].

Insulin requirements tend to peak between 32 and 36 weeks' gestation and a fall in insulin doses is not uncommon in late pregnancy. Small falls from the peak insulin dose do not seem to be of clinical significance [209, 210], but larger falls (>15%) may be associated with pre-eclampsia and placental insufficiency [211]. Very large falls in insulin requirements in late pregnancy (>35%), particularly if accompanied by severe headache, can indicate the rare event of antepartum pituitary necrosis [212]. Insulin requirements drop abruptly after delivery. In women with T1DM, doses typically average two-thirds of the prepregnancy insulin dose, or one-third of the dose at the end of pregnancy by the third postpartum day, and the same as that before pregnancy by the end of the first postpartum week [213]. If insulin treatment was first started in pregnancy, it can be stopped after delivery in almost all women with GDM and many with T2DM.

Retinal assessment

NICE guidelines (Table 61.7) suggest that retinal photographic screening be performed at booking and at 28 weeks' gestation in all women with pre-existing diabetes, with more intensive follow-up of those with any retinopathy. The ADA similarly recommends that women with no or minimal retinopathy on the initial examination should have follow-up retinal examination in the third trimester; those with mild retinopathy should be evaluated every trimester, and those with more advanced retinal disease should be evaluated at intervals determined by an ophthalmologist. The ES recommends ocular assessment soon after conception and then "periodically as indicated"—meaning more intensive follow-up in those with established retinopathy. In practice, it appears safe to omit the 28-week review in low-risk women (no retinopathy and low glycated hemoglobin levels in early pregnancy).

NICE specifically comments that the presence of diabetic retinopathy should not be considered a contraindication to rapid optimization of glycemic control in women who present with a high HbA_{1c} in early pregnancy. None of the guidelines discusses retinal screening for women presenting with GDM whose early pregnancy blood glucose or HbA_{1c} suggests that they have previously unrecognized diabetes. However, this should be considered, as retinopathy may be present (Figure 61.4).

Renal assessment

If renal assessment has not been undertaken in the preceding 12 months in women with pre-existing diabetes, NICE recommends that this is arranged at booking. If the serum creatinine is abnormal (≥120 μmol/L), the urinary albumin : creatinine ratio is > 30 g/mol, or total protein excretion exceeds 2 g/day, referral to a nephrologist should be considered. Women with known renal disease should be carefully monitored by regular measurements of blood pressure, urine albumin or protein excretion, and serum creatinine. eGFR estimates are not accurate in pregnancy, but a rising serum creatinine has serious implications. Antihypertensive agents suitable for use in pregnancy include methyldopa, nifedipine, hydralazine, and labetolol; the aim should be to keep blood pressure below 140 mmHg systolic [214]. NICE suggests that thromboprophylaxis should be considered for women with proteinuria >5 g/day.

Management of T2DM in pregnancy

T2DM in pregnancy was rare until the 1980s, but it is a problem of ever-increasing importance [3, 79]. T2DM is prevalent amongst the poor, in migrant and minority communities (including, in North America, Australia, and Aotearoa [New Zealand], marginalized indigenous peoples), and in the mentally unwell. Although, on average, the duration of diabetes is shorter and glycemic control better, there are often special difficulties that make it a challenge to achieve optimal outcomes. The challenges include language and cultural difference, poverty, low educational attainment, and obesity. These are reflected in the frequent late presentation to diabetes services and low rates of referral and attendance for prepregnancy counseling [3, 215].

The management of T2DM in pregnancy is similar to that of T1DM. Many women are taking metformin, sulfonylureas, or other antidiabetes agents at the time of conception. The great majority (>95%) of women with T2DM require insulin therapy and, because of obesity, insulin doses may be greater than in T1DM. With the exception of metformin, all the other antidiabetes agents should be stopped as their safety has not been determined. There is no trial evidence to indicate that in T2DM pregnancy the use of metformin in addition to insulin is superior to insulin alone, but it does not appear to be harmful [216, 217]. A large RCT in Canada is examining whether the addition of metformin to standard insulin treatment is beneficial.

Obstetric monitoring

Fetal ultrasound examination has become an indispensable tool, used at various stages of pregnancy. The NICE guidelines [102] outline the standard approach:

- *Scan at 7–9 weeks* (or at first presentation, if later) to confirm viability and gestational age.
- *Scan at 12–14 weeks* for nuchal translucency, if screening for trisomy 21 is being undertaken (in conjunction with β-HCG and PAPP-A serum measurements). (Note: this screening method is likely soon to be superseded by cell-free DNA analysis.)
- *Scan at 18–20 weeks* for detecting structural anomalies and examination of the four-chamber view of the fetal heart and outflow tracts. If major congenital anomalies are identified, then elective termination can be discussed with the women.

- *Scan at 28, 32, and 36 weeks* to monitor fetal growth and amniotic fluid volume. Accelerated growth of the fetus—particularly the abdominal circumference (Figure 61.3)—and polyhydramnios are common features of poorly controlled diabetes, but neither is specific. Accelerated fetal growth is common in obese women and in those with excess gestational weight gain. The normal range for amniotic fluid volume varies considerably.

Other tests advocated as routine assessments for women with diabetes in some countries include *non-stress testing* (NST) and performing a *biophysical profile* (BPP) [218]. The NST involves recording of the fetal heart rate and uterine activity for 20–40 min in late pregnancy. If the fetal heart rate baseline is 110–160 beats per minute (bpm), and has a variability of 5–25 bpm with at least two acceleration peaks of 15 bpm for > 15 s, and no concerning decelerations, the NST is called "reactive," which suggests that the baby is actively moving and is not acidemic or hypoxic. The NST is called "non-reactive" when it does not meet these criteria. A reactive NST is reassuring and over 99% of cases are expected to survive over the following week, but the value of this test in predicting late fetal death or guiding intervention in diabetic pregnancy has not been proven, and the false-positive rate is very high. This test is most valuable in pregnancies with intrauterine growth restriction. NST may be used in conjunction with the other ultrasound variables in the BPP. Four measures derived from 30-min continuous ultrasound monitoring are made: fetal breathing, gross body movement, tone (the movement from flexion to extension and back again of a fetal limb), and the depth of amniotic fluid. Each is scored from 0 to 2 points, with scores of 8–10 considered reassuring. As with NST, the value of this test in predicting late fetal death or guiding intervention is unproven in diabetic pregnancy, and its value lies mainly in the evaluation of the fetus affected by intrauterine growth retardation.

Doppler studies of the fetal umbilical artery are useful for assessing placental vascular resistance. In particular, routinely measuring the systolic/diastolic flow ratio in the umbilical artery in fetuses with intrauterine growth retardation has been shown to improve offspring outcomes by optimizing the timing for delivery (mostly by reducing induction of labor and delaying delivery), but also aiding the differentiation of the truly growth-restricted fetus from those that are constitutionally small, but with a normal umbilicoplacental circulation. Doppler velocimetry has not been shown to be effective in the surveillance of the large fetus in which the pregnancy may be complicated by problems other than those affecting the uteroplacental circulation.

Appointment scheduling additional to the ultrasound appointments outlined above should be determined on an individual basis. When easy telephone or email contact can be maintained with a woman whose glycemic control is good and there are no complications, unnecessary clinic attendance should be avoided, but visits will become more frequent closer to the end of pregnancy when monitoring for pre-eclampsia and decisions about the timing and mode of delivery are needed. Women with difficult-to-manage glycemic control, diabetic complications, or fetal growth abnormalities need more frequent visits.

Labor and delivery

NICE and other expert bodies recommend that women with T1DM or T2DM and no other complications should have an elective birth by induction of labor, or by elective cesarean section between 37 weeks + 0 days and 38 weeks + 6 days of pregnancy. Birth before 37 weeks + 0 days should be considered for women if there are concerning metabolic problems or any other maternal or fetal complications [102, 219]. Women with T1DM are, on average, delivered earlier than those with T2DM. In the recent UK audit, 60% of women with T2DM had pregnancies continuing into the 39th week, compared with 39% in women with T1DM [3].

The rates of preterm birth (delivery at <37 weeks' gestation) are 2–3-fold higher among women with pregestational diabetes than among women without diabetes. The majority of this increase is due to elective preterm delivery (6–7-fold higher than in women without diabetes), but spontaneous preterm delivery is also increased (~50% higher). Rates of both elective preterm delivery at <35 weeks' gestation and spontaneous preterm delivery are also higher in women with diabetes [220]. Nulliparity, progression of nephropathy, pre-eclampsia, and HbA_{1c} ≥53 mmol/mol (7%) at delivery are all strongly associated with indicated preterm delivery [221], as is poorer maternal mental health [222]. Preterm delivery is associated with significant neonatal morbidity, particularly neonatal hypoglycemia and respiratory distress syndrome [221].

The practice of early delivery means that rates of induction of labor are high, and inevitably this means that there will be cases of failure of labor to progress and increased rates of maternal and fetal distress. This is one of the main drivers behind the high rates of cesarean section in women with diabetes, which in most series varies between 40 and 65%. Once a woman has had a primary cesarean section then the probability is high that any future pregnancy will be delivered in the same way. Several diabetes-related factors such as maternal obesity, fetal macrosomia, polyhydramnios, and microvascular complications have also been associated with an increased risk of cesarean delivery [223–226]. Cesarean section rates are similar in T1DM and T2DM [227, 228]. Secular trends towards increasing maternal age and obesity mean that it is unlikely that the high cesarean section rates can be substantially reduced.

Management of glycemia during labor

Avoiding intrapartum maternal hyperglycemia may reduce the likelihood of subsequent neonatal hypoglycemia [101]. In women using insulin in pregnancy, maternal glycemia is usually controlled during induction of labor by an intravenous infusion of regular insulin, titrated to maintain hourly readings of blood glucose at 4–7 mmol/L [102, 229]. Women having elective cesarean sections can often continue their usual insulin regimen. Women who are using an insulin pump may continue their basal infusion during labor where units are familiar with pump use.

General management

Breastfeeding

Breastfeeding is encouraged in women with diabetes, but the rates are often disappointingly low [230, 231]. One factor is that babies born early are often separated from their mothers at birth for neonatal care, and so there is difficulty establishing breastfeeding. Previous positive experience of breastfeeding and higher educational level are strong predictors of success in breastfeeding [232, 233]. In women who are breastfeeding and still taking insulin, the postpartum insulin requirements are typically ~10% lower than before pregnancy [232]. For women with T2DM, metformin, glibenclamide (glyburide), and glipizide all seem to be safe during lactation, as the levels appearing in breast milk are low [234].

Family planning

Having a baby is no small undertaking for women with diabetes, and given a natural concern for their own long-term health (particularly in those who already have diabetic complications), many women choose to limit the size of their families [235]. One of the most important conversations that physicians, midwives, and obstetricians need to have with women with diabetes concerns their long-term outlook, their future plans, and the need for contraception (see Chapter 49). This discussion should begin before delivery, particularly if a cesarean delivery is likely, as many women elect to have tubal ligation at the time of their cesarean section.

Fetal overnutrition: gestational diabetes, obesity, and gestational weight gain

The traditional view of diabetes in pregnancy has been dominated by the importance of maternal hyperglycemia in providing excess nutrition, and hence accelerating fetal growth. However, both maternal obesity and excessive weight gain in pregnancy are characterized by energy intake in excess of need and so are also important factors in fetal overnutrition. In high-income countries there has been a marked secular trend towards increasing obesity that has driven the rising incidence of T2DM. This is also reflected in the obstetric population [236]. The trend to increasing birth weight is largely explicable by increased maternal obesity and a reduction in cigarette smoking [237].

Maternal obesity is associated with an increased risk of early miscarriage [56] and late fetal death [4–8]. The risk of late fetal death is clearly related to the degree of obesity [4, 5, 8] and is particularly linked to placental diseases, hypertension, fetal anomalies, and umbilical cord abnormalities [238]. The risk of many other poor outcomes is also increased by maternal obesity. These include: pre-eclampsia, pregnancy-induced hypertension, respiratory, wound, and urinary tract infections, venous thromboembolism, large-for-gestational-age infants, shoulder dystocia, perineal tears, and increased rates of cesarean section (and operating time) and neonatal intensive care admission [8, 239–248]. Although GDM is associated with maternal obesity, the latter has a greater impact on these adverse outcomes [239, 249–251]. Interpregnancy weight gain is also associated with poorer outcomes in subsequent pregnancies [252, 253].

These same pregnancy and neonatal morbidities are also associated with excessive gestational weight gain [250, 251, 254–260] and, although GDM is associated with greater weight gain (particularly in early pregnancy [261, 262]), it is the weight gain that has the dominant effect on fetal growth [248, 249]. In an RCT of limiting gestational weight gain in obese women, the proportion of large-for-gestational-age babies was reduced by 65% in the intervention group [259]. The same effects of gestational weight gain, independent of HbA_{1c}, can also be found in the pregnancies of women with T1DM and T2DM [263–267].

The US Institute of Medicine has issued guidelines [268] suggesting targets for healthy weight gain in pregnancy, with women who were overweight or obese at the onset of pregnancy having lower targets than underweight or normal weight women (Table 61.8). These guidelines suggest that obese women limit their total pregnancy weight gain to 5–9 kg, but even lower targets (including weight loss) might be associated with better outcomes [269, 270]. Obese women who lose or gain <5 kg in weight in pregnancy have babies that are on average 190 g lighter than those with weight gain >5 kg (with a rate of small-for-gestational-age babies that matches that in the non-obese) [271].

Gestational diabetes

Background

The concept of GDM arose from observations made in the 1930s and 1940s that women who later developed what we now call T2DM were overweight and had reproductive histories with an unexpectedly high incidence of large babies and fetal losses. The term "gestational diabetes" was introduced in the 1950s for women with poor obstetric histories who, during a subsequent pregnancy, had high glucose levels (on oral glucose tolerance testing). Treating hyperglycemia in the subsequent pregnancy seemed to be associated with better perinatal outcomes [2].

In the 1960s, O'Sullivan and colleagues published a series of studies of glucose tolerance in pregnant women. These women were followed postpartum with annual glucose tolerance tests, and a significant proportion went on to develop T2DM. From these studies, diagnostic criteria for GDM were proposed on the basis of the pregnancy glucose tolerance test's ability to predict future diabetes. According to these criteria, the prevalence of GDM at that time was ~2%.

A crucial change occurred in 1979, when the US National Diabetes Data Group (NDDG) recommended that GDM be recognized as a distinct diagnostic entity [272]. The NDDG argued that recognition of GDM was important not only because of the high risk of later developing diabetes, but also because "therapy can prevent much of the associated perinatal morbidity and mortality" (although this had not been demonstrated at the time). It was recommended that all pregnancies should be screened, using a two-step testing procedure (a 50-g non-fasting glucose challenge test,

Table 61.8 Institute of Medicine weight gain recommendations for pregnancy.

Prepregnancy[a] weight category	BMI[a] (kg/m^2)	Recommended range of total weight gain (kg)	Recommended rate of gain[b] in 2nd and 3rd trimesters: mean and range (kg/week)
Underweight	<18.5	13–18	0.45 (0.45–0.59)
Normal weight	18.5–24.9	11–16	0.45 (0.36–0.45
Overweight	25.0–29.9	7–15	0.27 (0.23–0.27)
Obese (grade 1)	30.0–34.9	5–9	0.23 (0.18–0.27)
Obese (other grades)	≥35.0	<5	<0.20

[a]Or early pregnancy (<10 weeks' gestation).
[b]Assuming a 0.5–2.0 kg gain in the 1st trimester.
Source: Modified from Institute of Medicine, National Academies of Sciences 2009 [268].

followed, if positive, by a formal glucose tolerance test). The definition of GDM adopted by the NDDG was *any degree of glucose intolerance with onset or first recognition during pregnancy.* This created a problem in that it conflated into a single entity a spectrum ranging from mildly, but transiently, elevated blood glucose levels in the third trimester through to previously unrecognized (most commonly type 2) diabetes. The concept of GDM as a specific diagnostic type of diabetes was adopted by the WHO in their 1980 guidelines. The NDDG proposals were adopted in North America and elsewhere, although many countries developed individual screening protocols, testing regimens, and diagnostic criteria. As with the NDDG criteria, all were decided by expert opinion and typically yielded rates for GDM of 2–6%.

There were a number of valid criticisms of this approach. First, the diagnostic criteria were based on the mother's future risk of diabetes [10], rather than immediate maternal and fetal outcomes. Second, it was not clear whether the links between dysglycemia in pregnancy and perinatal morbidity were causal or incidental associations. Finally, there was uncertainty as to whether treatment conferred significant benefit [273, 274].

RCTs of treatment of mild GDM

Some clarity concerning the final point came from two RCTs of the treatment of mild GDM: the Australian Carbohydrate Intolerance Study in Pregnant Women (ACHOIS) and the Maternal–Fetal Medicine Units Network (MFMU) [275, 276] (with "mild" GDM defined as levels of hyperglycemia that would not meet the diagnostic criteria for diabetes outside pregnancy). In both studies, GDM was identified using a two-step diagnostic procedure (but with different diagnostic criteria for the 2-h glucose tolerance test), and ~1000 women with mild GDM were randomized to treatment or no treatment The women in the MFMU study were somewhat less hyperglycemic than those in the ACHOIS cohort, and so fewer women in the active management group were treated with insulin in the MFMU study (8% vs. 20%). Both studies used composite endpoints as their primary outcome measure, because too great a sample size would be required to demonstrate an effect on individual components. Neither study reported the between-group difference in achieved blood glucose measurements.

In the ACHOIS study [275], the composite primary outcome of "any serious perinatal complication" was more frequent (4% vs. 1%) in the routine care group. The significance of this difference was critically dependent on the high number of perinatal deaths (five deaths, or 1% vs. 0%) in the routine care group). However, some of the deaths could not plausibly be attributed to the non-treatment of GDM; for example, one infant had a lethal congenital anomaly and another had severe intrauterine growth retardation. A number of secondary outcomes differed between the groups: maternal weight gain was less and the mean birth weight was 145 g lower in the intervention group. Consequently, there were fewer babies born weighing >4 kg (10% vs. 13%), and the rate of shoulder dystocia was reduced from 3.2% to 1.4%. The rate of pregnancy-associated hypertension was lower in the intervention group (12% vs. 18%) but the cesarean delivery rate was the same. There was a significantly increased rate of induction of labor in the intervention group (39% vs. 29%) and a higher proportion of infants in the intervention group were admitted to neonatal intensive care (71% vs. 61%), with more neonates in the intervention group developing either hypoglycemia requiring treatment or respiratory distress syndrome.

In the MFMU trial [276], there were no differences between the groups in the composite primary outcome score and so the trial produced a clear negative result. A number of secondary outcomes, however, did differ between the groups: maternal weight gain was less and the mean birth weight was 106 g lower in the intervention group, with fewer babies born weighing >4 kg (6% vs. 7%), and the rate of shoulder dystocia was reduced from 4.0% to 1.5%. The rate of pregnancy-associated hypertension was lower in the intervention group (8.6% vs. 13.6%) and the cesarean delivery rate was also lower (27% vs. 34%).

The effectiveness of GDM treatment compared with usual antenatal care in the prevention of adverse pregnancy outcomes has been the subject of two meta-analyses, which were dominated by data from the ACHOIS and MFMU trials. Both meta-analyses concluded that detection and treatment GDM defined by two-step testing were associated with a reduction in macrosomia and large-for-gestational-age infants by ~50%, with a similar reduction in rates of shoulder dystocia. There was moderate quality

evidence that treatment reduces pre-eclampsia and hypertensive disorders in pregnancy [277, 278]. In summary, the intervention trials in mild GDM (defined by two-step testing) confirmed that treatment makes babies 2–3% lighter (so the incidence of large babies is lower), reduces the incidence of shoulder dystocia, and may reduce the incidence of hypertensive disorders of pregnancy. However, it is not clear if these effects were primarily due to lower maternal blood glucose values or to less maternal weight gain.

The Hyperglycemia and Adverse Pregnancy Outcomes (HAPO) study

To clarify better the association of fetal morbidity and other pregnancy outcomes with the degree of maternal hyperglycemia, a major international collaboration, the HAPO study, was established. In the study, 23,316 women had a 75-g glucose tolerance test performed at 24–32 weeks' gestation. All women who had a fasting blood glucose ≤5.8 mmol/L and 2-h values up to 11.1 mmol/L were included. The study was observational and clinicians were blinded regarding the glucose tolerance test results. The major aim was to determine a level of glycemia beyond which maternal and infant risks clearly increased, to inform the selection of scientifically valid universal diagnostic criteria for GDM.

The study had four primary endpoints: two were of direct clinical importance (primary cesarean section rate and neonatal hypoglycemia), one was an intermediate outcome (birth weight), and one a surrogate outcome (cord-blood serum C-peptide level >90th centile for gestational age) [279]. The major findings were of continuous, independent relationships between untreated maternal blood glucose (fasting, 1-h and 2-h post-glucose load) and each of the outcomes, with the cord blood C-peptide level (reflecting fetal hyperinsulinemia) and birth weight >90th centile showing the strongest association with maternal blood glucose. There was no association between perinatal mortality and blood glucose levels. The differences in mean birth weight between the lowest and highest glucose categories for the three glucose measures ranged from 242 to 305 g [279].

The International Association of Diabetes Pregnancy Study Groups (IADPSG) recommendations

In the light of the HAPO findings, the IADPSG met in 2008 to determine the glucose thresholds for diagnosing GDM. The group mainly comprised physicians, with notably little input from primary care providers, midwives, public health experts, or patient representatives. The group made four important consensus recommendations [280]:

- Screening for "overt diabetes" be undertaken at the first prenatal visit, with the diagnosis based on a fasting plasma glucose ≥7.0 mmol/L or an HbA_{1c} ≥48 mmol/mol (6.5%).
- Glucose levels associated in the HAPO study with a 1.75-fold increased risk above the mean for birth weight, cord C-peptide, and percentage body fat >90th percentile would constitute a diagnosis of GDM.
- One abnormal glucose value of three in a 75-g glucose tolerance test would suffice for diagnosis (fasting 5.1–6.9 mmol/L; 1-h value ≥10.0 mmol/L; 2-h value 8.5–11.0 mmol/L).
- A single glucose tolerance test could be adequate and that two-step testing be abandoned.

The ADA endorsed the IADPSG recommendations in 2011, and they have also been adopted by diabetes associations in several countries, including Australia, Brazil, and China. While the first recommendation—screening for undiagnosed diabetes—has been generally welcomed, there has been considerable disquiet about the others. Adoption of the IADPSG regimen and diagnostic criteria has meant that in most countries the prevalence of GDM has doubled or trebled to ~20% or more of pregnancies; in southern China it is nearly 40% [281]. Although one report has suggested that the IADPSG criteria might be effective at reducing morbidity and costs [282], several others have not [281, 283–285]. This has led to considerable debate about the wisdom and affordability of the move and concerns about overdiagnosis [286–289]. The main concerns (summarized in Table 61.9) fall into two broad categories: issues regarding the scientific validity and the undesirable downstream impact.

The key scientific concerns are as follows: (a) the reliance on a single blood glucose result, given the known high variability

Table 61.9 Concerns about the WHO/IADPSG diagnostic criteria for GDM.

Concern	Comment
Reliance on a single blood sugar result	Post-load blood glucose values are very variable, with poor reproducibility
The arbitrary 1.75 risk threshold	Relative risks derived from observational studies should be >3 for reliability [290]
Criteria not based on clinically significant outcomes	Birth weight, percentage body fat, and cord C-peptide are surrogate or intermediate outcomes
No evidence of treatment benefit	No RCT of treatment in the additional women diagnosed by the IADPSG criteria. Clinical benefits likely to be modest at best
Increased intervention	A diagnosis of GDM makes interventions more likely, irrespective of glycemia and fetal size
Cost-effectiveness	Modeling suggests criteria would be cost-effective only if cesarean section or maternal diabetes can be prevented
Resource diversion	Large number of mild "cases" diverts resources from women with pregestational diabetes who benefit most
Medicalization	Pathologizes pregnancies that were hitherto thought to be healthy

Table 61.10 Recent international guidelines concerning the diagnosis of GDM.

Item	Country/organization				
	UK NICE	International IADPSG–WHO	USA ADA[a]	Canada CDA[a]	New Zealand Ministry of Health
Year	2015	2013	2015	2013	2014
Early pregnancy testing					
Selective or all criteria	Selective[b]	All	Selective[c]	Selective[c]	All
HbA_{1c} (mmol/mol)	NR	NR	≥48 (6.5%)	NR	≥50 (6.7%)
Random glucose (mmol/L)	≥11.1[d]	≥11.1[d]	≥11.1[d]	≥11.1[d]	≥11.1[d]
Glucose tolerance test (mmol/L)					
Fasting (mmol/L)	≥5.6	≥7.0	≥7.0	≥5.3	≥7.0
2 h (mmol/L)	≥7.8	>11.0	>11.0	≥8.5	–
24–28 weeks' gestation testing					
Selective or all	Selective[e]	All	All	All	All
50-g glucose challenge test	No	No	Yes	Yes	Yes
1 h (mmol/L)	–	–	≥7.8	≥7.8	≥7.8
Glucose tolerance test					
Glucose load	75 g	75 g	100 g[f]	75 g	75 g
Fasting (mmol/L)	≥5.6	≥5.1	≥5.3 or 5.8	≥5.3	≥5.5
1 h (mmol/L)	-	≥10.0	≥10.0 or 10.6	≥10.6	-
2 h (mmol/L)	≥7.8	≥8.5	≥8.6 or 9.2	≥8.5	≥9.0
3 h (mmol/L)	–	–	≥7.8 or 8.0	–	–
No. of abnormal readings to confirm GDM	1	1	2	1	1

[a]Both the ADA and CDA have the IADPSG–WHO criteria as alternatives.
[b]Only in women with previous GDM.
[c]Only if there are clinical risk factors.
[d]If symptomatic.
[e]In women with BMI >30 kg/m^2 and/or previous macrosomic baby (≥4.5 kg) and/or first-degree relative with diabetes and/or ethnic origin with a high prevalence of diabetes.
[f]Two alternative criteria: Carpenter–Coustan (the lower values) or NDDG (the higher values).
NR, not recommended.
Source: World Health Organization 2013 [37], NICE 2015 [102], Thompson et al. 2013 [183], Ministry of Health 2014 [292], and American Diabetes Association 2015 [293].

of post-load glucose values; (b) the use of surrogate measures of limited clinical significance as the main outcome descriptors; (c) the arbitrary 1.75 risk threshold, which epidemiologists regard as too low—risk ratios of 3–4 derived from observational studies are more reliable [290] (note: if the IADPSG criteria were used but requiring a high fasting *and* at least one high post-load result for diagnosis, then the risk threshold would be ~3 [291], which could resolve both the statistical and "one abnormal test" issues); and (d) the lack of any RCT data on benefits of treatment at these thresholds, given that the trials of treatment in GDM at conventional thresholds showed only modest benefit [275–278].

Despite the concerns outlined above, the WHO's committee (in which IADPSG members were prominent) adopted the IADPSG criteria in 2013 [37]. The priority of the WHO committee seemed to be the establishment of an international standard rather than strong science, admitting that the quality of evidence for the position was "very low" and the strength of their recommendation was "weak" [37].

However, the hoped-for unanimity in the diagnosis of GDM has not materialized. For example, neither the 2013 National Institutes of Health Consensus Conference nor the American Congress of Obstetricians and Gynecologists endorsed the IADPSG guidelines. Most recently, the 2015 NICE guideline opted for different diagnostic criteria [102].

A number of countries have continued to develop their own approaches. A summary of some recent international guidelines is given in Table 61.10.

The IADPSG–WHO [37] and the New Zealand criteria [292] have a distinct focus on the early detection of previously unrecognized diabetes, with all pregnancies being screened by random glucose in the former and HbA_{1c} in the latter. The current UK [102], Canadian [183], and American [293] guidelines recommend testing for unrecognized diabetes only if there are risk factors. The New Zealand approach creates a new pathophysiological "entity," that is, women with an HbA_{1c} in the prediabetes range in early pregnancy. Around one-third of women in this category will have GDM when tested later in pregnancy [294], but it is not yet

known whether earlier treatment (after detection in early pregnancy) has definite advantages over later treatment (from 24 to 28 weeks).

With regard to testing at 24–28 weeks' gestation, the UK remains the exception in recommending risk factor-based testing, whereas other countries recommend testing of all pregnancies. The NICE criteria were based on evidence derived from routine observational data sets comprising more than 40,000 pregnant women across 14 centers, including the HAPO centers in the UK and Australia, along with other UK centers. The majority of centers used risk factor-based selective screening, but just over 12,000 women had been screened by a universal screening process. NICE rejected the IADPSG criteria, deeming them to be not cost-effective based on health economic modeling in a subset (n = 18,974) of these women for whom fasting, 1-h, and 2-h glucose values were available. There are many uncertainties in such analyses. In particular, the cost-effectiveness of selective versus "universal" screening depends on the prevalence of GDM within a given community [295]. The UK glucose tolerance test 2-h threshold for diagnosis is substantially lower than those in all the other guidelines, and the differences in the fasting and 2-h criteria between the IADPSG–WHO and the NICE guidelines mean that different populations are identified as having GDM: the former include more women with mild elevations in fasting blood glucose and the latter more with mild elevations in postprandial blood glucose. The concordance rate for a diagnosis of GDM may be as low as 55%.

The continued divergence in the approach to diagnosis is confusing for healthcare practitioners and pregnant women. To add to the confusion, both the CDA and ADA guidelines suggest that the IADPSG–WHO criteria are alternatives to previously developed criteria in these countries, despite doubling the chance of being diagnosed [183, 293], and, in the USA, the 100-g glucose tolerance test has two alternative sets of diagnostic criteria [293] (Table 61.10).

GDM: disease or risk factor?

That this unsatisfactory situation persists despite a great deal of research (more than 7000 papers on GDM have been published since 2000) suggests that perhaps we have not been addressing the right questions. There seem to be two conceptual roadblocks: first, the conflation of all degrees of glucose intolerance in pregnancy into a single entity, and second, the idea (enshrined in 1979) that GDM is a distinct disease entity. We know that both the risks to the fetus and the mother's risk of later T2DM are continuously related to the degree of glycemia, and so hyperglycemia in pregnancy might be more usefully viewed as a risk factor rather than a "disease" requiring "diagnosis" [286, 289, 292]. The questions that then arise include: What is it a risk factor for? How do we quantify the risk? What are the other risk factors for these outcomes? Who benefits, and by how much, from what intervention?

At the top end of the spectrum, in women with previously undiagnosed diabetes, the risks of major congenital anomalies and perinatal mortality are comparable to those seen in women with established diabetes [33–35], hence the growing consensus that it is worth identifying such cases as early as possible in pregnancy. At the lower end of the spectrum, the risk is primarily of excessive fetal growth (macrosomia) [285], but, as discussed above, it is by no means the only risk factor. We should not forget that macrosomia itself is not a disease, but a risk factor for a number of adverse outcomes [70, 286]. As currently defined, not all women with GDM have significant risk, and only a minority benefit from treatment [296]. Perhaps future research needs to be less "glucocentric" and should concentrate on identifying those fetuses at greatest overall risk of the adverse outcomes we are trying to prevent, and determining which would benefit most from what treatment.

Management of GDM

Nutritional therapy is an integral part of the treatment of women with GDM, with the key principles being to reduce overall energy intake and limit the proportion derived from carbohydrates (see Chapter 25). Several dietary modifications can lower glucose levels effectively. These include reducing caloric intake for overweight and obese women (e.g. to ~25 kcal/kg body weight) [297] and limiting carbohydrate content to 35–40% of total calories [298] while focusing on carbohydrates with a low glycemic index. Similar lifestyle interventions implemented in early pregnancy can reduce gestational weight gain and the incidence of GDM [299].

Women with GDM are also encouraged to undertake self-monitoring of blood glucose to help decide if additional pharmacological therapy is needed. Women are usually asked to measure capillary glucose levels before breakfast and 1–2 h after breakfast, lunch, and dinner, but the optimal timing and frequency of monitoring have not been determined. One study, often cited as proof that postprandial glucose targets are more important than preprandial targets, compared rather low postprandial targets with fairly high preprandial targets [300], thus biasing the design in favor of postprandial monitoring. Treatment targets have varied among studies that have demonstrated improved perinatal outcomes. The NICE-recommended targets are fasting plasma glucose levels <5.3 mmol/L, 1-h postprandial glucose levels <7.8 mmol/L, and 2-h postprandial glucose levels <6.3 mmol/L [102]. Most other international bodies recommend a higher 2-h postprandial target of <6.7 mmol/L, a figure with support from clinical trials [274, 275]. Fasting blood glucose levels of ≥5.8 mmol/L are associated with an increased risk of preventable perinatal complications [301, 302] and are thus an indicator that pharmacological treatment is likely to be of benefit. NICE recommends that women with a fasting blood glucose level of ≥7.0 mmol/L at diagnosis of GDM should be treated with insulin in preference to oral antidiabetes drugs [202].

The major effect of treating mild GDM is to slow fetal growth to reduce fetal macrosomia. It is not clear whether fetuses that are small or normal sized benefit from treatment. Buchanan's group used fetal abdominal circumference measurements obtained by ultrasonography to help identify the substantial proportion of pregnancies that will not incur a perinatal complication in

the absence of intensified treatment. In pregnant women with a fasting plasma glucose level <5.8 mmol/L, a fetal abdominal circumference of <70th centile for gestational age between 29 and 33 weeks of gestation was associated with no excess risk of large-for-gestational-age infants or cesarean deliveries compared with that in pregnant women without diabetes [301], and intensified insulin treatment in pregnancies with a fetal abdominal circumference of >70th centile eliminated the excess of large-for-gestational-age infants [67, 301]. The peripheral blood glucose targets were fasting levels <4.4 mmol/L and 2-h postprandial levels <6.1 mmol/L. These low targets were possible because, when directed to fetuses with accelerated growth, there is virtually no risk of these offspring becoming small for gestational age [302]. None of the major guidelines have endorsed this specific targeted approach, but it has definite attraction, as it matches the major effect of treatment (slowing growth) to the most affected fetuses.

Insulin remains an important treatment option and regimens should be tailored to meet glycemic targets. Regular exercise is often recommended, and there is limited evidence that it may reduce fetal birth weight [303].

Oral antidiabetes agents in GDM

Two important RCTs have explored pharmacological options for mild GDM. One study compared glibenclamide (glyburide) with insulin in women who were deemed in need of intensified treatment on the basis of maternal self-monitored glucose level results [304]. Equivalent perinatal outcomes were observed in the two groups. Only 4% of women assigned to glibenclamide also received insulin to meet prespecified glycemic targets. The other study compared metformin with insulin [305]. Perinatal outcomes were similar in the two treatment groups, but a high proportion (46%) of women assigned to metformin received supplemental insulin to achieve glycemic targets. Unsurprisingly, supplemental insulin was required more often in the most hyperglycemic women; according to the fasting plasma glucose levels at diagnosis of GDM, 20% of those with <5.3 mmol/L, 53% of those with 5.3–6.0 mmol/L, 68% of those with 6.1–6.9 mmol/L, and 81% of those with ≥7.0 mmol/L needed additional insulin treatment.

Glibenclamide use in GDM increased considerably, particularly in the USA, following publication of the RCT in 2000 [304]. With widespread use, concern about its use as a first-line agent has grown [306]. Comparisons with metformin or insulin indicate that glibenclamide use is associated with greater risks of macrosomia and admission for neonatal care, predominantly because of respiratory distress and hypoglycemia [306–311]. The latter effect may be related to placental transfer of glibenclamide to the fetus [312].

Delivery

NICE recommends that women with pharmacologically treated GDM should be delivered before 40 weeks' gestation is reached [202]. A US modeling analysis suggested that delivery at 38 weeks' gestation may be optimal at balancing the risks of late intrauterine death and death from the consequences of prematurity [313], but in practice obstetricians estimate risk on an individual basis, and women with mild GDM well managed with diet and lifestyle, without macrosomia and with no other pregnancy complications, can safely go to near term before delivery.

Postpartum reclassification of diabetes

Women diagnosed with GDM need to be reclassified postpartum. Some will have newly recognized or incipient T1DM or genetic diabetes, but the majority will be on the metabolic syndrome spectrum and postpartum demonstrate either normal glucose tolerance, pre-diabetes, or T2DM. It cannot be assumed that all those diagnosed with "overt diabetes" in pregnancy will continue to have it postpartum, particularly if significant weight loss has been achieved. Reclassification has traditionally been on the basis of a glucose tolerance test 6 weeks after delivery, but if HbA_{1c} is being used for diagnosis, then testing should be delayed until at least 3 months postpartum.

Long-term effects of GDM

Maternal

GDM is well known to be an antecedent of T2DM, and indeed was originally defined on this basis. For women with GDM, the risk for developing diabetes is increased relative to women with a normoglycemic pregnancy, 4.7-fold within 5 years of having GDM, and 9.3-fold after 5 years or more [314]. It should be noted that this estimate is derived from studies in which GDM was identified by two-step testing, and not from studies in which women were identified by the IADPSG criteria. The risk is likely to be substantially lower if women are identified only by a single blood glucose value.

Unsurprisingly, women with the highest blood glucose levels at diagnosis of GDM, those who needed insulin treatment in pregnancy, those with impaired β-cell function, and those who are overweight and gain most weight after their GDM pregnancy tend to develop T2DM the earliest [314–316]. The identification of women with previous GDM offers a potential opportunity to intervene with modification of lifestyle risk factors to delay the development of T2DM, but there is little evidence that this is being achieved on any large scale.

All guidelines recommend periodic screening for T2DM after a diagnosis of GDM; the new NICE recommendations suggest annual screening by HbA_{1c} starting after the early postnatal (3-month) test [202], although the long-term adherence to such follow-up plans is often poor. GDM is uniquely linked to pregnancy, but in its foreshadowing of T2DM, it is best regarded as a form of prediabetes, with the same risk factors [296], and in this regard not unique to women. If one were to test all the male partners of pregnant women and stratify this population according to the degree of glycemia, then undoubtedly the same phenomenon would be found: the higher the blood glucose, the sooner diabetes will develop.

Offspring

Otherwise healthy newborn babies of women with diabetes tend to be heavier and fatter than average and it has also become evident that later in life the offspring of mothers with T2DM or GDM are at

increased risk for becoming obese and developing diabetes themselves. A widely accepted interpretation of these observations is that exposure to hyperglycemia *in utero* directly drives the development of obesity and diabetes through fetal metabolic programming [317–319]. Although this mechanism cannot be discounted, its importance may well have been overstated [320]. Longitudinal population studies indicate that the most robust risk factors for adolescent obesity are maternal BMI, paternal BMI, maternal occupation, birth weight, maternal gestational weight gain, the number of household members, and smoking habits [321], but the clinical studies claiming to demonstrate a link with maternal glucose tolerance and later obesity and diabetes in the offspring have rarely taken these factors into account. The importance of paternal BMI is emphasized by the observation that GDM in mothers also signals incident diabetes in the babies' fathers, an effect presumably mediated by shared deprivation level and ethnocultural background [322].

The most commonly cited evidence in favor of the theory that exposure to maternal diabetes *in utero* is a risk for T2DM in the offspring comes from the National Institute of Health group studying the O'odham (Pima) people of the Gila River community in Arizona [323–331]. In the Pima studies, the offspring of women with diabetes were significantly heavier than offspring of women without diabetes and women who subsequently developed diabetes [323], but obesity in the offspring was significantly related to both maternal and paternal BMI [324]. Subsequent reports related maternal diabetes status and 2-h blood glucose on a pregnancy glucose tolerance test to the incidence of T2DM in the offspring [325, 326, 331], but no adjustments were made for maternal or paternal BMI. In a study that compared offspring born to the same mother before and after her diagnosis of T2DM, mean BMI was higher in the offspring of the diabetic pregnancy than in the non-diabetic pregnancy, but again no adjustment was made for paternal or maternal BMI or inter-pregnancy weight gain [330].

Further evidence that exposure to hyperglycemia *in utero* is unlikely to be directly causative is that there is no epidemic of obesity and T2DM in the offspring of women with T1DM. Follow-up studies of children in the two large RCTs of treatment of GDM have not demonstrated any effect of treatment on offspring adiposity [332–334].

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62 Diabetes in Old Age

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Key points

- The prevalence of diabetes is increasing in older people because of increased life expectancy.
- The phenotype of diabetes in old age is characterized by an increased prevalence of multiple comorbidities, geriatric syndromes, and frailty.
- A comprehensive geriatric assessment should be performed at the initial diagnosis of diabetes and annually thereafter.
- A multidisciplinary team approach with a multidimensional assessment, including screening for physical and cognitive function, is important to meet the complex needs of older people with diabetes.
- Hypoglycemia is common in older people with diabetes owing to multiple comorbidities and can be less easily recognized or misdiagnosed because of reduced autonomic symptoms.
- A deterioration in glycemic control, unexplained hypoglycemia or reduced adherence to self-care should alert the clinician to the presence of dementia or depression.
- Tight glycemic control is reasonable in fit older people but a relaxed approach is more appropriate in frail elderly at risk of hypoglycemia.
- An individualized and holistic care plan is key for diabetes care in older people.
- Older people with diabetes living in care homes are particularly vulnerable and require greater specialist input.
- Quality of life should always be the focus for individualized care.

Introduction

With increasing aging of the population and urbanization of lifestyle, the prevalence of diabetes has or is likely to reach epidemic levels in most countries, especially in older people ≥75 years [1]. Aging is associated with body composition changes that lead to increased insulin resistance, glucose intolerance, and increased risk of diabetes [2]. As a result, an increasing number of older people are developing diabetes. The lifetime risk of developing diabetes is high reaching 22.4% for women and 18.9% for men from the age of 60 years [3]. Older people with diabetes are exposed to the interplay between metabolic dysfunction, vascular disease, and the aging process in combination with other age-related disorders. Geriatric syndromes and frailty are emerging as a third category of complications in addition to the traditional micro- and macrovascular disease [4]. Therefore, diabetes in old age may lead to considerable disability. Unlike other chronic conditions, diabetes care is dependent on self-management, which may be compromised by the presence of comorbidities and geriatric syndromes. Owing to the heterogeneous nature and variations in comorbidity, life expectancy and functional status, ranging from a fit individual living independently in the community to a fully dependent person living in a care home, therapeutic interventions and metabolic targets should be individualized taking into consideration individual preference while putting quality of life at the heart of the care plans. This chapter reviews the phenotype of diabetes in old age and addresses the key areas and special considerations for the care of older people with diabetes to meet their complex needs.

Epidemiology

The prevalence of diabetes rises with increasing age. Worldwide, the greatest proportional increase in the number of people with diabetes by age group is expected to occur in people aged 60–79 years [3]. For example, in France, the prevalence has increased to 14.2% in those aged 65–74 years, peaking at 19.7% in men and 14.2% in women aged 75–79 years. More than half of those with diabetes were ≥65 years [5]. In the USA, 14% of the population are estimated to have diabetes and the prevalence is highest in those aged ≥65 years; by 2050 diabetes prevalence could be as high as 33% of the whole population [6]. However, a similar number may remain undiagnosed. In the National Health and Nutrition Examination Survey the prevalence of diagnosed diabetes in those ≥75 years was 14.9% and undiagnosed diabetes based on fasting plasma glucose and 2-hour oral glucose

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tolerance test was 13.4%, making a total prevalence of diabetes of 28.3% with undiagnosed diabetes constituting around 47%. The prevalence of "pre-diabetes" defined as either impaired fasting glycemia (IFG) or impaired glucose tolerance (IGT) was 46.7% in those aged ≥75 years. Therefore, the total prevalence of diabetes and pre-diabetes was approximately 75% in older people ≥75 years [1]. Low- and middle-income countries will have the greatest burden of diabetes, where the prevalence will increase in adults (aged 20–79 years) by 69% by 2030 compared to only 20% in higher income countries [7]. This is likely driven by the growth and aging of the population and urbanization of lifestyle in these countries. The prevalence of diabetes among older Chinese in rural Taiwan aged 72.6 years was 16.9% in 2000 and increased to 23.7% in 2005 [8]. In minority ethnic groups living in high-income countries, the incidence and prevalence of diabetes is higher than in white European populations. For example, the prevalence of diabetes in older Mexican Americans (≥75 years) has almost doubled between 1993–1994 and 2004–2005 from 20.3% to 37.2% in comparison to an increase from 10.4% to 16.4% in the general population of the same age [9]. Diabetes prevalence in care homes is also high. In 2004, 24.6% of US nursing home residents had diabetes; among residents aged 65–74, 75–84, and ≥85 years, the prevalence of diabetes was 36.1%, 29.5%, and 18.3%, respectively [10]. The prevalence of diabetes has steadily increased in US nursing homes (16.9% to 26.4% in men and 16.1% to 22.2% in women) between 1995 and 2004. A more recent survey showed a further increase in the prevalence of diabetes with 32.8% of residents living with diabetes [11]. Ethnic disparities in diabetes prevalence are also well documented in care home settings. In US nursing homes, the adjusted odds of diabetes are approximately twofold higher in African American and Hispanic residents relative to white American residents with diabetes present in 22.5% of white Americans and 35.6% of those from other ethnic groups [10].

Pathogenesis

Glucose homeostasis requires both normal insulin secretion by the pancreatic β cells and normal glucose utilization by the peripheral tissues that are sensitive to insulin. Diabetes in old age is linked to increased insulin resistance and decreased insulin secretion with a principle defect of insulin resistance in obese individuals and insulin secretion in lean ones. It is likely that both genetic and environmental factors are involved in the pathogenesis of insulin secretory dysfunction and insulin resistance. As older people are heterogeneous, the extent and rate of deterioration in glucose homeostasis is variable, leading to insignificant changes in some individuals and diabetes in others (Box 62.1).

Increased insulin resistance

Aging is associated with body composition changes that result in increased insulin resistance [12]. Increased visceral fat is associated with increased rates of lipolysis causing high levels of free fatty acids which may have a role in reducing peripheral insulin sensitivity [13]. Reduction of muscle mass or sarcopenia occurs with aging through physical inactivity and as the muscle is the main site of glucose consumption, the loss of muscle mass increases insulin resistance [12]. Accumulation of lipids within the muscles is another factor reducing insulin sensitivity. A reduction in mitochondrial function [14] may also contribute to age-related glucose intolerance by reducing oxidative metabolism, physical fitness, and oxidative capacity. Low concentrations of adiponectin, leptin, and insulin-like growth factor-I (IGF-I), and high concentrations of tumour necrosis factor alpha (TNF-α) are associated with aging and linked to increased insulin resistance and incident diabetes [14–16].

Box 62.1 Determinants of glucose intolerance in old age

- Decreased β-cell function
- Reduced β-cell mass
- Increased visceral fat
- Reduced muscle mass
- Mitochondrial dysfunction
- Low concentrations of adiponectin*
- High concentrations of tumour necrosis factor alpha**
- Reduced insulin-like growth factor-I concentration***
- Reduced leptin concentration****
- Physical inactivity
- Altered lipid metabolism

*Secreted by adipose tissue which improves insulin resistance by increasing fat oxidation.
**Induces anorexia, weight loss, and insulin resistance.
***A peptide hormone which stimulates glucose uptake.
****Secreted by adipose tissue which decreases appetite, and its decline may contribute to the increased adiposity and body composition changes seen in the elderly.

Decreased insulin secretion

Insulin secretion diminishes by 0.7% per year with increasing age because of reduced function and increased apoptosis of pancreatic β cells [17]. β-Cell autoimmunity may lead to activation of an acute phase response in older people with diabetes with hypersecretion of interleukins, C-reactive protein, and TNF-α which may reduce insulin secretion [18]. Disturbances in the physiology of the gut-derived incretins, gastric inhibitory polypeptide (GIP), and glucagon-like peptide-1 (GLP-1), may be another factor involved in β-cell dysfunction [19]. Both peptides enhance insulin secretion after meals and may have a role in maintaining β-cell growth, proliferation and inhibition of apoptosis. Aging is associated with reduced levels and function of these peptides [20].

Diabetes phenotype in old age

Diabetes in older people is associated with coexistent multiple comorbidity burden, geriatric syndromes, and frailty (Box 62.2).

Box 62.2 Diabetes phenotype in older people with diabetes

- Multiple comorbidities
- Cognitive dysfunction
- Depression
- Physical dysfunction
- Falls and fractures
- Urinary incontinence
- Polypharmacy
- Less muscle mass and poor muscle quality
- Malnutrition
- Frailty
- Nutritional need and hydration
- Irregular eating pattern especially in people with dementia
- Vulnerability to hypoglycemia

Comorbidity burden

Diabetes in older people is associated with increased atherosclerosis, premature aging, and increased disability. Older people with diabetes frequently have at least one comorbid chronic disease in addition to diabetes and as many as 40% have at least three conditions [21]. The comorbidity burden is even higher in care home residents with diabetes. For example, those with diabetes have more cardiovascular disease, visual problems, pressure sores, limb amputations, and kidney failure than residents without diabetes [22]. In a retrospective case note review of 75 nursing home residents with diabetes in the UK, significant levels of disability were shown in areas of continence, feeding, mobility, and communication. The average number of comorbidities per individual was four (range 1 to 8) [23]. The mortality rate was 34% after 1 year of follow-up indicating severe comorbidity [24]. In another study, residents with diabetes had a greater comorbidity burden (Hierarchical Condition Category 1.90 vs. 1.58), more prescribed medications, and experienced more hospitalizations (37% vs. 18%) than residents without diabetes [11].

Geriatric syndromes

Geriatric syndromes, such as cognitive and physical dysfunction, depression, falls, and urinary incontinence are common in older people with diabetes and may have subtle presentations [25]. Diabetes is associated with a twofold increased risk of being unable to perform daily physical tasks, such as walking, doing house work or climbing stairs, and 1.6-fold greater risk of difficulties performing basic personal care, such as bathing, using the toilet, dressing, and eating. Diabetes complications, such as neuropathy, arthritis, and vascular disease, are contributors to physical disability in older people with diabetes [26, 27]. The Study of Osteoporotic Fractures has shown that diabetes also increases the risk of falls (odds ratio (OR) 2.78; 95% confidence interval (CI):1.82–4.25). History of arthritis, musculoskeletal pain, depression, poor vision, and peripheral neuropathy are the main predictors of falling among older people with diabetes [28]. The risk of developing Alzheimer's disease or vascular dementia is twofold higher in older people with diabetes compared to age-matched people without diabetes [29]. In the Health, Aging, and Body Composition Study, older people (70–79 years old) with diabetes had an increased incidence of depression compared with persons without diabetes (23.5% vs. 19.0%, hazard ratio (HR) 1.31; 95% CI:1.07–1.61) [30].

Frailty

Frailty is a condition characterized by a reduction in physiological reserve and in the ability to resist physical or psychological stressors [31]. Its definition is largely based on the presence of three or more phenotypes (weight loss, weakness, decreased physical activity, exhaustion, and slow gait speed) [32]. Frailty is viewed as a wasting disease with weight loss being one of its criteria. Undernutrition, which is common in older people, seems to be a risk factor for frailty. In the USA, ~16% of elderly persons living in the community are undernourished. These figures rise to 59% in long-term care institutions and 65% in acute care hospitals [33]. Sarcopenia or muscle mass loss is a component of frailty which seems to be accelerated when diabetes is present. In a community study of 3153 participants ≥65 years, appendicular lean mass loss in men with diabetes was twice that of men without diabetes (3.0% vs. 1.5%) and in women with diabetes was 1.8 times that of those without diabetes (3.4% vs. 1.9%) over 4 years of follow-up. The mechanisms explaining these results may be related to reduced muscle protein synthesis as a result of lower testosterone and IGF-I and increased muscle protein breakdown caused by a higher rate of inflammation [34]. Diabetes also causes sarcopenia through the catabolic effect of insulin deficiency and by increasing intramyocellular lipid accumulation [35]. In another study, older persons with type 2 diabetes (T2DM) had accelerated decline in leg lean mass, muscle strength and longer sit to stand time compared to those with normoglycemia [36]. Another factor related to malnutrition and frailty may be oral health. For example, optimal nutrition may not be maintained because of poor dentition, dry mouth, reduced taste sensation, palatability, and appetite change with increasing age [37].

Clinical presentation

Diabetes can be asymptomatic in up to 50% of older people [38]. However, when symptoms are present they are mostly non-specific and may be attributed to aging. Non-specific symptoms, such as general malaise, fatigue or lethargy, are common manifestation of diabetes in old age. Geriatric syndromes, such as falls and urinary incontinence, may be the first manifestation of diabetes. Symptoms may be atypical, for example, anorexia rather than the typical polyphagia. The classic osmotic symptoms are usually less prominent because of the increased renal threshold for glucose (reducing the intensity of polyuria) and impairment of thirst sensation (reducing the intensity of polydipsia).

Box 62.3 Diagnosis and assessment of diabetes in old age-special considerations

Clinical presentation and diagnosis

- Fasting blood glucose may be normal in up to one-third of cases
- Postprandial or 2-hour oral glucose tolerance test are more reliable
- HbA_{1c} is specific but less sensitive as a diagnostic test
- Symptoms may be absent in up to 50% of patients
- Osmotic symptoms are less prominent
- Other symptoms may be non-specific such as fatigue or lethargy

Comprehensive geriatric assessment

Comprehensive geriatric assessment should be performed on initial diagnosis and annually including assessment of:

- Cognitive function
- Screening for depression
- Assessment for frailty
- Falls risk
- Activities of daily living ability
- Presence of urinary incontinence and chronic pain
- Nutritional status
- Medication adherence and polypharmacy
- Social circumstances

Hyperosmolar hyperglycemic state may be the presenting symptom or diabetes may be first diagnosed during an acute illness or following a routine blood test (Box 62.3).

Diagnosis

The diagnostic criteria for diabetes are the same irrespective of age (see Chapter 2). Clinicians should be aware that fasting glucose concentration may be normal in the early stages of diabetes and is therefore less sensitive in diagnosing diabetes in old age; however, the 2-hour OGTT appears to capture undiagnosed cases [39].

Since February 2011, glycated hemoglobin (HbA_{1c}) has been used as a diagnostic test for diabetes. However, although HbA_{1c} has high specificity (98.7%), its low sensitivity (46.8%) means that it can miss more than half of people with diabetes [40]. There are a number of pitfalls to using HbA_{1c} in older people. HbA_{1c} increases with age after adjustment for glucose suggesting that non-glycemic factors contribute to this increase. Furthermore, iron deficiency anemia, which is common in older people, is associated with an increase in HbA_{1c} independent of changes in blood glucose. Both of these factors will lead to an over-diagnosis of diabetes in older people if HbA_{1c} is used in preference to glucose. The diagnosis should be confirmed by a second laboratory test in the absence of diabetes symptoms as for younger people.

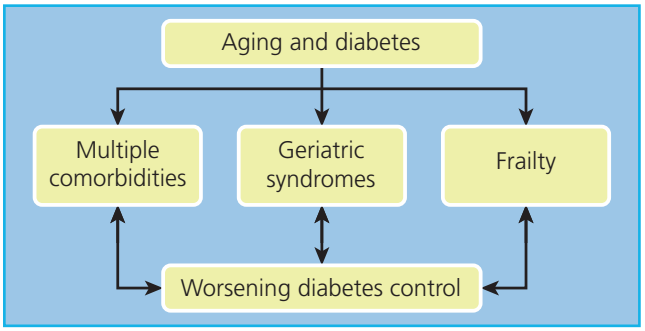

Figure 62.1 Interaction between diabetes phenotype in old age and diabetes control. The interplay between aging and diabetes leads to the development of the characteristic phenotype of diabetes in old age of multiple comorbidities, geriatric syndromes, and frailty, which in turn may lead to worsening of diabetes control setting a vicious circle.

Management

The phenotype of diabetes in old age is highly variable and affected by comorbidity, geriatric syndromes, and frailty. Therefore, the diabetes management should take into account the heterogeneous nature of the diabetes and the complex needs of the individual. A comprehensive geriatric assessment should be performed after the initial diagnosis and annually as age-related comorbidities may impair diabetes control. (Figure 62.1) Hyperglycemia should not be treated in isolation but as part of a multifactorial intervention to reduce cardiovascular risk. Cardiovascular complications remain the main cause of mortality accounting for 50–75% of all deaths in people with diabetes [41]. Management includes lifestyle modification and pharmacological interventions for hyperglycemia and cardiovascular risk factors (Box 62.4).

Lifestyle modifications

Lifestyle modification includes changes in diet, weight reduction, smoking cessation (the single most effective means of reducing mortality [42]), and regular exercise to reduce visceral obesity and improve insulin sensitivity.

Aging is associated with increased insulin resistance through the loss of skeletal muscle mass [12]. Muscle mass is dependent on a balance between muscle protein synthesis and breakdown; protein intake with exercise training synergistically increases skeletal muscle mass in older people. In one trial, protein supplementation for frail older people who were engaged in resistance training resulted in muscle hypertrophy, and increases in muscle strength, muscle mass, and performance [43]. A diet that is high in fiber and potassium and low in saturated fats and refined carbohydrates and salt may help achieve an ideal body weight as well as improving the lipid profile, significantly lowering blood pressure and reducing the overall cardiovascular risk [44]. In the Diabetes Prevention Program, lifestyle intervention including modest weight reduction, a healthy low-fat diet, and regular exercise reduced the development of diabetes and this beneficial effect persisted for up

Box 62.4 Management of cardiovascular risk factors in older people with diabetes

Lifestyle modifications

- Smoking cessation.
- Balanced diet with adequate nutrition especially in frail individuals.
- Regular exercise.
- Weight loss in overweight persons.

Hyperglycemia

- Tight control in fit or newly diagnosed people.
- Conservative approach in frail persons.
- Avoid hypoglycemia.

Hypertension

- A target systolic BP of 140 mmHg is reasonable in fit individuals but higher targets around 150–160 are appropriate in frail or very old (≥85 years) persons.
- Achieving target BP is more important than the antihypertensive drug class used and most people will need more than one drug to achieve the target.

Dyslipidemia

- Statin therapy in older people with diabetes is beneficial and should be offered unless specifically contraindicated or life expectancy is limited by frailty and comorbidities.
- The routine use of fibrate or niacin in addition to statin is not recommended.

Aspirin

- Aspirin therapy should be considered selectively in older people with diabetes and high cardiovascular risk but after assessment of their bleeding risk.

Multiple intervention

- Hypoglycemia should not be treated in isolation but as part of a multiple cardiovascular risk factors reduction.
- Statins and antihypertensive drugs have the largest effect in reducing cardiovascular events followed by hypoglycemic agents and aspirin.

Reverse metabolism

- In frail individuals targets should be relaxed because of the inverse relationship between cardiovascular risk factors and mortality.

BP, blood pressure; CV, cardiovascular.

to 10 years after the end of the study especially in older people (≥60 years) [45]. Additional benefits of exercise for older people may include increased muscle strength and improved walking balance. The Look AHEAD (Action for Health in Diabetes) study in the middle aged and older people with T2DM showed that weight loss and improved fitness lowered the risk of loss of mobility [46].

Hyperglycemia

Although the evidence in reducing microvascular disease by tight glycemic control is established, there is ongoing debate about whether reducing blood glucose to near normal levels results in lower cardiovascular events (Table 62.1) [47–50]. In frail older people, the benefit of blood glucose control diminishes in the presence of other comorbidities. In a decision analysis to assess the effects of baseline health status on prioritization of therapy, blood pressure control conferred a larger benefit than glucose control at advanced ages (75–79 years) and the expected benefits of both therapies steadily declined as the level of comorbidity and functional impairment increased [51]. Therefore, in older people who are frail with multiple comorbidities and functional impairment, tight control may be more harmful by inducing hypoglycemia. It is important to address individual goals of therapy, guided by patient preferences, life expectancy, comorbidities, and the influences of therapy on quality of life. The advantages and disadvantages of antidiabetes medications in older people are detailed in Table 62.2.

Hypertension

A target systolic blood pressure of ~140 mmHg is reasonable in older people with diabetes as maintainence of a systolic pressure between 130–140 mmHg is associated with a reduction of adverse cardiovascular outcomes in older people with hypertension and diabetes. Tighter control, however, is not warranted as this may be associated with increased adverse events. In the International Verapamil SR-Trandolapril (INVEST) study controlling systolic blood pressure to <130 mmHg was not associated with better cardiovascular outcomes than usual control of 130–140 mmHg in individuals aged ≥55 years, and it was associated with a non-significant increased risk of mortality (11.0% vs. 10.2%; adjusted HR 1.20; 95% CI: 0.99–1.45, $p = 0.06$) [52]. Tight blood pressure control (target <120 mmHg systolic) was also not beneficial and was associated with adverse outcomes in older people (40–79 years) with diabetes [53]. The Ongoing Telmisartan Alone and in Combination with Ramipril Global Endpoint Trial (ONTARGET) also had similar conclusions for older individuals, mean age 66 ± 7 years, of whom 57% were aged ≥65 years [54]. Two meta-analyses of older people with diabetes did not show reduced myocardial infarction or mortality rates with systolic blood blood pressures <140 mmHg [55, 56]. In very old people (>80 years), the targets may be even more relaxed. The Hypertension in the Very Elderly Trial (HYVET) which included older people aged ≥80 years with sustained systolic blood pressure >180 mmHg, 7% of whom had diabetes, showed a significant 33.7% (HR 0.66; 95% CI: 0.53–0.82, $p < 0.001$) reduction in cardiovascular events with a target blood pressure control of 150/80 mmHg. However, the individuals included in HYVET were healthier than those in the general population with a low baseline rate of known cardiovascular disease (11.5%), myocardial infarction (3.1%), or heart failure (2.9%). Therefore, the results may not apply to all older persons, especially those with multiple comorbidities or living in care

Table 62.1 Summary of recently published trials [47–50].

	UKPDS Follow-up	ACCORD	ADVANCE	VADT
Number of participants	3277	10,251	11,140	1791
Mean (SD) age (years)	62 (8.0)	62.2 (6.8)	66 (6.0)	60.5 (9.0)
Inclusions criteria	Newly diagnosed T2DM	Age 40–79 with history of CVD, age 55–79 years with evidence of atherosclerosis, albuminuria, LVH, or two additional risk factors for CVD	Diagnosis of T2DM at ≥30 years of age or age ≥55 years or history of macro- or microvascular disease	T2DM with inadequate response to maximum dose of an oral agent or insulin therapy
History of cardiovascular disease	People with significant CVD were excluded	35%	32%	40%
Duration of diabetes on entry (years)	Newly diagnosed	10.0	8.0	11.5
Cardiovascular outcome	Benefit	Harm	No benefit	No benefit
Hypoglycemia intensive vs. standard therapy (%)	2.4% for sulfonylurea, 1.8% for insulin, and 0.7% for standard therapy.*	16.2 vs. 5.1	53 vs. 38	24.1 vs. 17.6

UKPDS, UK Prospective Diabetes Study; ACCORD, Action to Control Cardiovascular Risk in Diabetes; ADVANCE, Action in Diabetes and Vascular Disease: Preterax and Diamicron MR Controlled Evaluation; VADT, Veterans Affairs Diabetes Trial; DM, diabetes mellitus; CVD, cardiovascular disease; LVH, left ventricular hypertrophy.
*Only rates of sever hypoglycemia reported in the intervention phase of the study.

homes [57]. In another community study of people aged ≥85 years old, there was a U-shaped relationship with a systolic blood pressure of 164.2 mmHg (95% CI: 154.1–183.8 mmHg) being associated with the lowest mortality suggesting that the optimal systolic blood pressure for this age group could be >140 mmHg [58].

Thiazide diuretics, angiotensin receptor blockers, angiotensin-converting enzyme inhibitors, and calcium channel blockers are reasonable first choice agents although higher doses of diuretics may worsen blood glucose and lipid profile. Most people will require more than one antihypertensive agent.

Table 62.2 Advantage and disadvantage of antidiabetes medications in older people.

Medication	Advantage	Disadvantage
Sulfonylureas	Suitable for those with renal impairment or low risk of hypoglycemia.	Increased risk of hypoglycemia and weight gain. Long-acting sulfonylureas should be avoided.
Metformin	Low risk of hypoglycemia, cardiovascular benefit, weight neutral.	Increased risk of lactic acidosis in those with renal impairment, heart failure, sepsis, and dehydration.
Meglitinides	Short-acting, suitable for those with erratic eating pattern.	Risk of hypoglycemia and weight gain but less than sulfonylureas.
Alpha-glucosidase inhibitors	Low risk of weight gain and hypoglycemia.	Weak hypoglycemic action, gastrointestinal side effects.
Pioglitazone	Suitable for those with renal impairment, less risk of hypoglycemia.	Fluid retention, worsens heart failure, increases fracture risk and possibly bladder cancer.
DPP-4 inhibitors*	Low risk of hypoglycemia, weight loss.	Gastrointestinal side effects, dose mostly needs to be adjusted with renal impairment.
GLP-1 receptor agonists**	Low risk of hypoglycemia, weight loss.	Injectable, weight loss in frail individuals, not suitable in renal failure, nausea is common and possible risk of pancreatitis.
Sodium glucose cotransporter 2 (SGLT2) inhibitors	Low risk of hypoglycemia, weight loss.	Not suitable for frail elderly with weight loss, heavy glucosuria increases risk of urinary tract infections, candidiasis, dehydration, and hypotension.
Insulin	Effective, tailored rapidly to changes in need, improves quality of life.	High risk of hypoglycemia and weight gain.

*DPP-4, Dipeptidyl peptidase 4
** GLP-1, Glucagon-like peptide-1.

Dyslipidemia

There are no large clinical trials of lipid-lowering interventions specifically in older people with diabetes. Post hoc analysis of the Heart Protection Study, which included participants with diabetes aged between 40 and 80 years, showed a significant 25% risk reduction of cardiovascular events [59]. A meta-analysis of 18,686 people with diabetes in 14 trials of statin therapy for primary prevention showed a similar 20% relative risk reduction in major adverse vascular outcomes in older (≥65 years) compared to younger (<65 years) people [60]. In the very elderly (>80 years), cholesterol targets are unclear. A review of observational studies including 13,622 participants showed that low total cholesterol (<5.5 mmol/L) was associated with the highest mortality rate in those >80 years old [61]. The routine use of a fibrate or niacin in addition to a statin therapy failed to reduce cardiovascular events beyond the effects of statins and is not recommended [62, 63]. Cardiovascular prevention with statins emerges fairly quickly (within 1–2 years) suggesting that statins may be offered to nearly all older people with diabetes except those with very limited life expectancy. Chronological age per se should not exclude people from receiving therapy but functional or biological age as well as the impact of long-term drug therapy on safety and quality of life should be considered.

Aspirin therapy

Aspirin reduces cardiovascular morbidity and mortality in people with a history of cardiovascular disease [64]. However, evidence for aspirin use in primary cardiovascular risk prevention is still unclear. A meta-analysis of aspirin treatment as primary prevention in people with diabetes demonstrated a trend towards a 10% reduction in the cardiovascular events but this needs to be balanced against an increased risk of hemorrhage [65]. Presence of diabetes per se does not justify aspirin use. However, most older people with diabetes have a high burden of cardiovascular risk factors and are likely to benefit from aspirin therapy. Therefore, aspirin use should be considered selectively in older individuals with diabetes and high cardiovascular risk after assessment of the risk of bleeding.

Multiple risk intervention

Cardiovascular risk factors tend to cluster in what is known as the "metabolic syndrome." Both age and diabetes increase the prevalence of metabolic syndrome. In a Norwegian study, the prevalence increased from 11.0% in men aged 20–29 years to 47.2% in men aged 80–89 years, and from 9.2% to 64.4% for women in the corresponding age groups [66]. In a population-based study of 5632 white European people (65–84 years old), the prevalence was 64.9% and 87.1% in men and women with diabetes, respectively, compared to 25.9% and 55.2% in men and women without diabetes [67]. Although metabolic syndrome is postulated as a risk factor for cardiovascular disease, in a prospective study of 1025 elderly people aged 65–74 years [68] and an analysis of the outcomes of two prospective studies in people aged over 60 years, the metabolic syndrome was shown to be a marker of cardiovascular disease but did not enhance risk prediction above and beyond the risk associated with its individual components [69].

Multifactorial interventions are appropriate and show that the use of statins and antihypertensive drugs have the largest effect in reducing cardiovascular events with antidiabetes agents and aspirin the next most important interventions [70]. More effort is needed to optimize this comprehensive approach as many older people do not receive this level of care [71].

Reverse metabolism

In frail older people, the power of traditional cardiovascular risk factors including hypertension, dyslipidemia, and hyperglycemia to predict risk of cardiovascular disease seems to diminish with age leading to a paradoxical relationship [72]. The more commonly proposed explanations include the association of low body weight and low cholesterol with increased protein energy malnutrition and increased inflammation associated with frailty [73]. In a study of 331 very old people (mean age 85 ± 7 years), low body mass index, low blood pressure, low total and high density lipoprotein (HDL) cholesterol, and high insulin sensitivity in individuals without diabetes predicted total mortality indicating a "reverse metabolism" that is probably attributable to malnutrition and chronic disorders which have a negative impact on survival [74]. Low albumin (a marker of malnutrition) and high C-reactive protein (a marker of inflammation) were associated with these cardiometabolic factors limiting their prognostic value for cardiovascular risk in older people [74]. It is important to recognize that many older people with diabetes are frail and the expected benefit of tight metabolic control declines as morbidity and functional impairment increase thus, functional status and level of comorbidity are important factors in assessing risk [51].

Special considerations in old age

Hypoglycemia

Hypoglycemia is commoner in older people with diabetes because of the associated comorbidities, geriatric syndromes, polypharmacy, long duration of diabetes and the increased prevalence of hepatic and renal dysfunction (Box 62.5). Although there is a paucity of data about the incidence of hypoglycemia in older people, the reported incidence of hypoglycemia varies in the literature owing to differences in the definition used and the age of the populations studied. In a US retrospective population-based study of 19,932 Medicaid patients, aged ≥65 years, the incidence of severe hypoglycemia was 1.23 episodes per 100 person-years for people treated with sulfonylureas and 2.76 episodes per 100 person-years in those treated with insulin [75]. However, the strict definition of severe hypoglycemia (an episode leading to fatal outcome or hospital admission) may have underestimated the true frequency of events. Also, the data collection was conducted before the publication of the evidence for the benefit of tight glycemic control in T2DM in 1998 [76]. The subsequent trends towards

Box 62.5 Hypoglycemia in older people with diabetes

Incidence

- Increased in old age due to multiple comorbidities, undernutrition, polypharmacy, long duration of diabetes, and renal or hepatic impairment.

Difficult recognition

- Non-specific symptoms.
- Misdiagnosed for stroke, vertigo, or visual disturbance.
- Misinterpreted as dementia-related symptoms such as agitation or behavior change.
- Atypical presentation, e.g. confusion or passive delirium.
- Little warning or unawareness of autonomic symptoms.
- People with dementia are unable to communicate their feelings or symptoms.

Consequences

- Acute events such as cardiac arrhythmias or stroke.
- Chronic consquences such as mental and physical dysfunction.

tighter glycemic control have resulted in more frequent hypoglycemic episodes with insulin becoming the second commonest medication associated with adverse events reported to the Federal Drug Administration with a threefold increase in reported events from 1998 to 2005 [77]. Insulin was the second most frequent medication associated with emergency department visits in older people ≥65 years; 95.4% of episodes were related to hypoglycemia, 24.1% involved loss of consciousness or seizure, and 25.1% required hospitalization [78]. More recently in a prospective study involving 3347 people, median age 66.1 years, from the DiaRegis, a multicenter registry of people with diabetes in Germany, the annual incidence of hypoglycemia of any severity was 14.1% [79]. Although hypoglycemia incidence is difficult to estimate accurately, it is likely to be higher in older than younger people. In a prospective observational study of 3810 people in primary care, 11% of participants reported at least one episode of hypoglycemia of any severity in a 12-month period. Older people (≥70 years) reported more episodes than younger (<60 years) people (12.8% vs. 9.0%, $p < 0.01$). Significant differences were also seen for symptomatic episodes without a need for help (9.2% vs. 5.6%) and symptomatic episodes with a need for medical assistance (0.7% vs. 0.1%) [80]. In care homes the incidence of hypoglycemia is likely to be much higher than in a community setting reaching up to 41.9% in one study over a one-year period (median 2, range 1–10 episodes per patient per year) because of the higher levels of comorbidities [81].

Recognition

Although hypoglycemia in older people with diabetes is common, its recognition and diagnosis can be difficult. For example, owing to the predominance of neurological rather than autonomic symptoms, hypoglycemia may present with symptoms such as dizziness or visual disturbance resulting in misdiagnosis [82]. Another diagnostic challenge is the similarity in the clinical presentation of hypoglycemia with that of dementia where people may present with agitation, increased confusion, or behavioral changes. Furthermore, symptoms of hypoglycemia tend to be less specific with increasing age. In a survey of hypoglycemia symptoms perception by older people with diabetes (age 82.3 ± 3.9 years) attending an outpatient clinic, the majority of respondents reported non-specific symptoms of being generally unwell when their blood glucose level dropped, making the recognition of hypoglycemic episodes more difficult for healthcare professionals [83]. This was also demonstrated in the Action to Control Cardiovascular Risk in Diabetes (ACCORD) study with non-specific fatigue or weakness being the commonest symptoms of hypoglycemia experienced by the participants (mean age 62.2 ± 6.8 years) [84]. In older people the threshold of autonomic symptoms of hypoglycemia occurs at a lower blood glucose concentration while cognitive dysfunction occurs at a higher level compared with younger adults. Therefore, autonomic and neurological symptoms occur almost simultaneously with little warning [85]. This is referred to as "impaired awareness of hypoglycemia" [86]. Subclinical hypoglycemia or episodes with fewer symptoms may further reduce awareness leading to a vicious cycle whereby one episode of hypoglycemia can induce further hypoglycemia [87]. Therefore, many episodes of hypoglycemia may be unrecognized and under-reported by both people with diabetes and physicians, and subsequently the frequency is likely to be underestimated.

Consequences

Older people with diabetes are likely to be at a higher risk of the adverse consequences of hypoglycemia because of the increased prevalence of comorbidities, undernutrition, and polypharmacy compared with younger people [88]. Severe hypoglycemia may lead to serious acute vascular events, such as stroke, myocardial infarction, acute cardiac failure, and ventricular arrhythmias [89, 90]. The morbidity attributed to recurrent episodes of hypoglycemia is associated with silent and chronic complications, which could lead to significant physical and cognitive dysfunction and eventually to frailty, disability, and increased mortality. In a Taiwanese study of 234 residents aged 77.5 years living in long-term care facilities, of whom 35.5% had diabetes, hypoglycemia was associated with disability and reduced function. Functional status was worse in those who experienced hypoglycemia in comparison with those with no history of hypoglycemia (mean Barthel Index score 22.5 vs. 38.2). Complete dependence, defined as Barthel Index score <30, was also commoner in people with hypoglycemia (69.2% vs. 50%) [81]. The burden of hypoglycemia leading to hospitalization is higher in old age and may contribute to increased frailty and reduced quality of life. In a US study of a 33,492 people with diabetes, aged ~60 years, accidents resulting in hospital visits occurred in 5.5% of those with hypoglycemia compared to 2.8% of those without. Hypoglycemia was associated with

significantly increased hazards for any accident (HR 1.39; 95% CI: 1.21–1.59, $p < 0.001$), accidental falls (1.36; 1.13–1.65, $p < 0.001$), and motor vehicle accidents (1.82; 1.18–2.80, $p = 0.007$) after adjustment for baseline characteristics. In an age-stratified analysis, the risk of falls was twice as high among older people, ≥65 years, compared with younger individuals and hypoglycaemia was significantly associated with a greater than 50% increase in the hazard of falls (adjusted HR 1.52; CI: 1.18–1.95) [91]. Hypoglycemia also increases the risk of fractures which may lead to disability and frailty. In a retrospective observational study of 361,210 Medicare-covered patients with diabetes ≥65 years old, those with hypoglycemic events had a significantly higher proportion of fall-related fractures compared to those without hypoglycemia (5.24% vs. 2.67%, $p < 0.001$). Hypoglycemic events increased the risk of falls and fractures by 70% (OR 1.7; 95% CI: 1.58–1.83) [92].

Dementia

Progressive decline in cognitive function leading to dementia is common in older people with diabetes. Persistent hyperglycemia increases the risk of cerebrovascular disease by inducing inflammation, endothelial dysfunction, oxidative stress, and insulin resistance leading to an increased incidence of vascular dementia [93]. Moreover, accelerated brain aging from altered amyloid metabolism, increased protein glycation and direct cerebral glucotoxicity may explain the increased incidence of Alzheimer's dementia [94]. Structural changes in the brain have been noted with diabetes and dementia. For example, cerebral atrophy and hippocampal atrophy are reported more frequently in older people with diabetes and contribute to cognitive dysfunction especially impairment in immediate memory [95]. It seems that brain insulin resistance increases in Alzheimer's disease suggesting that Alzheimer's may be caused by a cerebral manifestation of diabetes.

Risk

Among people with diabetes, the relative risk of Alzheimer's disease is 1.56 (95% CI: 1.41–1.73), while vascular dementia is increased 2.27-fold (1.94–2.66) and all types of dementia by 1.73-fold (1.65–1.82) compared to those without diabetes [96]. In a prospective study of older people (>60 years old) with diabetes, age, microvascular disease, diabetic foot, cerebrovascular disease, cardiovascular disease, acute metabolic events, depression, and education were used to develop a risk score for dementia. Over 10 years, the risk of developing dementia was 5.3% (95% CI: 4.2–6.3) for the lowest score (-1) and 73.3% (64.8–81.8) for the highest (12–19) sum scores [97]. The presence of diabetes also accelerates mortality rate in people with dementia. In a retrospective Australian study, the mortality rate for people with diabetes and dementia was almost twice that of those with dementia but without diabetes (HR 1.9; 95% CI: 1.3–2.9) [98].

Implications

Older people with diabetes and dementia experience difficulties in performing self-care tasks. In a community-based study of 1398 people with diabetes, aged 70 years, adherence to diabetes self-care tasks decreased as cognitive impairment increased, with exercise and diet adherence being the most strongly associated with cognitive impairment [99]. The combination of diabetes and dementia is likely to be associated with an increased incidence of treatment adverse events, such as severe hypoglycemia [100]. Due to erratic eating patterns associated with dementia, older people with diabetes are also at risk of malnutrition, dehydration, and worsening diabetes control. Carers of people with diabetes and dementia face extraordinary challenges to care for both conditions especially in people who develop behavior changes. Their needs should be identified early to allow for greater support from the healthcare system.

Management

Although there is an association between hyperglycemia and cognitive dysfunction, intensive glycemic control does not prevent a decline in mental function [101]. Once dementia develops diabetes self-care deteriorates and so clinicians need to check for cognitive dysfunction if non-adherence to self-care tasks occurs. Clinicians should also be aware that dementia may be associated with language impairment, disorientation, and personality changes that may mimic the symptoms of hypoglycemia [102]. The Mini Cog test is a simple screening tool for dementia which has a sensitivity of 86.4% (95% CI: 64.0–96.4%) and a specificity of 91.1% (85.6–94.6%) and takes only 3 minutes to perform [103].

Older people with diabetes and dementia have complex needs because of increased dependency and unpredictable behavioral changes as the decline in cognitive function continues. For example, hydration should be maintained because of impaired thirst sensation to avoid risk of volume depletion and hyperglycemic crises. In people treated with insulin, the new class of long-acting insulin analogs may be a good option as they reduce the risk of hypoglycemia and can be conveniently injected once daily [104]. People who have erratic eating patterns and unpredictable caloric intake could be managed with a regimen where short-acting insulin analogs are administered only after meal consumption, thus reducing the risk of hypoglycemia if a meal is missed or only partly consumed (Box 62.6).

Hypoglycemia–dementia interaction

The brain is highly dependent on glucose for its metabolism and is particularly vulnerable to hypoglycemia especially in older people. After each hypoglycemic episode major cognitive changes occur leading to post-hypoglycemic encephalopathy. Repeated episodes of hypoglycemia may contribute to cognitive dysfunction and the relationship appears to be bidirectional. History of severe hypoglycemia increases risk of cognitive dysfunction [105] and cognitive dysfunction increases risk of hypoglycemia [106]. Therefore, recurrent hypoglycemia may be associated with impaired cognitive function and development of dementia. In a retrospective study of 16,667 older people with diabetes, mean age 65 years, the risk of dementia increased by 26% (HR 1.26; 95% CI: 1.10–1.49), 80% (1.80; 1.37–2.36) and 94% (1.94; 1.42–2.64) in those with a history of one, two, and three or more

Box 62.6 Dementia in older people with diabetes

Screening
Should be performed annually or earlier if one of the following is observed:
- Less medication adherence.
- Forgetfulness in how to handle insulin injections.
- Forgetting how to recognize or treat hypoglycemia.
- Difficulties in how to interpret blood glucose results or to make decisions regarding adjusting insulin doses.
- Non-adherence with general self-care.
- Erratic eating pattern and missing meals.
- Non-adherence with dietary requirements.
- Recurrent unexplained hypoglycemia.

Screening tool (Mini-Cog)
Ask the patient to repeat three items such as lemon, key, and balloon then provide a clock face:
- Ask the patient to draw the numbers of the clock face.
- Ask the patient to draw the hands of the clock to show the time as ten to three.
- Ask the patient to recall the three items.

Give one mark for each task performed and for each item remembered. A score 0–3 out of maximum 5 defines cognitive impairment.

severe hypoglycemic episodes (defined as hypoglycemia needing hospital admission or emergency department visit), respectively independent of glycemic control, medications, and comorbidities. The attributable risk of dementia was 2.39% (1.72% to 3.01%) per year in people with compared with those with no history of hypoglycemia [105]. In an observational cohort study of 302 participants with diabetes, mean age 75.7 ± 4.6 years, a cross-sectional association between severe hypoglycaemia and cognitive function was observed. People with dementia (16% of participants) or cognitive impairment (14%) were significantly more likely to have been hospitalized with hypoglycemia than people with normal cognitive function (3.8%), $p = 0.004$ [107]. A prospective association between historical hypoglycemia and cognitive decline in a subsample of the participants without dementia was not found. However, the prospective phase of this study was limited by the small number of participants ($n = 205$) and short duration of follow-up (18 months) which may have limited the power to detect any association between incident hypoglycemia and cognitive dysfunction [100]. More recently, in the Edinburgh population-based cross-sectional study of 1066 people with T2DM, mean age 67.9 ± 4.2 years, self-reported history of severe hypoglycemia was associated with poorer late life cognitive ability. Those who reported at least one episode of severe hypoglycemia demonstrated poorer performance on tests of verbal fluency (34.5 vs. 37.3, $p = 0.02$), digit symbol testing (45.9 vs. 49.9, $p = 0.002$), letter–number sequencing (9.1 vs. 9.8, $p = 0.005$), and trail-making ($p < 0.001$) independent of diabetes duration, vascular risk factors, or vascular complications. These associations persisted after adjustment for estimated prior cognitive ability suggesting that the association may be attributable to an effect of hypoglycemia on age-related cognitive decline [108]. A linear relationship was observed between poorer general cognitive ability and increasing frequency of severe hypoglycemia over the year preceding cognitive testing supporting results of earlier studies.

Management of Diabetes

Glycemic targets

Glycemic targets should be individualized taking into consideration overall health and life expectancy.

Fit older people

For healthier older people with low prevalence of cardiovascular risk factors especially those with a new diagnosis of diabetes, tight glycemic control with an HbA_{1c} around 53 mmol/mol (7%) is reasonable as this is likely to reduce diabetes complications [47] while persistent hyperglycemia is associated with increased risk of falls [109] and mortality [110] regardless of the associated comorbidities.

Frail older people

For frail older people or those with established cardiovascular disease a safer target around 58–64 mmol/mol (7.5–8%) is appropriate. The presence of multiple comorbidities is a potential competitor for the benefit of tight glycemic control in this population. In a decision analysis to assess the effects of comorbid conditions and functional impairment, the expected benefits of tight glycemic control, HbA_{1c} 53 versus 63 mmol/mol (7% vs 7.9%), declined steadily as the level of comorbidities and functional impairment increased. One to two points were allocated for each comorbidity, according to severity, to create a mortality index score. In people aged 60–64 years with new-onset diabetes, the quality-adjusted days declined from 106 (95% CI: 97–117) days to 44 days (range 38–50) with three additional points in mortality index score, and to 8 days (range 5–10) with seven additional index points [51].

Very frail older people

For very frail older people and those residents in nursing homes and with limited life expectancy, a target HbA_{1c} of 64–75 mmol/mol (8–9%) is suitable. Tight glycemic control in this population may be harmful by inducing hypoglycemia and reducing quality of life. However, higher HbA_{1c} >75 mmol/mol (>9.0%) is associated with increased mortality [111]. Targets in this population should focus on short-term day to day blood glucose control, rather than long term HbA_{1c}, to avoid both hyperglycemia, which may lead to lethargy, dehydration, visual impairment and infections, and hypoglycemia which may lead to falls and confusion (Figure 62.2).

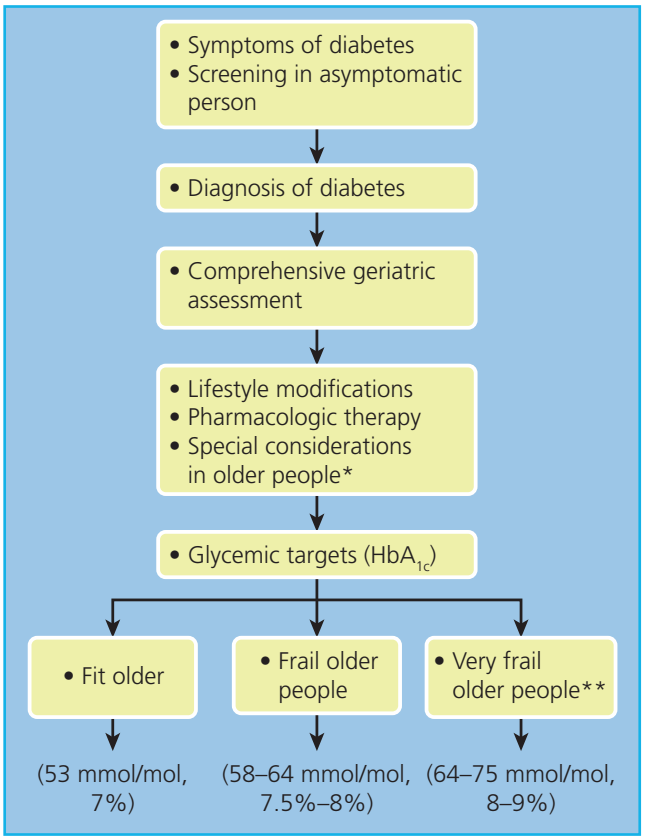

Figure 62.2 Diabetes diagnosis, management and glycemic targets. *Considerations such as risk of hypoglycemia, dementia, polypharmacy, and residents in care homes. **In very frail older people with limited life expectancy, short-term targets of blood glucose >4 but <15 mmol/L is more important than the long-term HbA_{1c} target.

Polypharmacy

Clinical guidelines are largely disease-specific, age-neutral, and driven by numerical surrogates, such as HbA_{1c} or blood pressure, but do not necessarily consider hard endpoints and outcomes relevant to older people, such as physical function, disability, or quality of life [112]. Indiscriminate application of guidelines may lead to over treatment and polypharmacy with potential harm and increased hospitalization in the elderly. For example, older people are more liable to experience adverse effects of antihypertensive medications, such as renin angiotensin system blockers leading to acute kidney injury, hyperkalemia, or hypotension with further deterioration of renal function especially in those with existing chronic kidney disease. Withdrawal of these drugs in elderly people (mean age 73.3 years) with stage 4 and 5 chronic kidney disease has been shown to improve kidney function [113]. A gradual decrease of blood pressure is an essential strategy in treating elderly people with hypertension to avoid an accelerated blood pressure drop with subsequent falls. Blood pressure should be measured both lying and standing and patients asked about orthostatic symptoms to avoid orthostatic hypotension. It is important to realize that the presence of orthostatic symptoms, such as dizziness, light headedness or faintness, is associated with an increased risk of falls (OR 8.21; 95% CI: 4.17–16.19) rather than orthostatic hypotension per se [114].

Avoidance of hypoglycemia is essential especially in those with impaired kidney or liver function which delays the clearance of antidiabetes medications [115]. Glycemic goals should be regularly reviewed and antidiabetes medications adjusted with increasing age especially in those with the onset of cognitive impairment or frailty. Declining weight, malnutrition, and frailty may lead to a reduced need for antidiabetes medications while increasing the risk of hypoglycemia. Antidiabetes medications have been safely withdrawn in a cohort of frail nursing home older people with T2DM, mean age 84.4 ± 6.8 years [116] and in another group in the community, mean age 86.5 ± 3.2 years attending outpatient clinics without a deterioration of their glycemic control [117]. The main characteristics of these individuals were significant weight loss, increased comorbidities including dementia and polypharmacy with recurrent hypoglycemia [117]. Therefore, people with these criteria appear to be suitable candidates for a trial of antidiabetes medication withdrawal. Higher doses of statins should be avoided in frail elderly people, who may be more susceptible to drug-related myopathy. Non-steroidal anti-inflammatory drugs should be used carefully in older people with diabetes especially those with chronic kidney disease because of the increased risk of acute kidney injury. Polypharmacy (taking >4 drugs) is common; in a British care home study, 84% of residents with diabetes were taking >4 drugs with a high proportion (59%) of residents prescribed drugs for cardiovascular disease prevention. This may be inappropriate in this disabled population with limited life expectancy as polypharmacy leads to increased risk of drug errors, hypoglycemia, and hospitalization. Therefore, regular medication review of care home residents with diabetes should be undertaken as it has the potential to reduce costs and minimize adverse drug reactions [118].

Care homes

Care home residents with diabetes are likely to be frail, with multiple comorbidities and limited life expectancy. Therefore short-term glycemic targets with minimal diabetes-related interventions are important to maintain quality of life. Maintaining a random blood glucose between 4–15 mmol/L (70–270 mg/dL) is reasonable as blood glucose outside this range is likely to be symptomatic and result in cognitive changes [119]. Maintaining blood glucose in this "comfort zone" may ensure "comfort care" avoiding both hyperglycemia and hypoglycemia thereby reducing malaise and improve mental function and general well-being [120] (Box 62.7).

Care plans

Care homes should have a policy for diabetes care including diabetes screening for residents on admission and an individualized care plan for residents. Care plans should be tailored to individual needs and take into consideration patients' values, preferences,

Box 62.7 Recommendation for care of older people with diabetes in care homes

On admission to care home

- Each resident should be screened for the presence of diabetes.
- Each resident with diabetes should have assessment for functional loss and interventions in place to delay disability.

During their stay at care home

- Residents should be regularly reviewed for the presence of hypoglycemic symptoms especially for those on insulin or sulfonylureas.
- Resident with diabetes should have optimal blood pressure and blood glucose regulation to help maintain cognitive and physical performance.

Good clinical practice in care homes

- All residents should have an annual screen for diabetes.
- Each resident with diabetes should have an individualized diabetes care plan.
- Care homes with diabetes residents should have an agreed diabetes care policy or protocol which is regularly audited.
- Diabetes education and training courses should be available to care home staff.
- Adoption of risk–benefit approach in the management of residents with diabetes in terms of medications, metabolic targets, and extent of performing investigations with a focus on enhancing quality of life, maintaining functional status, and avoiding hospital admission for diabetes-related complications.

life expectancy, comorbidities, and the impact of diabetes management (polypharmacy, glucose monitoring) on quality of life. Medications should be reviewed to switch those taking longer acting sulfonylureas to shorter acting agents and polypharmacy reviewed regularly. Screening for complications relevant to older people, such as cognition, physical function, and depression, should be included in their annual review.

Nutrition

Nutritional guidelines should not be too restrictive but tailored to be healthy and to reflect personal preferences. Individuals are free to exercise personal choices with respect to food selection. Diabetes treatment is then adjusted accordingly. The aims of nutritional intervention include maintenance of healthy body weight and avoidance of malnutrition.

Holistic approach

An individualized holistic care plan is recommended to address care home residents' complex needs [121]. Residents with diabetes should have an annual comprehensive foot examination to identify risk factors for ulcers and amputations. Podiatry input should be available regularly. Residents with diabetes should have an initial comprehensive eye examination and annually thereafter. Domiciliary optometric services may be an option for residents who are not able to travel.

Education

As older people are at increased risk of hypoglycemia [82, 90] and may tolerate low blood glucose with no specific symptoms due to diminished autonomic response, it is important that residents and care home staff are educated to recognize the symptoms and to treat hypoglycemia. In a study that delivered a diabetes educational program to care home staff, staff knowledge improved and was retained at 12 months and led to improved quality of care up to a year after the intervention [122].

Conclusion

Aging is associated with increased insulin resistance, due to decreased muscle mass, increased visceral fat, and decreased insulin secretion, because of diminished β-cell mass and function, leading to glucose intolerance and diabetes in genetically susceptible individuals. Through population aging and increased life expectancy, diabetes is increasingly becoming a disease of older age. The phenotype of diabetes in old age is characterized by an increased prevalence of multiple comorbidities, geriatric syndromes, and frailty. Therefore the assessment of older people with diabetes on diagnosis and annually thereafter should be comprehensive and include screening for these syndromes, especially cognitive and physical dysfunction. Older people are a highly heterogeneous population ranging from a fit person living in the community to a frail individual with multiple comorbidities living in a care home. Management should therefore be individualized with variable metabolic targets from tight control in fit individuals to a conservative approach in frail ones. More attention should be focused on optimal management of undernutrition in frail older people by improving nutrition and physical activity to maintain muscle mass and improve overall function. Quality of life should be at the center of the management plans.

Future perspectives

Although tight glycemic control will continue to be the aim for older fit and independent people with diabetes, this is not suitable for those who are frail and at a high risk of side effects due to polypharmacy [123]. A new approach to defining glycemic targets based on the level of function has recently been introduced by the International Diabetes Federation and represents the first comprehensive guidance in this area [124].

There is a need for clinical trials specifically designed for older people with diabetes to explore the real benefit of glycemic control

in this diverse group. Comprehensive geriatric assessment including physical and mental health assessment will continue to be essential in view of the epidemiological shift of diabetes towards older age. Frailty and geriatric syndromes are emerging as complications in older people with diabetes and will need interventions beyond glycemic control. There remains a lack of intervention studies that reduce disability and improve quality of life in older people with diabetes. A focus on improvements in function may be of greater clinical relevance in frail older people with diabetes than metabolic targets alone. The proposed MID-Frail study will evaluate the clinical, functional, social, and economic impact of a multimodal intervention (resistance training exercise, diet, and education) in frail and pre-frail participants aged ≥70 years with T2DM compared with usual clinical practice [125]. This may have an impact on reducing functional decline, promoting independence, and maintaining quality of life.

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63 Diabetes at the End of Life

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Key points

- Although diabetes is common worldwide, only a minority of deaths in people with diabetes are directly attributable to diabetes. However, diabetes as a cause of death is underreported.
- It is estimated that 4.9 million people with diabetes died in 2014.
- Diabetes is not usually the main cause of death; the causes of death in people with diabetes are in general the same as for those without diabetes, but cardiovascular deaths (especially heart failure) and some cancers are overrepresented.
- People are approaching the end of life when they are likely to die within the next 12 months.
- Generic end-of-life guidance applies to people dying with diabetes and healthcare professionals need to be trained and competent to care for this population; however, this should be supplemented by diabetes-specific guidance.
- Glycemic targets may be relaxed in the last year of life; HbA_{1c} is not required during this time but the blood glucose should be kept between 6–15 mmol/L (110–270 mg/dL).
- Hypoglycemia in people taking insulin or oral hypoglycemic agents is predictive of mortality.
- Insulin treatment must never be stopped in dying people with type 1 diabetes.

Dying with diabetes

Diabetes is common with an overall global prevalence of 8.3% which is rising [1]. The prevalence is higher in the elderly; 10–30% of people in Europe of pensionable age have diabetes and 25% of care home residents in the UK have diabetes [2].

Although survival with diabetes has been improving, people with diabetes have reduced life expectancy compared with the general population [3–7]. The National Diabetes Audit for England and Wales in 2012–2013 revealed a standardized mortality ratio (SMR) of 134 for people with all types of diabetes. The effect was larger for people with type 1 diabetes (T1DM) (SMR 232), for younger age groups, and for women [3]. In Africa 76% of deaths occur in people aged <60 years [1].

It is estimated that globally 4.9 million people with diabetes died in 2014, which equates to one death every 6 seconds. In the United States diabetes was the seventh leading cause of death in 2010, with 69,071 death certificates listing diabetes as the underlying cause of death, and a further 234,051 death certificates listing diabetes as an underlying or contributing cause of death. This may be an underestimate as only 35–40% of recorded deaths in people known to have diabetes stated diabetes on the death certificate and only 10–15% had it listed as the underlying cause of death [8]. In England approximately 500,000 people die each year, 75,000 of whom will have diabetes [9]. There are apparent variations in mortality related to diabetes across Europe with age standardized death rates ranging from 4.0 per 100,000 in Greece to 17.9 in Portugal and even higher levels for Israel (36.1) and Armenia (46.8) [10].

Deaths attributed primarily to diabetes include ketoacidosis, severe hypoglycemia, and hyperosmolar hyperglycemic state, but these account for only 3% of all diabetes deaths. In high-income countries, the premature mortality in people with diabetes is predominantly caused by a higher prevalence of cardiovascular disease, particularly heart failure, which accounts for 75% of all deaths and is associated with a 10-year reduction in life expectancy [3, 11]. The next most common causes of death are chronic kidney disease (10%) [12] and cancer. Individuals with type 2 diabetes (T2DM) are at increased risk of developing certain cancers as both conditions share many of the same risk factors including aging, gender, obesity, physical inactivity, diet, alcohol, and smoking [7, 13].

It follows that healthcare professionals working with adults will encounter people with diabetes who are dying in various settings, and should know how to address their needs at the end of life.

Textbook of Diabetes, Fifth Edition. Edited by R. Holt, C. Cockram, A. Flyvbjerg and B. Goldstein.

End of life

Palliative medicine is a surprisingly young specialty even in high-income countries, probably because death has been regarded as a failure of medical care. This attitude was changed by the pioneering work of those such as Dame Cicely Saunders and international declarations about the rights of the dying person. In 1976 the Parliamentary Assembly of the Council of Europe resolved that:

> *"The prolongation of life should not in itself constitute the exclusive aim of medical practice, which must be concerned equally with the relief of suffering" [14].*

The principles of care at the end of life apply to everyone who is terminally ill, and have been articulated in numerous publications, which have themselves been revised in line with evidence and experience (Table 63.1) [15]. The sensitive application of such principles tailored to the individual, and supplemented by excellent communication with them and their families, is likely to result in the best possible outcome under the circumstances.

Although self-evident, end-of-life care cannot start until it is recognized and acknowledged that an individual is nearing the end of their life. This is not intuitive, particularly when medical and nursing staff have until then been providing active management intended to bring about a cure. Guidance has been produced to assist healthcare professionals in making this diagnosis. The General Medical Council UK [16] states that "Patients are 'approaching the end of life' when they are likely to die within the next 12 months." This includes patients whose death is imminent (expected within a few hours or days) and those with:

- advanced, progressive, incurable conditions;
- general frailty and coexisting conditions that mean they are expected to die within 12 months;
- existing conditions if they are at risk of dying from a sudden acute crisis in their condition;
- life-threatening acute conditions caused by sudden catastrophic events [16].

Table 63.1 Key principles of end-of-life care.

- Provision of a painless and symptom-free death
- Tailor glucose-lowering therapy and minimize diabetes-related adverse treatment effects
- Avoid metabolic decompensation and diabetes-related emergencies:
  - frequent and unnecessary hypoglycemia
  - diabetic ketoacidosis
  - hyperosmolar hyperglycemic state
  - persistent symptomatic hyperglycemia
- Avoidance of foot complications in frail, bed-bound patients with diabetes
- Avoidance of symptomatic clinical dehydration
- Provision of an appropriate level of intervention according to stage of illness, symptom profile, and respect for dignity
- Supporting and maintaining the empowerment of the individual patient (in their diabetes self-management) and carers to the last possible stage.

Source: Based on Diabetes UK 2013 [21]. Reproduced with permission.

The Gold Standards Framework for end-of-life care developed in the UK [17] identifies three triggers that may help the healthcare professional to determine if the individual is nearing the end of life:

1 *The "Surprise Question"*: Would you be surprised if this patient were to die in the next few months, weeks, days?

The answer to this question should pull together a range of clinical, comorbidity, social, and other factors that give a whole picture of deterioration. If you would not be surprised, then it is important to consider what measures might be taken to improve the patient's quality of life now and in preparation for possible further decline.

2 *General indicators of decline—deterioration, increasing need or choice for no further active care.*

These include:

- Decreasing activity—functional performance status, declining limited self-care, in bed or chair 50% of day and increasing dependence in most activities of daily living.
- Comorbidity, which is regarded as the biggest predictive indicator of mortality and morbidity.
- General physical decline and increasing need for support.
- Advanced disease with an unstable, deteriorating complex symptom burden.
- Decreasing response to treatments.
- Decreasing reversibility.
- Choice of no further active treatment.
- Progressive weight loss (>10%) in past 6 months.
- Repeated unplanned or crisis admissions.
- Sentinel event, e.g. serious fall, bereavement, transfer to nursing home.
- Serum albumin <25 g/L.
- Considered eligible for additional financial support and benefits.

3 *Specific clinical indicators related to certain conditions.*

These relate to specific conditions. Although diabetes is not mentioned, it frequently occurs in association with those conditions that are specifically mentioned including cancer, chronic obstructive airways disease, heart disease, renal disease, general and specific neurological disease, such as motor neuron disease, Parkinson's disease and multiple sclerosis, frailty and dementia, and stroke.

The Gold Standards Framework also defines four main stages of end of life [17]:

1 Stable from diagnosis (usually lasting years);
2 Unstable, advanced disease (usually lasting months);
3 Deteriorating, exacerbations (usually lasting weeks);
4 Last days of life pathway (usually lasting days).

This model has been adapted in Canada and their guidance is separated into five stages as they included death and bereavement which is considered an integral part of care provision [12]:

1 Disease advancement
2 Experiencing life-limiting illness

3 Dependency and symptom increase
4 Decline and last days
5 Death and bereavement.

For people with diabetes who are taking insulin or β-cell secretagogues, we recommend adding hypoglycemia to the indicators that a person is at the end of life. It has long been recognized that the development of hypoglycemia in people who have not previously been prone to this is a poor prognostic sign. This is true for hospitalized patients, in whom the excess mortality is not caused by hypoglycemia per se, but by associated comorbidities [18]. It seems that this also applies to out-of-hospital hypoglycemia. An audit of the introduction of a community-based scheme in Leicestershire, UK that assessed emergency callouts for people with diabetes experiencing hypoglycemia who were treated at home by paramedics revealed that 5% of patients triaged died within *30 days* of the initial call-out, mainly from previously undiagnosed malignancies. Hypoglycemia in this context is multifactorial, arising from a reduced food intake, weight loss, and/or impaired kidney function without adjustment of the dose of hypoglycemic medication.

The management of diabetes at the end of life

The care of the dying person with diabetes is challenging, encompassing changes to glycemic targets, patient and carer expectation, reducing risk of hyperglycemia and hypoglycemia, managing the effects of other medications, such as glucocorticosteroids, and tailoring of diabetes medications depending on the stage of end of life. Planning for end-of-life care in people with diabetes is often seen as a direct choice between treating or withdrawal of treatment for diabetes [1]; in practice caring for the dying patient is more complex.

Until 2010 there was a dearth of information or guidance on care for these individuals [19, 20]. Generic end-of-life guidelines did not attempt to address the specific issues encountered by people with diabetes. In acknowledgement of this in 2010 Diabetes UK commissioned a working party to review available data and the existing guidance from around the world. The agreed aim of the working party was to summarize a consistent but high-quality approach towards end-of-life care for people with diabetes by providing guidelines and clinical care recommendations. These were developed in partnership with multiple professional groups and formed a consensus of opinion across care and professional boundaries [21]. This guidance has formed the basis of clinical recommendations by the International Diabetes Federation [1] and Diabetes Australia [22].

The key principles underlying high-quality diabetes care at the end of life are summarized in Table 63.1 [21]. The consensus recommendations addressed the major clinical problems that people with diabetes at the end of life experience, and how these could best be managed. The recommendations were aligned to the generic Gold Standards Framework for End of Life Care [17]. They included a review of the use of glucose-lowering therapies and set glycemic targets that aimed to minimize hypoglycemia and improve patient safety [21].

Algorithms were developed for specific situations, such as use of once daily steroid therapy or to treat hypoglycemia. Relevant competencies for various health professionals were suggested and care outcome metrics for assessment of care discussed. It was hoped that these documents would contribute to the development of a consistent approach in care delivery and act as a platform for future partnership working with the third sector and the public.

Glycemic targets

There have been no well-designed studies supporting or providing insight into glucose regulation, diabetes self-management, or the use of particular glucose-lowering therapies at the end of life. Maintaining appropriate metabolic control at all terminal stages of life might seem an achievable goal in most people with diabetes but the influences of the stress response to severe illness, disturbances in glucose metabolism caused by malignancy, use of steroids, and frequent infections can be challenging for clinicians tasked with providing this care. Patients dying with diabetes may have an increased frequency of symptoms such as pain, constipation, and fatigue, which can be difficult to ameliorate unless there is experience in providing tailored glucose-lowering therapy in combination with adequate pain relief including use of opiates.

No published evidence existed at the time to justify any particular glucose or HbA_{1c} target for end-of-life diabetes care management; more recently there have been suggestions that a less demanding HbA_{1c} target of 7.5% (58 mmol/mol) may be safer for some individuals [23]. Others have argued that the testing of HbA_{1c} should cease when estimated survival is only a few months, not least because the use of HbA_{1c} for diagnosis of diabetes in this situation is not validated [24, 25].

As imposed fasting is inappropriate in this context, fasting glucose readings will not always be available. It is likely that the optimal glycemic range will vary according to the stage of illness, the ability to eat and drink normally, the presence of hypoglycemia, the nutritional status, and concomitant treatments. Many people prefer not to have blood glucose estimations done frequently, particularly if they understand that the result may not have an immediate impact on management; their wishes should be respected. Some have argued for a blood glucose target range of 180–270 mg/dL or even up to 360 mg/dL (10–20 mmol/L), although this latter figure may not be appropriate because of an increased risk of ketoacidosis in people with T1DM. The consensus glycemic target recommended by Diabetes UK is 6–15 mmol/L

Box 63.1 Blood glucose targets for end-of-life care [21]

Aim 1: No glucose level less than 6 mmol/L (110 mg/dL)
Aim 2: No glucose level higher than 15 mmol/L (270 mg/dL)

Table 63.2 End-of-life medicine management: non-insulin therapies.

Metformin (standard or modified release Metformin)	Sulfonylureas (e.g. gliclazide, glipizide, glimepiride)	Pioglitazone	Gliptins (saxagliptin, sitagliptin, linagliptin, vildagliptin)	GLP-1 analogs (e.g. exenatide, liraglutide, lixisenatide)	Sodium glucose co-transporter 2 agents (SGLT2) (dapagliflozin, canagliflozin, empagliflozin)
Review dose according to changing renal function	Review if dietary intake is reduced and/or there is significant weight loss	The risk-benefit ratio for pioglitazone in people with terminal disease requires review and should be only prescribed if benefits can clearly be identified	Review doses in accordance with individual licenses if renal function deteriorates	Review if eating patterns change or significant weight loss occurs	Review dose if liver function deteriorates
Withdraw if creatinine >150 µmol/L or eGFR < 30 ml/L/1.73m^2	Review dose if renal function deteriorates and consider a switch to tolbutamide		Some gliptins can be used for all stages of renal disease	Withdraw if abdominal pain or pancreatitis develops	Review individual product characteristics for use in chronic kidney disease. Withdraw if there is evidence of dehydration, poor nutrition, and in acute illness or major surgery
Review if gastrointestinal disease is present or symptoms of nausea, heartburn, diarrhea or flatulence are making patients miserable with discomfort	Review dose if liver function deteriorates as hypoglycemia may occur	Should not be used in people with or at risk of bladder tumor or heart failure	Combination with sulfonylurea increases the risk of hypoglycemia		Use with caution in over 65 year olds (canagliflozin) Limited evidence for use in people over 75 years old

(108–270 mg/dL), and this range is one of the suggested quality metrics for end-of-life care (Box 63.1) [21].

Since people with diabetes are increasingly used to a care planning approach in which they take informed decisions about their care, everyone with capacity should continue to be involved in their care planning for as long as possible, including decisions about target setting and the frequency of monitoring.

Medicines management during the last year of life

Specific recommendations which are aligned to life expectancy are given in the UK guidelines. In general, non-insulin glucose-lowering therapies can be reduced and eventually stopped depending on other factors such as poor appetite, weight loss, and anorexia (Table 63.2). It may be necessary to discontinue insulin treatment in people with T2DM, but insulin should never be stopped in those known to have T1DM (Table 63.3).

Other medication

Once it has been recognized that a person has reached end of life a review of all prescribed medication is indicated. Many people with diabetes are taking medication intended to reduce the risk of cardiovascular events in the long term, including ACE inhibitors or angiotensin II receptor antagonists, other antihypertensives, aspirin or antiplatelet agents, statins and other lipid-lowering agents. There are significant potential side-effects associated with these medicines, and stopping some or all of them may improve quality of life. This decision should be taken in conjunction with the patient and their family to avoid giving the impression that their medical advisors are "giving up on them."

The flowchart for diabetes at end of life (Figure 63.1) provides guidance on how to manage diabetes in the dying patient. It can be reassuring for relatives and carers to know that this additional pathway of care is being followed and that the diabetes is being *managed differently* rather than being *ignored*. The flowchart has been devised to minimize symptoms of diabetes and keep invasive testing to the minimum needed to achieve that aim.

Insulin

The general principles of insulin management are summarized in Table 63.3.

Continuous subcutaneous infusion of insulin—insulin pumps

Although insulin pumps are increasingly being used to manage diabetes in an end-of-life phase, there seems limited value in extensive training of health professionals in their use as patients are likely to be well informed about adapting their pump settings

Table 63.3 End-of-life medicine management: insulin therapies.

- Doses may need to change with changes in renal function
- Equipment for insulin delivery may need to be reassessed if physical capabilities alter, vision is poor, or carers become involved in giving insulin
- Hypoglycemia risk will need to be reassessed with changes in eating patterns
- Evening isophane (Insulatard/Humulin I, or Insuman Basal) in combination with daytime oral hypoglycemic drugs may be a good first-line treatment choice
- A change of insulin regimen may be needed to match changes in activity levels
- The simplest regimen should be chosen if switching to insulin only, both once or twice daily injection can be considered

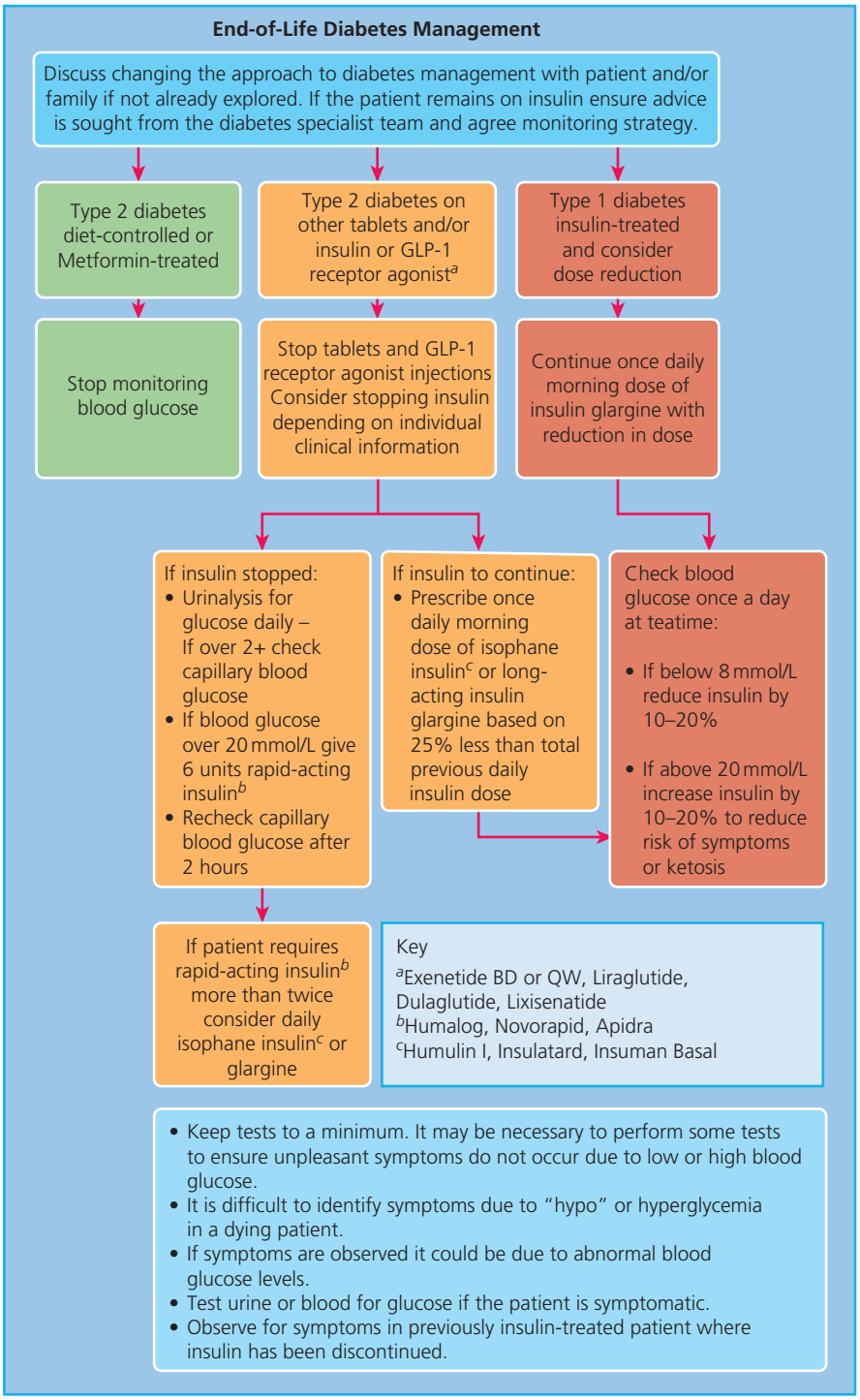

Figure 63.1 Flowchart for diabetes at end of life. Source: Adapted from Diabetes UK, *End of Life Diabetes: Clinical Care Recommendations*, 2nd edn, 2013. https://www.diabetes.org.uk/upload/Position%20statements/End-of-life-care-Clinical-recs111113.pdf.

for illness and have a good awareness of food intake in terms of carbohydrate and protein content. If the person with diabetes feels capable of using the pump, they should be encouraged to do so; however, carers may need education in pump adjustment if it is physically difficult for the person with diabetes to make setting and cannula changes. Members of the specialist team who are adept at dealing with lifestyle and appetite changes in managing pumps may need to develop their understanding of the implications of chemotherapy or radiotherapy regimens in order to give appropriate advice.

Should the person with diabetes wish to remain on their pump, the infusion rates can be adapted to cope with even the last days of life. In this situation close cooperation between diabetes specialist teams is crucial since the caring team may be unfamiliar with

the equipment. The diabetes specialist team can advise about alternative insulin regimens in situations where pump treatment is no longer considered to be appropriate or feasible, but planning ahead will minimize the understandable anxiety associated with switching. On a practical note insulin pumps may be returned to the issuing department when they are no longer required, as they can be reconditioned and re-issued.

Nutrition

It is important that people at end-of-life care are reviewed regularly to determine whether they are becoming malnourished or dehydrated. If there are concerns that an individual is not receiving adequate nutrition or hydration by mouth, even with support, an assessment of their condition, their individual requirements and consideration given to different forms of clinically assisted nutrition must be undertaken. If the individual refuses to eat or drink or has swallowing difficulties, an assessment of the underlying cause, for example depression, dry mouth, oral candidiasis, or painful mouth ulcers, and possible treatment should be offered [26].

Poor appetite or reductions in meal size along with swallowing difficulties experienced by some individuals will impact on glycemic control and may lead to hypoglycemia. People with T2DM may be taking several oral glucose-lowering therapies, which may be difficult to swallow because of tablet size, or the number of medications prescribed. In these instances, a medication review should be undertaken and treatment regimens simplified. Individuals may also prefer to take smaller meals more frequently. Avoidance of glucose-rich foods may no longer be considered appropriate and so diabetes therapies may need adjustment to reduce hyperglycemic symptoms. It is entirely appropriate to relax dietary restrictions originally designed to minimize weight gain and stabilize blood glucose control. Patients can be offered any of their favorite foods in order to tempt them to eat. Other guidance includes:

- Consider using metformin in powdered form or syrup if patients are not coping with tablets.
- Avoid long-acting sulfonylurea preparations (e.g. glibenclamide).
- If small meals are being taken, repaglinide can be useful for managing small regular meals with dose adjustments according to intake.
- Low-dose insulin may be the only option for those whose glucose levels are high despite a significantly reduced oral intake.
- People receiving insulin with poor intake will need lower doses [21].

Management of diabetes in those treated with glucocorticosteroids

The use of steroid therapy in people in end of life can alleviate symptoms, reduce fatigue and improve quality of life [27, 28].

Table 63.4 Suggested treatments for hyperglycemia when using steroids.

Regimen	Treatment
Once daily steroid therapy	Morning administration of a sulfonylurea, e.g. gliclazide, or morning isophane insulin, e.g. Insulatard, Humulin I, or Insuman Basal
Twice daily steroid therapy	Consider using a twice daily sulfonylurea (e.g. gliclazide) or isophane insulin. If hypoglycemia is a concern consider changing to a long-acting analog insulin, such as insulin glargine or insulin detemir

Source: Adapted from the Joint British Diabetes Societies Inpatient Care Guidelines 2014 [29].

They can be given using various regimens and in variable doses. The most common method is a short course of, for example, prednisolone given in the morning which will lead to raised blood glucose readings later in the day but reducing overnight. People with cancer are more frequently treated with dexamethasone twice daily which can lead to hyperglycemia throughout the 24-hour period. The commonest treatment for steroid-induced hyperglycemia is a sulfonylurea, such as gliclazide, or isophane (NPH) insulin (Table 63.4) [29]. People on very short courses of steroids (less than 3 days) may only require close monitoring. Targets should include a blood glucose concentration between 6–15 mmol/L (108–270 mg/dL) and no osmotic symptoms. Any diabetes treatments should be reduced or stopped in tandem with steroid reduction to avoid hypoglycemia.

Withdrawal of diabetes and other medication

The decision to withdraw from treatment including medication used in diabetes is difficult. Recognizing the concept of a "good death" for all people entering an end-of-life phase can be an awkward aspect of caring to communicate. Key priorities should be freedom from pain, being with family and loved ones, and being treated with dignity and respect at all times.

The use of an advanced or a living will is becoming more common; this is a legal document that needs to be signed and witnessed and enables the person with diabetes to refuse specific types of treatment at an indeterminate time in the future. Health professionals need to know if an advanced directive is in place [1, 12, 30–34]. The UK guidance [21] recognizes that any withdrawal of diabetes-related treatments warrants close liaison with the person with diabetes, the family, and the family doctor, and *must* take into account the patient's wishes, family concerns, and the presence of an advanced directive.

Treatment withdrawal can be considered:

- when the person with diabetes is entering the terminal phase of life;

- where frequent treatment-related hypoglycemia is causing distress and significant management difficulties;
- where continued treatment with insulin poses an unacceptable risk of hypoglycemia or where the benefits of stricter glucose control cannot be justified;
- where continued use of blood pressure or lipid-lowering therapy cannot be justified on health benefit considerations;
- where continued food or fluids is not the choice of the patient;
- where prescribing anti-infective therapy is unlikely to benefit the patient.

Workforce

Dissatisfaction with and complaints about care provided at end of life still occur too frequently, and are usually attributable to inadequate understanding of the complexities of the situation, a failure of communication, or both. Lack of workforce knowledge and training in end-of-life care is a common feature of professionals delivering diabetes care both in hospital and community settings [21, 33]. Conversely palliative care clinicians may lack up-to-date skills in diabetes medication and management, impacting on their ability to offer holistic packages of care. Healthcare professionals need to know where their area of responsibility lies and recognize when they need to consult with other team members and colleagues, specialist teams, social services, or voluntary organizations in order to ensure a holistic approach to care [35]. All staff caring for individuals at the end of life should have received initial and ongoing training and have been assessed for competency [21, 34].

Competency is defined as "the state of having the knowledge, judgment, skills, energy, experience, and motivation required to respond adequately to the demands of one's professional responsibilities" [34]. The competency framework from the comprehensive *Integrated Career and Competency Framework for Diabetes Nursing* illustrates the different competencies expected from healthcare professionals and unregistered practitioners involved in the care of someone with diabetes at the end of their life [36].

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12 Delivery and Organization of Diabetes Care

64 The Role of the Multidisciplinary Team Across Primary and Secondary Care

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Key points

- The rising prevalence of diabetes coupled with increasing life expectancy makes it impossible for specialist care to cope with the demands of diabetes care, thus necessitating a shift to primary care.
- In an integrated diabetes care model, innovative collaboration between primary care and specialists can result in the creation of new healthcare organizations that can provide integrated diabetes care for their local populations.
- Care provision in community settings other than within general practices requires a collaborative unit of diabetes specialist support teams based on the needs of the local population.
- Multidisciplinary teams are essential for the care of people with diabetes from early life to end of life.
- Multidisciplinary teams are essential to manage the various complications of diabetes.
- The composition of multidisciplinary teams should span a wide range of specialties and community care workers in order to address the complexities of diabetes.

Background

Diabetes has now been recognized as an epidemic globally. In 2015, the prevalence of diabetes was estimated to be 415 million worldwide, and this is expected to rise to 642 million by 2040 [1]. It is a complex chronic disease affecting multiple organ systems, often accompanied by other comorbid conditions with an associated disease management burden for people with diabetes. The rising prevalence coupled with the increasing life expectancy makes it impossible for secondary care to cope with the demands of diabetes care, which was the case until 20–30 years ago, thus necessitating a shift to primary care (i.e. by general practitioners or family physicians) [2]. The community (i.e. outside the hospital setting) or primary care management of diabetes is therefore a logical focal point for implementing strategies that improve the care of people with diabetes [3]. Multifactorial intervention in the management of type 2 diabetes mellitus (T2DM) is known to lead to reductions in cardiovascular disease (CVD) mortality [4]. The control of the multiple strands of cardiovascular risk factors in diabetes care requires multidisciplinary teams (i.e. the coming together of health professionals to achieve a common goal). The organization of the teams needs clinicians not just to have the necessary expertise in their chosen fields but to be skilled in an interprofessional approach. The multidisciplinary approach to diabetes management (i.e. the combination of various healthcare disciplines to care for people with diabetes) is based on the premise that, on a background of a common framework, decisions on the aims of treatment should be dictated by the insight of several professions. This normally requires team building, focusing on developing a common culture and giving priority to professional and social interaction. The purpose of this multidisciplinary approach is to ensure that the activities around the complexities of screening, diagnosis, early and late management, and treatment of complications are coordinated, with the aim of ensuring an optimal individualized management plan for each person with diabetes. The patient thereby will be expected to receive a seamless integrated approach to their care in a coordinated way.

Coronary heart disease (CHD) is a frequent complication and a major cause of mortality in people with diabetes. Therefore, its presence can create added complexity for an already burdensome regimen. Individuals with diabetes also experience added burden from other, non-CVD comorbidities (e.g. osteoarthritis, chronic obstructive pulmonary disease), with only 17.6% having diabetes alone [5]. The treatment of the complications and these comorbidities requires coordination across a number of specialists. System management is therefore essential, including the flexibility to deliver personalized care and identifying and meeting the individual needs of people with complex needs. In dealing with these complexities, integration of care around the person with

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diabetes is pivotal to delivering seamless, optimal, and effective care. Integration refers to the bringing together of people of different healthcare professional backgrounds into unrestricted association with the aim of delivering a seamless care package for people with diabetes.

Upskilling of primary or community care professionals in multidisciplinary teams

In an integrated diabetes care model (referring to a system of care worthy of emulation), innovative collaboration between primary care and specialists can result in the creation of new healthcare organizations that can provide integrated diabetes care for their local populations. With the person with diabetes at the center, delivery of care can revolve around them, with the aspiration of having an organizational structure, clinical pathways and financial planning that all align seamlessly [6]. The subsequent care pathway that is developed should be customized to the wide-ranging needs of the local population and adapted to the evolving needs and the changing national health agendas instead of a "one size fits all" model. The prime focus of the integrated diabetes service is the integration of a healthcare system and the coordination of services around a person with diabetes, bringing together primary and specialist care in a setting nearer the patient's home, where applicable.

In order to maintain successfully or even improve patient outcomes and reduce variations in care, while supporting this "left shift" of care, upskilling of general practitioners, practice nurses, and healthcare assistants and ongoing support from specialists in this field are required. This comprehensive upskilling process of healthcare professionals needs to be based on psychological theories of learning [7–9] with the necessary knowledge repertoire. It is hoped that this will equip the diabetes care workforce with the appropriate knowledge and skills to provide them the confidence to deliver the highest quality care and improve patient outcomes.

Possible areas of training could include mentorship and case management at practice level to support clinical development, training, and care planning. Not only should the education and training be available at different levels, but also they need to be provided by multiple alternative and complementary methods, including workplace-based learning, distance learning, modular format, journal clubs, and mentorship [10]. The multidisciplinary team creates an adaptable and responsive model with a feedback mechanism that encourages the improvement of the quality of care through their knowledge of local needs. Furthermore, and crucial for such an educational program's longevity, it has to be developed so that it can reflect the continually changing approaches to diabetes management in relation to new therapies and national drivers [10].

Practices that participate and engage in this training process can gain accreditations based on the breadth and level of diabetes care that they provide [10]. A stepwise and ongoing accreditation process could start from the provision of a basic core service, including screening of all individuals at risk for diabetes, diabetes prevention interventions, regular surveillance of all persons with diabetes, i.e. measuring and managing HbA_{1c} according to guidelines, blood pressure and cholesterol measurements, eye and foot examinations, reduction of CVD risk, evidence-based prescribing, auditing care provision, and evidence of referral and attendance at evidence-based patient education interventions/programs [10].

A step up on the accreditation ladder will be practices that can provide elements of an enhanced service, including the management of those with complex conditions on insulin, including in-house initiation and titration for people with T2DM, management of those with stable type 1 diabetes mellitus (T1DM), initiation and management of glucagon-like peptide 1 (GLP-1) receptor agonist therapies, high quality of care for housebound patients (including nursing/residential homes), and proactive discharge of suitable patients currently under specialist follow-up [10].

Support of multidisciplinary teams in structured patient education in diabetes

People with diabetes have to live the rest of their lives with the condition and therefore need to improve their knowledge, skills, and confidence, enabling them to take better control of their own condition through the positive improvement of their beliefs. They also have to integrate effective self-management into their daily lives. These aims can be achieved through structured patient education programs [11].

The multidisciplinary team will need to consider a range of issues in order to ensure that their patient education programs meet the expected standards. The program must have a written curriculum, and include areas such as health professional training, quality assurance, and learning needs assessment [12]. Healthcare professional training should incorporate modules around patient centeredness. Professional training in cultural diversity awareness in diabetes, self-management initiatives including motivational interviewing and other behavior change interventions, and psychosocial aspects of diabetes will help multiprofessional teams develop working plans to achieve desired goals [11]. This structured training for diabetes educators has to address the theoretical base and the underlying philosophy of structured education in diabetes. The program itself therefore has to be underpinned by the philosophy that it will be adaptable to the needs of people with diabetes and involve them in its ongoing development. It should be evidence based and have clear aims and learning objectives that are shared with people with diabetes and their carers and family. Health professionals have to plan with people with diabetes on issues around the care of their condition.

Local multidisciplinary teams have the responsibility of ensuring that there is an internal quality assurance process in place for the structured education programs. This ensures that practitioners are carrying out self-reflection during the delivery of the program with ongoing review of the biometric outcomes and patient satisfaction and experience in order to maintain standards

[13]. External reviewers will have a role in ensuring that the internal quality assurance program is robust to ensure that the center is delivering sufficient programs to maintain educator skills. They will ensure that there are organizational processes in place to guarantee that the program can be delivered according to the set philosophy and standards.

Multidisciplinary teams in diabetes care models

In developing a diabetes service, it is important to know what the components of the service ought to be and the mode of implementation required. Even though the models of care delivery in diabetes vary from country to country, the components required are broadly similar; it is the implementation that varies from place to place. The choice of implementation strategy depends on the local needs and the availability of various component resources. In many developed countries, there is usually a national strategy in delivering diabetes care.

In a generic service model, there must be integration across all levels of the service in order to provide a seamless transition for people with diabetes and to ensure that appropriate referrals take place, with clear and agreed referral criteria and clinical protocols for chronic and emergency management (Figure 64.1). Good communication links and joint working between the practice diabetes leads and specialist care teams are essential for the planning of services and to provide a framework for audit, quality assurance, and performance monitoring.

Care provision in community settings (i.e. other than within general practices) requires a collaborative unit of diabetes specialist support teams. These teams are constructed based on the needs of the local population and can comprise a collaborative team of diabetes specialist nurses, diabetes consultants, dieticians, diabetic retinopathy screening teams, and podiatrists. They can offer clinic-based care, outreach support to practices and nursing homes, rapid-access community clinics, development of agreed clinical care pathways for various aspects of diabetes care and referrals, and telephone- and web-based support for complex cases, again depending on the needs of the locality. This support should be flexible in approach and multistranded to reflect the varying gaps in knowledge of the healthcare professionals. The fundamentals of any such program should be applicable and transferable to other diabetes care providers.

These components require a coordinated approach between multiple healthcare professionals in different sectors of health and social care. For local populations, a local model of care is required, which can be developed in more detail, with roles and responsibilities clearly identified. Ideally, care should be provided within each locality to agreed care pathways, and each care provider should be clear about their role and relationship with other providers. The delivery of integrated diabetes care in any locality requires leadership and teams working through cooperation, coordination, and collaboration, working to a shared vision of healthcare, and drawing together the skills and relationships across the healthcare community. This integrated collaborative approach has been shown to be effective not only in mental illness but also in the management of people with other chronic physical multi-morbidities [14]. Specialist diabetes teams, often with extended roles, working in primary care through community consultants, form a central "hub" of expertise to support the delivery of high-quality and effective diabetes care.

In the United States, there is a drive to incorporate elements of the chronic care model into diabetes care. System redesigns, self-management, and decision support and organization of diabetes care in the community could collectively improve outcomes in diabetes and reduce costs [15]. Organizations such as Kaiser Permanente are using these components in diabetes care and have shown improvements in admission rates and outpatient clinic attendances [16].

The situation is much more challenging in developing countries such as sub-Saharan Africa, where diabetes care, largely driven by specialist care, faces competition for resources from infectious disease care. The lack of financial, infrastructural, and human resources is a major drawback for any effective service implementation in diabetes care, thus leading to a shorter life expectancy in individuals with diabetes [17].

Enhancement of multidisciplinary teams through the use of information technology

Local information technology (IT) infrastructure allowing shared records between primary, community, and secondary care and providing secure data centers to facilitate monitoring of clinical outcomes and service improvement is also required. This can assist people with diabetes, carers, and healthcare professionals in the choice of therapeutic options, understanding of the disease and its complications, and self-management [18]. Through the use of integrated IT systems, the provision of therapies and services to people with diabetes in different healthcare regions is made possible by ensuring effective responses to the needs and preferences of those with diabetes, improvements in healthcare processes and intermediate outcomes, patient–clinician communication, and access to medical information [19]. However, appropriate consideration needs to be given to potential problems with access to the IT infrastructure due to older age, low income, poor education, and cognitive impairment and also to physicians' concerns about increasing their workload.

Multidisciplinary teams in the management of complexities in CVD risk prevention

The presence of a complex health and illness profile is found to be associated with worse control of cardiometabolic risk factors independent of regimen intensity and history of CHD [20]. This is compounded by the fact that management of the major CVD risk factors in diabetes has raised questions about the benefits of

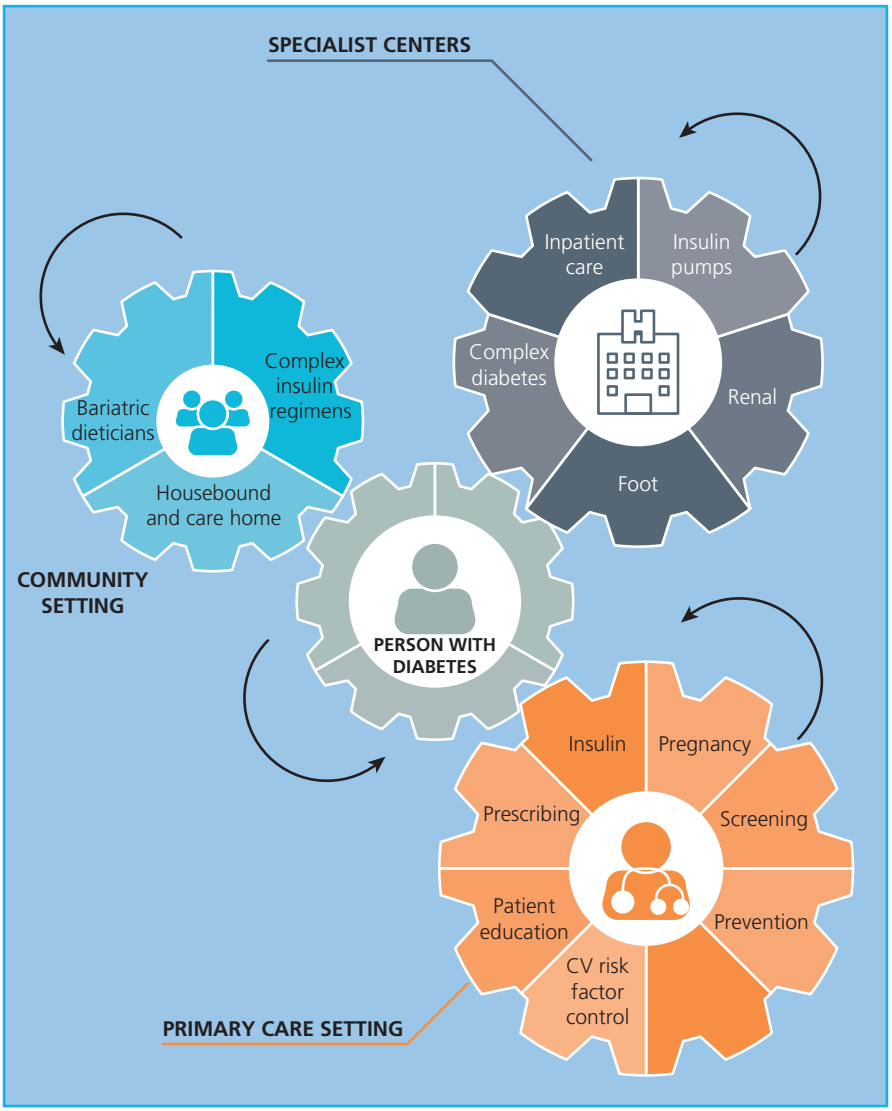

Figure 64.1 An illustration of integration of care across the levels of the service in order to provide a seamless transition for people with diabetes and ensure that appropriate referrals take place.

high risk factor control. In glycemic control, for example, although early intensive treatment in diabetes results in lasting benefit, including CVD risk reduction [21], intensive glycemic control in people with late diagnosis and background CVD does not reduce major cardiovascular events and indeed may increase mortality [22]. Similarly, even though major reductions in cardiovascular outcomes are seen in people receiving tight control of blood pressure compared with those receiving conventional control, if the baseline blood pressure was high [23, 24], tight control of systolic blood pressure among people with diabetes and CHD has not been shown to improve cardiovascular outcomes [25]. Indeed, increased mortality in intensively treated people with newly diagnosed diabetes has also been noted and caution in lowering blood pressure too aggressively is therefore recommended in these patients [26]. Regarding cholesterol, a reduction of 1 mmol/L in low-density lipoprotein leads to a 20–25% reduction in cardiovascular events (major coronary events, coronary revascularization, and ischemic stroke) [27]. However, among persons at increased risk for diabetes (those with baseline evidence of impaired fasting glucose, metabolic syndrome, severe obesity, and elevated HbA_{1c}), the risk of developing diabetes among those treated with statins appears to be raised. However, the overall cardiovascular and mortality benefits of statin therapy exceed the risk for developing diabetes [28]. Nevertheless, this finding introduces another complexity into CVD risk management in diabetes. Hence the control of the various risk factors could potentially require inputs from other team members with expertise in particular areas.

Multidisciplinary teams in renal disease in diabetes

The presence of chronic kidney disease increases the risk of CVD morbidity and mortality and increases the risk of progression to end-stage renal disease [29]. Diabetic nephropathy is progressive and its management requires the input of a number of

healthcare professionals at various stages of the disease trajectory. The primary care teams, after initial diagnosis of early disease, can reduce the progression of renal disease with the use of angiotensin-converting enzyme inhibitors or angiotensin receptor blockers [30, 31]. Specialist assessment should be available to individuals with or at high risk of renal disease through referrals by the primary care teams as the disease progresses. The late management and treatment of complications should be well coordinated, with the diabetes renal service working closely with nephrology services. Diabetes nephrology services should have appropriately trained staff and systems in place not just to organize the service effectively in a timely manner during disease deterioration but also to manage acute complications such as hypoglycemia during episodes of dialysis. Multicomponent structured patient educational interventions have been shown to be effective in predialysis and dialysis care [32]. The role of the dietician is invaluable in this group of patients not only to maintain adequate nutrition but also to prevent abnormal electrolyte excursions [33].

Multidisciplinary teams in the care of people with diabetic retinopathy

The implementation of a diabetes retinopathy service should involve a multidisciplinary team of clinicians who understand the natural history of the condition and options for early detection and treatment. The service will normally comprise permanent staff at a fixed or mobile retinal screening unit who are engaged in regular professional development updates. The aims of the service should to be to improve access to retinopathy screening, particularly for those for whom access has traditionally been limited, for example individuals who are housebound, disabled, elderly, indigenous, or from non-native-speaking backgrounds. In the pediatric and adolescent populations, it is essential to have an ophthalmologist with expertise in diabetic retinopathy and an understanding of the risk for retinopathy in the pediatric population, backed up by a team that has experience in counseling young persons and their families on the importance of early prevention and intervention [34]. The coordination and supervision of such a service requires effective leadership to identify clinical incidents, make safety assessments, and draw up proper interventions to tackle these deficiencies. The general practitioner keeps an updated register of people with diabetes for a call–recall system for retinopathy screening. This is coordinated through appropriate liaison between the hospital eye service and screening program.

Successful multidisciplinary coordinated retinal screening services should have the necessary components not just for screening but also for investigations and management. There has to be immediate access to facilities for fluorescein angiography and optical coherence tomography to allow individuals with maculopathy to be treated within 10 weeks [35] and those with new proliferative retinopathy to receive laser treatment within 2 weeks [36–38]. Patients needing urgent photocoagulation should be able to have it carried out immediately. For patient convenience, it is better to have the laser treatment carried out on the day when diagnosis of the problem is made, hence there should be sufficient laser clinics or staff available to undertake the treatment outside laser clinics. Intravitreal drug delivery facilities will be needed at any treatment center [37], but vitreo-retinal surgery, if not available locally, can be referred to a tertiary referral center. For individuals with visual impairment, appropriate counseling services should be available.

Multidisciplinary teams in the care of people with diabetic foot problems

Many people with acute diabetic foot ulcers also have other multi-morbidities including macrovascular complications, hence healthcare professionals must be mindful of these aspects [39]. Foot ulceration has been reported as the leading cause of hospital admission and amputation in individuals with diabetes [40]. Acute diabetes-related foot ulcers require multidisciplinary management and best-practice care, including debridement, offloading, dressings, management of infection, modified footwear, and management of extrinsic factors [41]. Treatment of diabetic foot ulcers varies widely, depending on the skills of the attending clinicians. Best practice is deemed to be a multidisciplinary approach, where the holistic view of the person with diabetes is sought, and a care plan developed around their individual needs. However, these multidisciplinary teams are not always available. Multidisciplinary teams ideally should include appropriately trained staff such as orthotists, podiatrists/podiatric surgeons or both, vascular surgeons, orthopedic surgeons, diabetologists, microbiologists, radiologists, diabetes specialist nurses (including a diabetes specialist inpatient nurse), ward link nurses, and consultants in pain management (with an interest in diabetic neuropathy) [41].

For individuals at no added risk, foot-care education is usually all that is required, but as they become at risk, twice-annually reviews including foot inspection, footwear assessment, and foot-care education become necessary. Those at high risk (i.e. the presence of more than two risk factors) need reviewing every 3–6 months, including foot inspection, footwear assessment, and potential need for vascular assessment or referral. Referral to a multidisciplinary foot-care team within 24 hours for management of ulcers and infection is mandatory [42]. To ensure a seamless package of care for people with foot-care problems, it is important that they are put at the center of the decision-making process, and have access to accurate information and support. The organization of care has to involve appropriate healthcare professionals, including community podiatrists who have a clear referral pathway to specialist services. The multidisciplinary specialist teams must endeavor to hold joint clinics in order for the service to be more effective and to reduce duplication of visits [43]. For the inpatient with diabetes, close observation for risk factors and prevention of foot ulceration is crucial, as this can be a vulnerable situation with increase in pressure-related ulcers.

For the seamless organization of care around the person with a diabetic foot problem, services to support the management must be readily available. Facilities for pressure area offloading include orthotic services, foot casting, and prosthetic services. Imaging facilities, including X-ray, computed tomography, and magnetic resonance imaging, and microbiological support services also need to be available.

Multidisciplinary teams in the care of women with diabetes in pregnancy

All women of child-bearing age who have diabetes should have access to preconception services [44]. This may often be in primary care. However, it is important that there is integration of care between primary, community, and specialist services. Specialist services can provide the leadership and support to raise awareness and provide education to primary and community services so that women with diabetes are aware of the need for preconception counseling and support. Through this leadership, guidance, and auditing of clear documentation of preconception counseling, pregnancy care and postpregnancy management can be carried out effectively.

The components of a multidisciplinary specialist diabetic pregnancy service should include clear signposting to different aspects of care, diet and lifestyle advice, provision of appropriate contraception, alcohol and drug counseling, higher dose folic acid supplementation, smoking-cessation support, assessment and management of diabetes complications, setting of glycemic control targets, and regular discussion of results of self-monitoring to enable the woman to achieve control that is as near to normal as possible before conception, discussion of diabetes pregnancy risks and expected management strategies, and clear documentation of care and counseling [45].

Once a woman with diabetes has become pregnant, a specialist multidisciplinary team with interest in diabetes in pregnancy, composed of an obstetrician, diabetologist, dietician, and diabetes specialist nurse and midwife, should be made accessible. The role of the specialist multidisciplinary team should be to agree an individualized care plan covering the pregnancy and postnatal period up to 6 weeks. The contents of such plans will include glycemic control targets, retinal and renal screening schedules, fetal surveillance, a plan for delivery, and a plan for immediate postdelivery diabetes care [46].

Multidisciplinary teams in the care of young people with T2DM

With recent increases in overweight and obesity, the prevalence of T2DM in the younger population is also rising. People with T2DM diabetes under the age of 45 years have a fourfold increased risk of myocardial infarction compared with those aged 45 years or more [46]. This age group will normally also include women of child-bearing age who require special care [47]. Diabetes occurring early in adult life appears to lead to more aggressive cardiovascular complications than in age-matched people without diabetes, although the absolute rate of CVD is higher in older adults [46]. These younger individuals may also have other conditions such as non-alcoholic fatty liver disease, sleep apnea and vitamin D deficiency. The implications of this are not just the development of complications for these persons, but also a tremendous knock-on effect on the economy as a whole as this is the age of maximal productivity. Hence strong leadership for the delivery and organization of services and the championing of the needs of younger people with diabetes is essential. Younger people with T2DM require tailored management strategies to engage them and manage their CVD risk factors intensively, because these risk factors are highly prevalent and insufficiently treated in this extreme phenotype of T2DM diabetes [48].

A service for young people with diabetes should include a consultant diabetologist, a diabetes specialist nurse, a specialist diabetes dietician, and a clinical psychologist with an interest in diabetes. The collaborative working of these healthcare professionals will ensure that a package of care encompassing psychological, dietary, and cardiometabolic risk control is delivered. These individuals are likely to be in active employment, so flexibility in the delivery of service at convenient times is essential to engage them. In the primary care setting, there should be adequate provision for routine care, including diagnosis, initial management, continuing care, surveillance, management of complications, and annual assessment. Access to family planning, contraception, and preconception services should be provided. In working together with consultants, there should also be an agreement for arrangements for shared access to records and ready access to specialist diabetes advice. Targeted glycemic levels can be established before any attempt at conception is considered [44]. Access to smoking-cessation and substance-abuse services should be integrated into any such service design.

Multidisciplinary teams in the care of elderly people with diabetes

Even though elderly people with diabetes have as high a risk of developing a range of macro- and microvascular complications as their younger counterparts with diabetes, their absolute risk for CVD is much higher. Older persons with diabetes suffer excess morbidity and mortality compared with those without diabetes [49]. Contributing factors to this increased risk in elderly persons with diabetes include cognitive impairment, functional disabilities, frailty, polypharmacy, depression, urinary incontinence, and persistent pain [50].

The components of a diabetes service for the elderly should be commissioned, delivered, and monitored to ensure that it is delivered as locally as possible, near to the families' homes. The multidisciplinary team staff with interest in diabetes must include a consultant geriatrician, a consultant psychiatrist for the elderly,

a diabetes specialist nurse, a consultant diabetologist, a specialist diabetes dietician, and a community pharmacist. Specific services aimed at elderly people with diabetes should include diabetes education programs aimed at healthcare professionals looking after elderly people [51]. This is particularly important for elderly individuals because of the complexities of varying targets in this population. Older people with diabetes are not a homogeneous population; rather, they may include persons who are functionally independent and residing in the community and those who may be functionally dependent with many comorbidities and are living in assisted care facilities or in nursing homes. Each group will have individualized targets for CVD risk factor control. In frail older persons with diabetes, avoidance of hypoglycemia, hypotension, and drug interactions due to polypharmacy is of great concern [52]. In addition, management of coexisting medical conditions is important, as it influences their ability to perform self-management.

Uncontrolled diabetes is associated with an increased risk for dementia, including the vascular and degenerative types. In addition, borderline and undiagnosed diabetes are related to Alzheimer disease without vascular comorbidities, which suggests a direct link between glucose dysregulation and neurodegeneration [53]. As a result, access to integrated memory clinics with psychological support and local counseling is needed for elderly patients with diabetes. Case management is best delivered by a dedicated community psychiatric nurse and a social worker who ensure that there is adequate provision for routine care, including diagnosis, initial management, continuing care, management of complications, and annual assessment. There should also be provision for rapid access to the service when needed, together with agreements with primary care for arrangements for shared access to records and 24-h access to specialist diabetes advice. It may well be that owing to the multimorbid state and frailty of these individuals, these services are delivered at home or in residential institutions.

The staff composition of a multidisciplinary diabetes team

Community pharmacists

A sustainable collaborative care approach for people with diabetes should make use of community pharmacists, a local and accessible resource that is increasingly regarded as the first port of call for patients to seek help with the management of chronic disease. By offering programs for monitoring therapeutic interventions, improving adherence with medication, and educating people about their lifestyle to improve their quality of life, community pharmacists play a vital role in managing diabetes and its complications [54, 55] On average, the community pharmacist consults with individuals with diabetes three to eight times more frequently than other persons [56]. As a result, in addition to bringing "medicines expertise" to the team-based care of people with diabetes and performing root-cause analyses of adverse events with diabetes medicines to contribute to the patient/medicine safety agenda, community pharmacists can help establish a collaborative care approach to managing diabetes and reducing associated CVD risk factors. The availability of such a collaboration can bridge the gap between a successful pharmacy screening program for diabetes and primary care follow-up of these persons [57]. This role can be extended to individuals in residential care or who are housebound.

Practice nurses

In the primary care setting, chronic disease management is increasingly being carried out by practice nurses with general practitioners intervening only in complex cases [58]. In the case of diabetes, this has become even more necessary because of the increasing prevalence and the burden of caring for people with the disease. It is known that despite the worsening of health-related quality of life and an increase in diabetes-related symptoms, practice nurses are able to achieve results that are comparable to those achieved by a general practitioners in terms of cardiometabolic risk factor reduction [58]. People being treated by practice nurses also reported as being more satisfied with their treatment than those being treated by a general practitioners [58]. The care of people with T2DM can therefore be safely delivered by practices nurses, using clinical guidelines. This makes the nursing team an important resource in a multidisciplinary primary care team. The extension of the practice nurse's role to include the initiation and titration of medications complements their other roles such as in supporting and educating people with diabetes and enabling them to manage their diabetes care, thus ensuring a holistic delivery of care closer to home. However, they can potentially overutilize insulin inappropriately, and close collaborative working between nurses and doctors can limit any potential overutilization of insulin management if it were to occur.

General or family practitioners

The use of primary care physicians (general or family practitioners) can be as good as if not better than hospital outpatient care if regular review of patients is guaranteed [3]. The enhancement of the generalist's care for people with diabetes with the use of quality improvement strategies such as audit and feedback is an effective tool for reducing the CVD risk profile [59]. The generalist's role often includes active case management of patients with multiple conditions. In these patient groups, continuity of care is of paramount importance. Multidisciplinary primary care teams, led by the generalist, therefore have a fundamental role in the prevention and identification of diabetes and also in routine care at a level that fits with their competencies. They will ensure that an accurate disease register is maintained to enable a call–recall system for annual reviews to be set up. They work cooperatively with other members of the team, seeking their views, acknowledging their contributions, and using their skills appropriately. People with poor CVD risk factor control and those with early signs of microvascular complications can be identified and referred on to more specialist centers. The generalist has a more

longitudinal relationship with patients with chronic conditions such as diabetes. They have the responsibility of coordinating the management of the patient's acute and chronic complications of diabetes over time. They have an understanding of the patient in relation to their socioeconomic and cultural background and, additionally, recognize the impact of the problem on the patient's family and carers. They will therefore use appropriate support agencies including primary healthcare team members targeted to the needs of the person with diabetes.

The pay-for-performance initiative started in the United Kingdom in 2004 is probably the most ambitious quality improvement strategy and initially yielded some obvious improvements in the care of people with diabetes [60], but these benefits reached a plateau across the population [61] and did not lead to reductions in the variations in care [62, 63]. The provision of primary care services for people with diabetes, whether traditional primary care clinics or diabetes clinics run by GPs with special interests, is effective in reducing HbA_{1c}, cholesterol, and blood pressure [64].

Diabetes specialists

The rising prevalence of diabetes coupled with increasing life expectancy makes it impossible for specialists to cope with the demands of diabetes care, which was the case until 20–30 years ago, thus necessitating a shift to primary care [50]. Hospital diabetes clinics developed historically from the need for supervision of insulin treatment. Inevitably, they also recruited large numbers of people with diabetes not managed with insulin. The work load has thus increased over the decades. With the majority of people with diabetes now being managed in primary care, the specialist's role in insulin management has become limited to the acutely ill patients with diabetes, including those with diabetic ketoacidosis, those with acute myocardial infarctions, those in intensive care, and those on renal wards who need meticulous insulin management to foster early recovery. People with T1DM or T2DM who require complex insulin regimens for the control of their diabetes, such as those needing very large doses and those needing insulin in combination with newer therapies, are managed by the specialist. Most consultants with a specialist interest in diabetes are based in acute hospitals where they also deliver general medicine, alongside training roles, general management, and research. As a result of these multiple roles, they are very well placed to provide multidisciplinary diabetes specialist teams with leadership, providing support and education to community diabetes services. In some areas, the integration of services has made it necessary to employ an increasing number of community diabetes consultants who deliver and coordinate services in a community setting only.

Dieticians

The use of dietary education has been found to improve anthropometric measures and glycemic control and the use of less prescribed medication [65]. By improving knowledge of diabetes self-managed, dietician-led diabetes management programs can be an effective strategy for glycemic control and improving dietary habits for individuals with poorly controlled T2DM [66]. Registered dieticians can therefore contribute greatly to the comprehensive care plans for persons with diabetes. They work as members of multidisciplinary teams across a variety of healthcare settings, including primary and specialist care. Their caseload might encompass working with children, adults, young people, and individuals with mental health problems. They also have an important role in the management of severely obese people with diabetes. The dietician can also offer support for those with T1DM in areas around carbohydrate counting. In primary care, their role could be in advising people at risk of diabetes and those who are newly diagnosed on the appropriate dietary requirements. In the case of patients with diabetes with complex needs requiring initialization or augmentation of insulin therapy, dietician support is normally necessary. Within a specialist care setting, they support antenatal and postnatal care of women with diabetes. They can provide dietary support before and after bariatric surgery. For patients with mental health issues such as eating disorders, dietician support to maintain weight and glycemic control can be sought. On dialysis units and inpatient wards, people with diabetes will normally need complex nutritional care such as enteral feeding. The dietician supports people with complex problems such as gastroparesis and pancreatitis.

Community health workers

Diabetes programs can include community health workers in the multidisciplinary teams in a variety of roles. They usually reside in the target community and are given special training to help bring health services, health education, and health promotion to their local communities. They also mobilize members of the community to adopt behaviors that improve their overall health and living conditions [67–69]. This important resource has to improvements in patients' knowledge and behavior and in some cases may even improve biochemical outcomes in diabetes and promote health [70]. The optimal role of peer support of community lay educators is particularly crucial in low-income, underserved populations, particularly for racial and ethnic minority communities [68, 71–73]. Their knowledge of the language, culture, and geographic background of communities can be used to coordinate care in partnership with healthcare systems [74]. Their functions include activities such as home visits, health education, and outreach activities for ambulatory care sites [69].

Conclusion

The management of diabetes through the integration of care between primary and specialist centers can result in the creation of new healthcare organizations that can provide multidisciplinary diabetes care for their local population. The multidisciplinary teams work together around various groups with diabetes, including pregnant women, adolescents, and the elderly. Other groups of patients include those with diabetic foot ulcers, kidney disease, and retinopathies. The teams comprise general or family physicians, community pharmacists, community health

advocates, podiatrists, diabetes specialist nurses, and specialist diabetes physicians, all working seamlessly in a coordinated fashion in the different sectors of a diabetes service.

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65 Models of Diabetes Care Across Different Resource Settings

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Key points

- A comprehensive approach to diabetes prevention and care includes policies and activities outside the formal health sector, particularly for primary prevention.
- Integrated care refers to the need to provide care for conditions coexisting with diabetes within the same primary healthcare service.
- Continuity of care, a cornerstone of effective healthcare organization, is associated with improved outcomes.
- Prerequisites for improving outcomes include ensuring that essential medications (including insulin) are either free or highly affordable and that tests for the diagnosis of diabetes, monitoring of control, and equipment to screen for complications are available.
- Living health systems should care for, empower, and nurture their staff so that they are enabled to do the same for their patients.
- If no-one is responsible for chronic care, the tendency is for it to be overlooked.
- A respectful, open, and curious stance may help different professionals and people to understand each other better.
- Patient-centeredness improves quality of life, increases patient satisfaction, improves adherence to treatment, enhances the integration of preventive and promotive care, and improves the provider's job satisfaction.
- In low-resource settings where large numbers of patients overwhelm facilities, it may make sense to extend care into the community.
- Ideally, a systematic process for reviewing the evidence and updating guidance accordingly should be in place in all countries.
- A quality assurance program should be in place for each district in every country.
- Advances in the use of information technology and the Internet are likely to provide increasingly important contributions to diabetes care in all settings.

Introduction

Almost no community worldwide remains unaffected by diabetes. Premature mortality and the morbidity caused by diabetes complications exact considerable personal costs on individuals and families. The economic burden of diabetes remains substantial at the individual, family, health system, and societal levels. It is concerning that there has been little progress in reducing the inequities of healthcare provision for people with diabetes between countries, and also within the same country, for example in rural versus urban settings, private versus public sectors, and hospital versus community-based services. This is typified by the fact that in 2013, while diabetes accounted for 10.8% of total health expenditure worldwide, the majority of this expenditure was in high-income countries where only 20% of the people with diabetes live [1]. As the largest growth in the number of people with diabetes in the future will occur in low- and middle-income countries, where lifestyles are transitioning, the need for diabetes prevention strategies has never been more apparent, nor has the urgent need to improve management and care for those who have already been diagnosed.

The challenges facing health planners and providers, whose goal is for their health system to deliver increasing health benefit at an individual and a societal level, are enormous, especially in less resourced countries and areas. This is because of the emergence of dual or multiple disease burdens, namely traditional infectious diseases, such as tuberculosis and malaria, and also HIV/AIDS, and the emerging scourge of chronic non-communicable diseases, including diabetes, results in competition for limited resources. Further, most healthcare systems have evolved from the basis of dealing with acute medical problems (mainly infectious disease, curative and reactive) and have been or, in most instances, remain ill-equipped to provide the kind of care that people with

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chronic diseases require. In addition, many low-income countries do not have the primary care infrastructure to cater for people with chronic conditions such as diabetes. This underscores the need for countries in the throes of the diabetes epidemic to focus on healthcare strengthening. That is not to say that well-resourced countries do not face challenges with healthcare delivery. In these countries, there are also problems in ensuring that quality healthcare is delivered in a cost-effective manner. Notwithstanding these challenges, each person with diabetes, wherever they live, should have access to the best care that can be provided in their setting and consequently have the opportunity to achieve the outcomes they seek. Unfortunately, this is not the current situation, even in well-resourced countries and settings.

Over the past 10 years, politicians have made a number of global agreements that might be expected to translate into national level actions to reduce the burden and impact of diabetes. The first was the United Nations Resolution on Diabetes in 2006. This encouraged "member states to develop national policies for the prevention, treatment and care of diabetes in line with the sustainable development of the health-care systems, taking into account the internationally agreed upon development goals, including the Millennium Development Goals" (Resolution 61/225, December 20, 2006). In 2011, the United Nations made a political declaration on the prevention and control of non-communicable diseases (NCDs) followed by the adoption by the World Health Organization (WHO) of a voluntary Global Action Plan for the same [2, 3]. The subsequent introduction of a WHO NCD progress monitor provides an assessment of member countries' implementation of their commitments to develop national responses to the NCD burden. Although many of the progress markers are difficult to measure accurately, it is a step in the right direction. The first report in 2015 indicated that only about one-third of countries have fully met the target of setting up national NCD targets and indicators and having guidelines for the management of NCDs. More recently, the sustainable development goals were launched globally to replace the millennium development goals. For the first time these include a specific target for NCDs that by 2030 we should have reduced by one-third premature mortality from non-communicable diseases through prevention and treatment, and promote mental health and well-being [4].

The International Diabetes Federation (IDF), the WHO, and the NCD Alliance need to work together in order to improve the suboptimal care and outcomes for people with diabetes. After all, it is not that a dearth of evidence exists for the effectiveness of a wide range of interventions to prevent complications associated with diabetes, but rather the reverse. Three interventions that are cost-saving and fully feasible (in terms of penetration of the target population, technical complexity, amount of capital required, and cultural acceptability), even in low- and middle-income countries, have been identified as [5]

1 improvements in glycemic control;
2 improvements in blood pressure control; and
3 delivery of effective foot care.

A fourth intervention, provision of preconception care, was found to be cost-saving, but not fully feasible because of concerns about not being able to reach all women with diabetes. The issue at hand is how to translate the evidence into practice. It also needs acknowledging that, almost without exception, health services are in need of strengthening. The specific interventions to be introduced or implemented will undoubtedly vary, depending on the healthcare structure and resources available. There is also the need to recognize that diabetes requires that people not only have access to sufficient resources, such as medication, but also the understanding, motivation, and skills to self-manage their condition. Healthcare cannot be seen in isolation, occurring as it does within a broad societal framework that places varying degrees of emphasis on ensuring that quality care is prioritized. Thus, in the first instance, for effective healthcare delivery, a positive policy environment needs to be in place, nationally and locally. The "macro" level of the WHO Innovative Care for Chronic Conditions (ICCC) framework focuses on this very issue (Figure 65.1), highlighting the components that can promote a positive policy environment [6]. Political will, building or strengthening partnerships (e.g. between community-based organizations, patient organizations, healthcare workers, and government), and ensuring consistent funding are key aspects of the process. So too is the need for an intersectoral approach or collaboration to building a healthy society, encompassing, for example, urban planning (with the provision of green areas, easy public transport, access to sports and recreation facilities), the introduction of health promotion activities within schools, and regulating the food industry.

The "meso" level in the ICCC framework relates to healthcare organization and links to the community. It is at this level that the concept of "model of care" comes into play. A healthcare model can be regarded as an overarching design for the provision of a service that is ideally underpinned by a theoretical framework, evidence base, and clearly defined standards [6]. The model has core principles and elements in addition to an agreed upon agenda for implementation and later evaluation. It is unlikely that a single healthcare model for diabetes exists that can be used effectively and efficiently in all settings—indeed, the model will take different forms or shapes in different settings. Where health systems are in transition, planners have to decide whether to pursue a diabetes-specific model of care or to incorporate multiple chronic diseases such as diabetes, hypertension, and chronic lung diseases in a common chronic care model. In many established healthcare systems, there is now active promotion of integrated models of care.

Given that type 2 diabetes mellitus (T2DM) frequently coexists with other NCDs, in particular hypertension, thus giving rise to multimorbidity, there are salient reasons for pursuing a common chronic care model and building on the commonality of aspects of care for these conditions. However, factors such as the available resources are likely to guide this decision. Regardless of the model selected, changing the value system in which healthcare is delivered, with the aim of ensuring motivated affirmed healthcare workers, is perhaps key to equipping or enabling people living with diabetes with the information, motivation, and skills to

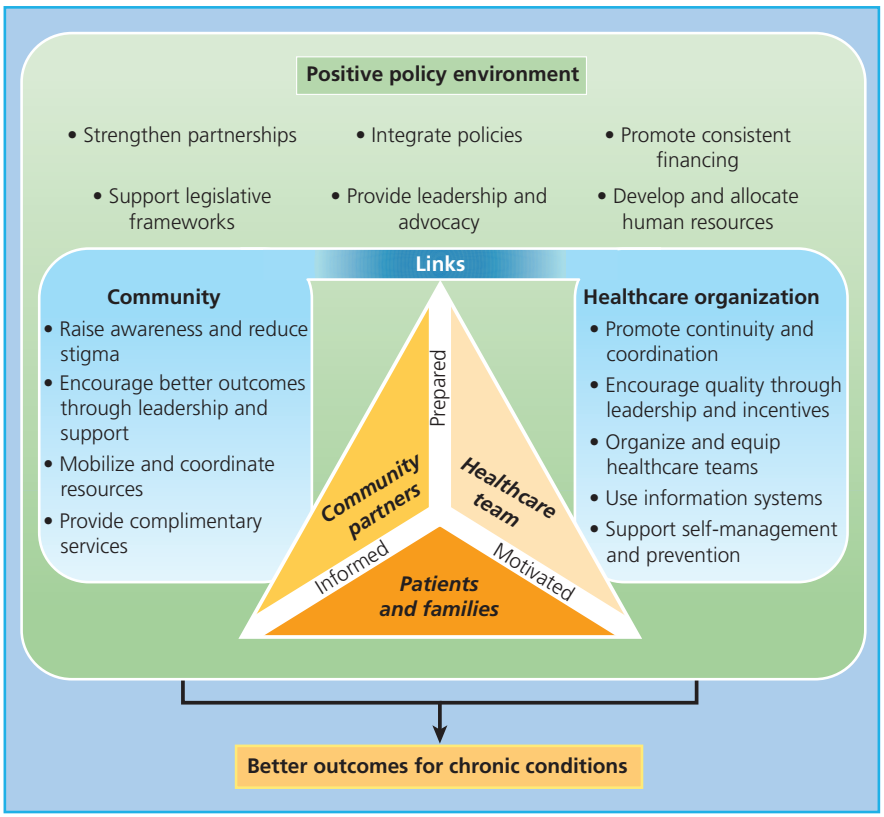

Figure 65.1 Innovative care for chronic conditions framework. Source: Adapted from WHO *Innovative Care for Chronic Conditions* 2002 [6]. http://www.who.int/chp/knowledge/publications/icccreport/en/. Reproduced with permission of WHO.

self-manage their diabetes. There is a real need to embrace the lessons that can be learned from the successful highly active antiretroviral therapy (HAART) programs for people with HIV/AIDS, which have yielded levels of adherence to therapy that most clinicians and public health specialists can only dream of in relation to diabetes [7]. There are certain core principles for diabetes care that could be applied across all resource settings [6]. These include establishing:

- A comprehensive approach that provides for health promotion to allow prevention and early diagnosis and management of diabetes and complications when they arise and rehabilitation when needed.
- Integrated healthcare, such that conditions coexisting with diabetes can be readily managed within the same primary healthcare service.
- Continuity of care, which has a number of connotations: in terms of the relationship between healthcare worker and patient; in terms of management strategies and decision-making; and in terms of patient information.
- Access to care, which can be understood in a physical or geographic sense, but extends to access to appropriate equipment for monitoring, diagnosis, and management in addition to medication.
- Coordination of care from primary to secondary and tertiary levels, with appropriate referral strategies and role delineation. Where multiple professionals and organizations are involved in primary care, horizontal coordination of care is also important.
- Teamwork between multiple health workers, professional categories, and disciplines, even in low-resource settings, is important. Establishment of teams whose focus is on delivering and improving the quality of care permits the development of shared goals, defining and clarifying roles, reflecting on how care can be improved, and holding each other accountable for decisions. The identification of a team leader may be a major factor in the success of this element.
- Person-centeredness implies a more collaborative approach and holistic understanding of the patient that elicits, acknowledges, and addresses relevant beliefs, concerns, and expectations. This is often a paradigm shift in the mind of the health worker from the traditional biomedical, technical, and sometimes authoritarian model to a more personalized, biopsychosocial, and goal-orientated model [8].
- Family and community orientation are integral to providing support for the individual with diabetes and also to raising awareness and extending care from the health centers into the community.
- The use of evidence as far as it is available, accessible, and relevant. The evidence base for diabetes is constantly expanding and all resource settings need to look at how they access the latest and ever-changing evidence base.

We now discuss how these principles are being incorporated into care for people with diabetes across different resource settings in high-, middle-, and low-income settings, and how information technology can be embraced and harnessed

appropriately in different settings with the goal of supporting these principles.

A comprehensive approach

Taking a comprehensive approach to diabetes prevention and care implies that policies and activities are put in place to address primary prevention, early diagnosis (including screening if appropriate), management of diabetes and its complications, and rehabilitation for those affected by complications. A comprehensive approach will include policies and activities outside the formal health sector, particularly for the primary prevention of T2DM. For example, promoting healthier diets and greater physical activity could involve policies on food production, marketing, and taxation, and policies on design of local environments and public transport. The WHO's strategy on diet and physical activity provides a framework for developing national and international policies that are relevant to countries at all levels of development [9]. The best indication of a comprehensive approach is a national government-led strategy that covers primary prevention through to rehabilitation, with the caveat that the presence of a strategy does not guarantee that it has been implemented. A survey carried out through IDF member organizations in 2008 [10] found that 61% of respondents (96 respondents) indicated that their country had a national diabetes program and the majority of the remainder confirmed plans to implement and develop components of such a program. At that stage, even in regions such as Europe, over 20% of responding countries did not have a national diabetes program. Examples of national diabetes programs in countries at opposite ends of the economic spectrum include the program in Cameroon [11] and the National Service Framework for Diabetes in England [12].

Integrated healthcare

Integrated care for people with diabetes refers to the need to provide care for conditions coexisting with diabetes within the same primary healthcare service. Within most high-income countries, primary healthcare has been developed to provide a range of services covering most of the needs of people with diabetes, and indeed with other chronic conditions, and also people with multimorbidity, which are almost invariably NCDs. In low- and

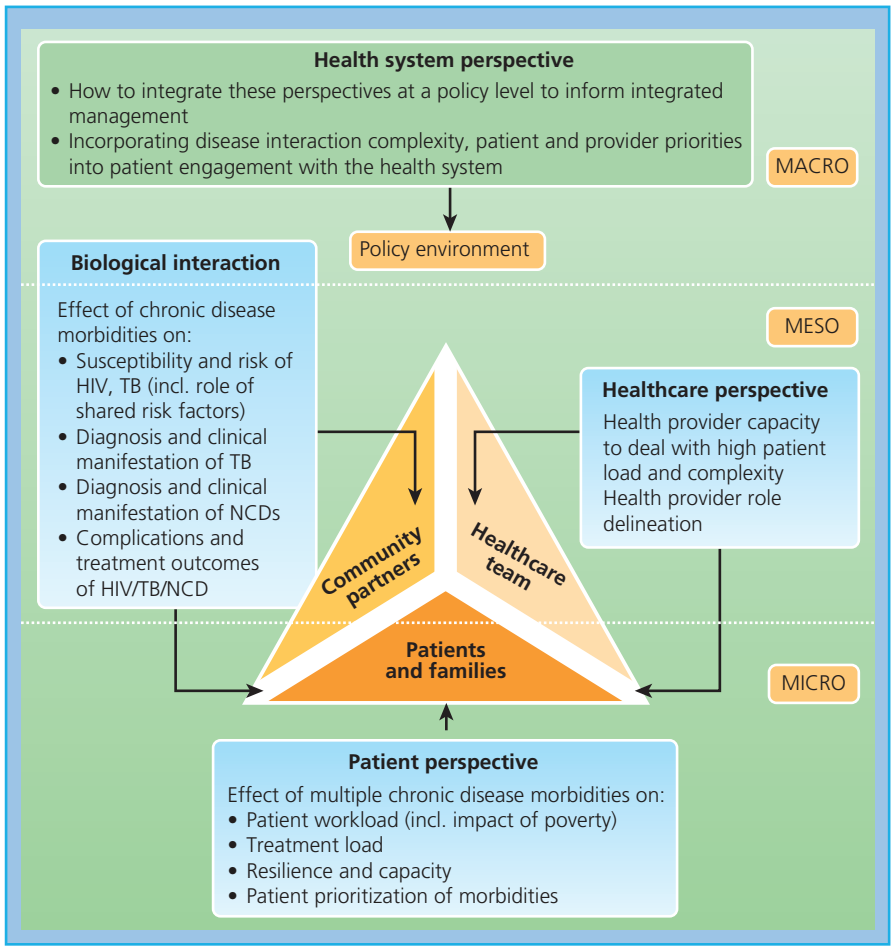

Figure 65.2 Conceptual modification of the WHO ICCC framework. The modifications are represented by the text in the three bubbles and arrows. Source: Modified from Oni et al. 2014, p. 575 [13].

middle-income countries, however, integration of care is often a challenge, as donor funding is most often given to specific disease programs such as HIV/AIDS, tuberculosis, or malaria, or large-scale government funding is allocated for specific vertical programs, such as HIV/AIDS. In these countries, however, there is increasingly an intersection between chronic non-communicable and infectious diseases, with these diseases coexisting in the same person. Hence the integrated model should enable the person with diabetes and several multimorbidities, such as hypertension and antiretroviral therapy, to receive all components of their care in a single clinic and by the same team of health workers.

The multimorbidity between these chronic non-communicable and infectious diseases may also alter typical clinical manifestations and prognosis, for example in comorbid T2DM and tuberculosis, where there may also be pharmacological interactions between the treatments for these two conditions that alter their efficacy. Therefore, the management of such cases is more complex for the health providers and the health system and more challenging for the individual. This level of complexity was not considered in the original WHO ICCC model of care and has led to a recent proposed modification of the model. The modification takes biological interactions, expectations of patients by health providers (patient workload), patients' capacity to deal with the workload, and health provider workload and capacity into consideration, and as such should be included in the thinking around setting up of integrated clinics (Figure 65.2) [13]. To highlight this complexity from the perspective of the person with diabetes, this includes the need for self-care, behavior change, adherence to numerous medications, often at different times, and multiple clinic appointments, while often having poor health literacy, a lack of family and social support, poor physical and/or mental functioning, and consequently a reduced capacity to meet these demands. It is concerning that the burden of multimorbidity is frequently higher in the poor, who often have a lower capacity to deal with ill-health and have worse outcomes.

Interestingly, although the subject of integration of care between chronic non-communicable and infectious diseases has received a great deal of attention, there are few concrete examples in the literature, other than the integrated chronic care clinic for HIV/AIDS, diabetes, and hypertension at provincial hospitals in Cambodia (Box 65.1) and a hospital-based pilot study in Ethiopia [14, 15]. There is no reason why such an approach could not be used in primary healthcare [16].

Box 65.1 Cambodia: integrated chronic disease clinics.

Chronic disease clinics for the combined care of HIV/AIDS, diabetes, and hypertension were set up in two provincial referral hospitals in Cambodia based on a number of assumptions that: a common approach is needed to respond to the needs of chronic disease patients, with the widespread acceptance that HIV/AIDS has become a chronic disease following increasing availability of antiretroviral therapy; attending a combined clinic would minimize the stigma that a specific HIV/AIDS clinic induces; and the care model should reflect estimates of disease burden. All patients were managed according to standard treatment protocols. A team of counselors promoted adherence and lifestyle changes to complement medical consultations, and peer support groups extended the efforts of the doctors and counselors.

After 2 years:

- 70.7% of people with diabetes (90% of those who attended for >3 months) and 87.7% of those on highly active retroviral therapy (HAART) remained in active follow-up.
- Median HbA_{1c} was 8.6% (70 mmol/mol), but the degree of improvement could not be assessed in the absence of a baseline measurement.
- Median CD4 count doubled in patients on HAART.

Hence integrated chronic care is not only feasible, but can produce good patient outcomes.

Continuity, access, coordination, and teamwork

These four core principles—continuity of care, access to care, coordination between different levels of care, and multidisciplinary team work—really belong together, as they concern the provision of quality healthcare for managing diabetes and preventing its complications. A particular challenge in low-resource settings is that of moving away from a focus on episodic curative care. High patient numbers, with acute infectious illness, and low numbers of trained professionals have nurtured this approach, which will tend to wait for the patient to present with gangrene of the foot rather than invest energy in identifying those at risk. Likewise, there is more focus on treating the problem than empowering the person. For example, a person presenting with an elevated blood glucose level is more likely to receive a change of prescription than a useful exchange of information about diet, physical activity, and how to overcome barriers to adherence.

Continuity of care

Continuity of care in chronic diseases is a cornerstone of effective healthcare organization and has been associated with lower mortality, better access to care, less hospitalization and referral, fewer emergencies, and better detection of adverse medical events [17, 18]. Continuity is easier to achieve when services are offered close to communities where access is easier. Care that requires visits to a distant referral hospital is unlikely to support continuity because of the costs and time involved in traveling. In many less-resourced countries and areas, diabetes care has not been part of primary healthcare offered in the community, although there is a clear drive by the WHO to change this.

Central to providing continuity of care is continuity of information, such that the status of individuals is known, in terms of when they attended their last appointment, the next appointment

due, and what was found, discussed, and prescribed at previous appointments. A diabetes register is therefore essential, providing a list of people with diabetes being treated at that facility, a record of their appointments, linked to a system to follow-up those who fail to attend for an appointment. In higher income situations, electronic diabetes registers are now the norm, and in some situations comprehensive community-based registers are maintained across all levels of care. In low-income situations, an adequate register can be kept using "pencil and paper" at the level of the facility at which most diabetes care is delivered. In addition to keeping a register of patients and their appointments, there is the need to provide continuity of relevant information between visits. In high-resource settings, electronic records linked between different levels of care can provide a state-of-the-art approach. In low-resource settings, a range of approaches have been tried (e.g. color coding of patient records, the use of annual summary sheets, and patient-retained records) [19]. A simple, but effective, approach in some settings can be a combined "paper and pencil" register and record, listing a small number of core items such as blood pressure, a measure of blood glucose control, whether feet were examined, advice given, and current medication.

Continuity of management aims to provide continuity with a specific group of healthcare providers. The challenge here is to maintain the same team of people for a reasonable period of time. Relational continuity with the same healthcare provider over time is occasionally possible and would be an ideal [20].

Access to all

Access to care, of any type at all, is still an issue in many low- and middle-income countries, particularly in more remote areas. In many urban and peri-urban areas in sub-Saharan African countries, people with diabetes receive their care from hospitals and not from the more accessible primary care services [21]. Another example is the lack of access to insulin, leading to unnecessary mortality in people with type 1 diabetes mellitus (T1DM) [22, 23]. Even when available, the cost of purchasing insulin is substantial and can be the equivalent of up to 20 days' wages for a 1-month supply of insulin. Hence addressing the supply chain for medication and ensuring that essential medication is either free or easily affordable is a prerequisite for improving outcomes, but that is not all that is required. Availability of tests for the diagnosis of diabetes, monitoring of control, and equipment to screen for complications are also essential.

A shortage of human resources is a serious barrier to providing access to care in many low- and middle-income countries, the irony being that these countries are often recruiting grounds for high-income countries seeking to staff their own healthcare systems. Given their shortage, health workers in low-resource settings often develop a broader scope of practice than their equivalents in high-resource settings and as a result need to have a wide range of skills. This is often necessitated by the absence of more highly trained professionals, particularly in rural and remote areas. Although a less qualified professional may offer lower quality care, there is also the potential for effective substitution, or task shifting, with the right training and organization. This has been well demonstrated by Gill et al. in rural Africa [24]. Using a wholly primary care-level nurse-led program, with key elements of education and drug titration by clinical algorithm and using drugs on the essential drug list, significant improvements in glycemic control were noted and maintained over an 18-month period (HbA_{1c} 11.6 ± 4.5% [103 ± 49 mmol/mol] [mean ± SD] at baseline, and 7.7 ± 2.0% [61 ± 22 mmol/mol] at 18 months). The impact of education alone was remarkable, as without any change in drug therapy the HbA_{1c} decreased from 10.6 ± 4.2% (92 ± 46 mmol/mol) at baseline to 7.6 ± 2.3% (60 ± 25 mmol/mol) at 18 months.

In primary care, well-trained nurses can offer equivalent care to doctors for routine follow-up of chronic conditions, minor illness, and preventive interventions [25]. In diabetes, this may mean the nurse conducting the consultation and reviewing results such as urinalysis, and HbA_{1c}, glucose, and cholesterol levels. The nurse may also screen the feet, take blood pressure, and calculate the body mass index (BMI). Nurses will then refer to the generalist doctor for complicated or uncontrolled patients. Patient satisfaction may even be higher as consultations are longer and contain more information. Nurses, however, may not necessarily be cost-effective as they are less productive and may not be well trained or informed [25, 26]. A range of mid-level workers such as health promoters and clinical associates/assistants may also provide effective substitution [27].

Management of diabetes and other chronic diseases involves providing access to screening and early intervention to prevent or at least limit the impact of complications [6]. In low-resource settings, some complications are easy to screen for (e.g. using a testing strip dipstick to assess for proteinuria or identifying the at-risk foot with a monofilament) provided that the necessary tools are available; however, screening for retinopathy is problematic as health providers seldom succeed in overcoming the many obstacles to effective ophthalmoscopy. Nevertheless, even in low-resource settings, appropriate technology using a fundal camera may be possible [28, 29].

Further decisions need to be made regarding the relative costs and benefits in different resource settings of macro- versus microalbuminuria screening, use (and frequency) of glycated hemoglobin versus random/fasting blood glucose, and total cholesterol versus high-density lipoprotein (HDL) and low-density lipoprotein (LDL) cholesterol measurements. Recent work in a middle-income setting in South Africa suggested that microalbuminuria testing in primary care would be cost-effective, although it is not implemented, while the current use of random blood glucose to determine control gives the wrong result in one-quarter of people with diabetes, but is used in many settings [30, 31]. Point-of-care testing is another option, for example for HbA_{1c}, which has been shown to improve glycemic control in well-resourced settings [32]. Recent work in our setting, however, suggests that clinical inertia in primary care due to high workload, inadequate training, and burnout may negate the benefits.

Coordination of care

The ideal is seamless care across the health system. This requires that care is coordinated between primary, secondary, and tertiary levels so that the full range of available therapeutic and management options is utilized. In well-financed and organized systems, this coordination includes well-developed referral pathways within health districts and regions, and well-developed systems of information exchange between the levels, and thus promotion of continuity of care. Specialist services likely to be available at a secondary level include the treatment of foot ulcers, retinal laser therapy, and the investigation and medical treatment of renal impairment. Renal dialysis and replacement are an example of services often provided at the tertiary level. In low- and middle-income settings, and even in some high-income countries where universal health insurance does not exist, access to secondary and tertiary care tends to be highly dependent on the ability to pay.

Teamwork

No single healthcare provider can engage effectively with the person with diabetes and deliver all of the many components of diabetes management. Consequently, teamwork is an essential feature of providing diabetes care. Even at the primary healthcare level, particularly in high-income settings, several professionals and disciplines can be involved in the routine care of people with diabetes, including, for example, doctor, nurse, podiatrist, and optometrist. In order to develop chronic care, the people involved in managing chronic conditions need to develop a team that meets regularly to focus on improving the quality of care [6], and one of the team should be appointed as the chronic care coordinator. If no-one is responsible for chronic care, the tendency is for it to be overlooked. For example, basic equipment, such as glucometers, monofilaments, or obese cuffs for blood pressure measurement, is not provided [19]. In addition, new ideas, initiatives, and procedures are not sustained in the absence of a leader who is present during a sufficient time period. Continuously rotating staff, such as nurses, erodes the ability to create effective teams and sustain changes. When teams meet, they should develop shared goals, clarify their complementary roles, reflect on how to improve care, and hold each other accountable for decisions. Health professionals need to be clearly aligned with the purpose of improving chronic care and not with defending professional identities. A respectful, open, and curious stance helps professionals and others to understand each other better [33].

When nurses working in a large, informal settlement in Cape Town were asked what would help improve diabetes care they replied, "caring for the carers," reminding us that building a good team begins by caring for its members. The nature of the relationship between health workers and managers, and the values embedded in the organizational culture, may be reflected in the nature of the relationship between health worker and patient and the culture of caring [34]. Organizations that operate too heavily in a mechanistic and bureaucratic model tend to treat health workers as human resources that can be used and replaced like parts in a machine [35]. Organizations should strive for congruence between individual values and behavior and organizational culture and structures. It is difficult for health workers to empower people for healthy living, motivate change, and care for patients when the organization is not congruent with the same values [36]. Wheatley [37] expressed this well when she said, "After years of being bossed around, of being told they're inferior, of power plays that destroy lives, most people are exhausted, cynical and focused only on self-protection … when obedience and compliance are the primary values, then creativity, commitment and generosity are destroyed." Living health systems should care for, empower, and nurture their staff so that they are enabled to do the same for their patients.

Patient-centered care

In low-resource settings, the need to be patient-centered is often dismissed as a luxury in the face of high workloads and sometimes broad differences in education, language, and culture between health providers and patients, although in high-resource settings patient-centered care is also difficult to achieve. Nevertheless, engaging people actively in their own healthcare improves people's experience and the quality of care, enhances health literacy, helps tailor treatment to the individual, builds a sense of partnership, promotes public health and reduces inequity, makes health systems more responsive, and reduces waste of resources [38, 39]. It does not necessarily imply a longer consultation and may improve the provider's work satisfaction. Patient-centeredness implies a more collaborative approach and holistic understanding of the patient that elicits, acknowledges, and addresses relevant beliefs, concerns, ideas, and fears [20]. It may mean balancing the evidence-based requirements of guidelines with the personal values and goals of patients, especially in the face of multimorbidity.

Patient-centeredness is in part a paradigm shift in the mind of the health worker from a biomedical, technical, public health, and sometimes authoritarian model to a biopsychosocial, holistic, personalized, and participatory model [20]. It is fundamentally a way of genuinely being with the patient. Nevertheless, a range of specific communication skills can be learnt, such as the ability to ask both open and closed questions, to make reflective listening statements, exchange information, or invite mutual decision-making [40]. Although the training of doctors has begun to include these communication skills, even in low-resource settings, the training of nurses and mid-level health workers often has not.

Supporting people in health-related behavior change is a key part of patient-centered care. Motivational interviewing is one patient-centered approach to help patients make decisions about lifestyle and behavior change [40]. Diabetes, which involves multiple changes in behavior (diet, exercise, smoking, alcohol, medication), particularly lends itself to adaptations of motivational interviewing. A challenge in low-resource settings is to see how

a range of health workers can incorporate such a guiding style into their consultations and, once this has been achieved, pivotally, how it can be sustained. Group diabetes education by mid-level healthcare workers with a guiding style has been shown to be cost-effective in a less well-resourced setting during a 12-month trial, even though the effects were less than reported on from better resourced contexts [41, 42].

In a model of care that emphasizes patient empowerment and self-care as key components [6], every consultation also needs to be seen as an opportunity for this. Health providers need to have the necessary expertise in the relevant topics, useful communication skills, and a range of educational materials appropriate to the literacy level of the community [26, 43].

A family and community orientation

Beyond the individual with diabetes is their family and community context. Clearly, family beliefs and customs and degree of social support will have an impact on the ability of an individual within that family to make lifestyle changes and cope with their diabetes. Involving family members in the consultation or educational program can strengthen the overall response to diabetes [44]. Likewise, an understanding of the individual's environment will inform discussions about appropriate changes and likely constraints.

In low-resource settings, where facilities are overwhelmed with large numbers of patients, it may make sense to extend care into the community [6]. For example, community-based support groups can be run by health promoters or local non-government organizations to offer some aspects of routine chronic care. People with diabetes can then return to the local clinic for periodic or annual review and help with complications. Support groups can also encourage lifestyle change and adherence to medication. Expert patients, an increasingly developed resource in both low- and high-income situations, may also be useful to enhance self-care, although further evaluation is required [42].

Community health workers have the potential to promote healthy lifestyle, provide home-based care, and link selected people with diabetes with the local facilities [45]. Although a number of individual studies have demonstrated that community health worker interventions were associated with improvements in glycemic control, this is not universal, as demonstrated by recent systematic reviews [46, 47].

Communities should not just be seen as additional platforms for care or targets for interventions, but representative structures or key leaders should be engaged with in order to understand how local health priorities are perceived and to elicit feedback and involvement in the planning and delivery of services [20].

Primary care workers usually have a responsibility not just for individual patients, but also for people living within specific communities or health districts [20]. Concern for the growing number of people with diabetes should lead to interventions that address the underlying determinants of obesity and reduced physical activity, for example, school-based healthy lifestyle programs, provision of green spaces in inner cities, marketing of food to children, sale of junk food on public premises, and labeling of food. Many of these require health workers to contribute to interventions in other sectors [48].

Clinical governance

Clinical governance refers to the people and processes that are put in place to ensure improvements in and maintenance of a high quality of care [49, 50]. Clinical governance activities can include some or all of the following:

- A national process for developing evidence-based guidelines, drawing on effectiveness research, relevant to the needs and context of the country. An example of such a system from a high-income setting is the National Institute for Health and Care Excellence (NICE) in the United Kingdom. This may be beyond the resources of lower income countries, but through regional cooperation, such as coordinated by the WHO, the IDF, and the World Bank, regular reviews of the evidence appropriate to different resource settings do take place.
- Financial incentives to providers for delivering processes of care and achieving targets for good clinical outcomes, for example, the UK quality outcomes framework tied to NICE guideline recommendations.
- A more local process for disseminating and implementing guidelines and integrating guidance on care for diabetes with other conditions.
- Quality improvement cycles that include audit of the technical quality of diabetes care and also the performance of the health services (e.g. continuity, coordination). Another example from the UK is the English and Welsh National Diabetes Audit, which has driven improvements in the quality of services and health outcomes for people with diabetes. The Audit addresses four questions based on the diabetes National Service Framework. These cover whether all people with diabetes diagnosed were included in a practice diabetes register. In addition, the percentage of those registered with diabetes who had the nine NICE key processes of diabetes care, the proportion who achieved NICE-defined glucose control, blood pressure, and blood cholesterol treatment targets, and the rates of acute and long-term complications (disease outcomes) are collected [51]. Incorporating patient voices in addition to the voices of health workers is also important in a comprehensive view of quality.
- Training and upskilling of health workers in terms of their clinical and communication competencies are a key part of clinical governance.
- Regular reflection on routinely collected data may also be important, for example, looking at the rational use of investigations and prescribing of medication.
- Attention to patient safety and risk management, for example, by analyzing the causes of unexpected or premature morbidity or mortality.

A model of care for diabetes should ensure that this condition is included in the approach to clinical governance.

Information technology

The widespread availability and affordability of mobile devices, increasing Internet access, and recent advances in the networking of physical objects and devices with electronics, software, sensors, and network connectivity ("Internet of things") have led to an explosion in the number of applications and programs that have been developed with the aim of improving healthcare in general and diabetes care in particular. These information technology interventions have been delivered through an ever-evolving and wide range of devices and modalities, and have been accompanied by a shift from computer-based technology and software to cloud-based computing and mobile devices, including phones, tablets, and smart watches, all with powerful computing capabilities. These advances have therefore opened up the possibility of strengthening some models of care and allowing the development of new ones.

To date, information technology has been used to support health systems, providers, and people living with diabetes at numerous levels and across multiple domains and settings, including in low- and middle-income countries where there is high mobile phone penetration and widespread telecommunication connectivity. At a health systems level, advances in electronic health records have created new and better ways for patient data to be securely shared, electronic registries have been utilized to track people with diabetes and to ensure comprehensive follow-up and monitoring, and telemedicine services have been used to provide care at a distance, including the reading of fundus images by experts when screening people for diabetic eye disease. At a provider level, clinical decision support tools have reduced errors and improved the quality of care, and online educational resources have created new training and continuous development opportunities. At a patient level, advances in sensors and mobile devices have made remote and self-monitoring easier, and online forums and health information systems have improved support among people living with diabetes and improved their access to information.

Although the use of information technology in healthcare has generated considerable enthusiasm among policy-makers, funders, healthcare providers, and patients themselves, widespread implementation and adoption of information technology have been limited by the lack of empirical evidence on the health outcomes and cost-effectiveness of these interventions and, in low- and middle-income countries, competing priorities for limited budgets available for health system strengthening [52, 53]. This section evaluates these information technology advances, summarizes the evidence where available, and highlights how these can be embraced in the different models of diabetes care. Given the large number of studies that have been undertaken in the past few years that have evaluated telemedicine, electronic health (eHealth) and mobile health (mHealth) intervention, our aim is to summarize systematic reviews and meta-analysis where available.

Electronic health records

Electronic health records (EHRs) have seen a number of advances in the past few years. Now they are often based in a cloud, can be updated and edited in real time, and can be accessed by authorized users on a range of devices, making patient information instantly and securely available across multiple facilities. These capabilities can support different models of care, by making patient data readily available to multiple providers. Although EHRs have been found to be effective in improving health system process outcomes, there is now also increasing evidence finding EHRs to be associated with improvements in the standard of diabetes care [54]. The sharing of up-to-date patient data between primary and tertiary care providers and also between the various multidisciplinary providers, such as ophthalmologists, podiatrists, dieticians, physiotherapist, and educators, is a critical component in ensuring an effective continuum and integration of care, with both models reliant on patient data being easily accessible. Privacy and data ownership laws are increasing the popularity of personal health records, where patients own their own clinical data and records [55]. Designing clinical information systems with patients at the center supports patient-centered models of care, where patients are empowered to manage, share, and use their data to access care and improve their health.

Registries

Patient registration systems facilitate tracking of patients and identification of those who are eligible for specific services. Registries enable comprehensive models of care to be developed and ensure timely follow-up [56]. Many countries, particularly high-income countries, have developed and utilized electronic diabetic registries for the management of clinical services and also for research purposes [57, 58]. These registry systems are also used to monitor people for complications of diabetes, such as diabetic retinopathy, where registers are becoming the standard for implementing national screening programs and monitoring and following up patients with this complication over time. In addition to scheduling people with diabetes due for annual screening, these systems can identify high-risk individuals who miss appointments, triggering reminders and follow-up by case managers, and also facilitate referrals for laser treatment once sight-threatening retinopathy is identified [59, 60].

Telemedicine and remote monitoring

Telemedicine refers to the use of information technologies to provide healthcare at a distance. In the past two decades, telemedicine has been used to provide education (to support self-management), for monitoring (of blood glucose), and to facilitate consultation with health providers (telephone and videoconferencing support and also to schedule follow-ups). Numerous studies and

systematic reviews have evaluated the effectiveness of remote glucose monitoring on improved glycemic control and, although telemedicine has been found to be feasible and acceptable, there is still a lack of strong evidence for its effectiveness in improving HbA_{1c} [61–63]. Further, a recent synthesis of evidence of the use of telemedicine in managing chronic diseases (including diabetes) over the past 20 years found that neither telemonitoring nor videoconferencing was superior to telephone support, and that the evidence base for the value of telemedicine in managing chronic diseases suggested that findings were inconsistent [64, 65]. A notable exception is telemedicine diabetic retinopathy screening systems, where fundus images taken at primary healthcare screening sites are transferred to central reading centers for assessment and grading of diabetic retinopathy. These telemedicine retinopathy screening systems have been shown to be both effective in identifying individuals requiring referral for treatment and cost-effective to implement across different resource settings [66]. Telemedicine interventions, whether synchronous and asynchronous, remain an important enabler of models of care that focus on providing better access, especially in resource-limited settings.

Clinical decision support tools

Information technologies are increasingly being used to provide clinical decision support in the form of electronic protocols, guidelines, and checklists. Clinical decision support tools have shown great promise for reducing medical errors and improving patient care, especially when utilized by a lower cadre of health provider. A systematic review of computer-based clinical decision support systems found that they enhance the clinical performance for drug dosing, preventive care, and other aspects of medical care, but not convincingly for diagnosis [67]. The use of a computer to generate the decision support was among the top four features of clinical decision support systems critical for improving clinical practice, with a close correlation between automatic provision and successful outcome. The other key features included providing decision support automatically as part of clinician workflow, delivering decision support at the time and location of decision making and providing actionable recommendations [68]. A number of diabetes-specific clinical decision support tools and algorithms have been developed and are used in clinical practice. Examples include algorithms that can calculate a person's risk of developing T2DM and those that can calculate a person's risk of developing complications such as cardiovascular disease or diabetic retinopathy [69–72].

Provider training and education

Access to information, via mobile devices and Internet connectivity, has created new opportunities for medical education and training of providers. Constantly available online resources and native applications create new and convenient learning opportunities for providers. Continuous medical education activities can be seamlessly incorporated into clinical practice and effortlessly recorded for accreditation and audit purposes.

Supporting self-management and behavior change

A number of information technology interventions are currently being used to make information accessible and actionable for people with diabetes and to support the domains requiring diabetes self-management. These include nutritional management, exercise and physical activity, blood glucose monitoring, and medication utilization and adherence [73, 74]. The use of the audio and video functionality of mobile devices to show educational and instructional videos has also been found to enhance counseling between providers and patients, especially in people with low health literacy. Evaluation of the effects that these technologies are having on people with diabetes has received considerable attention by researchers and in systematic reviews. These reviews have shown: (1) that computer-based interventions to improve self-management have a small beneficial effect on glycemic control, with mobile phone-based interventions having a larger beneficial effect on glycemic control [75]; (2) that behavioral interventions targeting one domain of self-management (physical activity) produced a statistically significant increase in exercise and a clinically significant improvement in glycemic control and BMI [76]; and (3) a small reduction in HbA_{1c} levels among the diabetes self-management interventions using mobile health technology-based health behavior change or disease management interventions. Understanding the specific underlying behavior change techniques being utilized in effective information technology interventions is increasingly being recognized as an important aspect when it comes to replicating or taking an intervention to scale [77]. More extensive use of behavior change theory in Internet-based interventions has been found to be associated with increases in effect size [78].

Digital glucose monitoring

Recent advances in the computing capabilities of mobile devices and in connected glucometers that can be linked to insulin pumps have created new opportunities for self-monitoring of blood glucose. In addition, novel glucose sensors, including non-invasive, continuous monitors that are capable of conducting, evaluating, storing, and transmitting glucose readings through connected mobile devices are being developed and tested [79–81]. These devices are able to detect abnormal measures and trigger an appropriate response, such as sending a message to the patient's phone or activating an emergency response number. Longitudinal data can also be stored for later review with health providers, providing better data for more informed decision-making. Personalized feedback has been shown to be an important component in remote monitoring following self-monitoring activities. A systematic review looking at remote monitoring and the impact on HbA_{1c} found significant change between groups to be associated with personalized feedback (whether it came from skilled healthcare providers or automated algorithms) [82]. Although these developments represent important advances towards fully automated glucose monitoring and control, further research is required to determine the safety and effectiveness of these technologies once integrated into clinical practice. Patient-centered

models of care and also those that are designed around access to care could benefit from remote- and self-monitoring technologies, but the likelihood of these being readily available in low-resource settings outside private or academic environments is very low.

Online health information, support groups, and social media

Healthcare providers are no longer the primary source of medical information. It is estimated that most people in high-income countries with chronic conditions such as diabetes search online for information on treatment options, tools for managing their condition, and scientific breakthroughs. This opens up the possibility of new and exciting models of care based on patient empowerment. Supporting patients by teaching them how to search for credible and reliable information or by directing them to vetted online resources may reduce the risk of misinformation. Online support groups, compared with face-to-face support groups, offer an easy and convenient way for individuals with diabetes to join a community of people with diabetes where they can compare experiences, symptoms, and treatments and also receive and give support. The number of diabetes-specific online communities has increased dramatically in the past decade, with hundreds of options available that cater for people from all walks of life and with varying needs. Social media are also being used increasingly by people to source information about diseases and services and to organize communities and groups. Family and community models of care are strengthened by the participation and engagement of friends and family. Information technologies that make it easy for communities, both on- and offline, to support people with diabetes create informed and empowered societies.

Conclusion

Although the advances in information technology described above hold immense promise in enhancing the different models of care for diabetes, embracing these technologies remains a challenge. Ad hoc implementations of information technology are likely to give way to more integrated approaches where these technologies are viewed as enabling components within the context of a health system or a specific model of care, instead of as a standalone solution.

Information technology has the potential not only to strengthen existing models of care but also to create new models of care for people living with diabetes. Mobile phones, for instance, have been used as tools for community health workers, enhancing the task shifting of health promotion and disease prevention activities in resource-limited settings [83, 84]. The uptake of text messaging between providers is improving coordination of care and creating new and simpler referral pathways, which are being further automated by clinical decision support plug-ins. Developments in non-invasive sensor technology, mobile applications capable of processing point-of-care biomedical signals and the connectivity between these devices, insulin pumps, and pharmacy drug ordering systems are likely to lead to the creation of new and more automated models of care. Although many of these information technology advances are currently unavailable and unaffordable in low- and middle-income countries, they are likely to become increasingly affordable in the future. Low- and middle-income countries will also benefit from the learning from the trials and errors of embracing these technologies and integrating them into health systems, and may have the opportunity to leapfrog high-income countries in implementing evidence-based information technologies that are both cost- and clinically effective.

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13 Future Directions

66 Future Drug Treatments for Type 1 Diabetes

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Key points

- One of the limitations of insulin therapy is the use of preparations that do not adequately reproduce the patterns of physiological insulin secretion.
- The essential need for improvement appears to be for insulin analogs with extended release, basal insulin analogs, and ultrafast-acting insulin analogs with faster absorption and action.
- The availability of newer ultrafast- and ultralong-acting insulin analogs offering efficacy in terms of glycemic control with a low risk of hypoglycemia and fewer side effects will help overcome some barriers related to treatment of type 1 and type 2 diabetes mellitus (T1DM and T2DM).
- Although initially targeted towards treatment of T2DM, adjunctive therapies including dipeptidyl peptidase 4 inhibitors, glucagon-like receptor peptide 1 agonists, and sodium–glucose co-transporter inhibitors show promise in the treatment of T1DM.
- Sensor-augmented insulin pumps with a feature that automatically suspends basal insulin for low sensor glucose levels have been demonstrated to reduce exposure to hypoglycemia without raising average glucose levels, and systems that suspend basal insulin for predicted low glucose levels are in development.
- Artificial pancreas systems consisting of an insulin pump, continuous glucose sensor, and control algorithm that dynamically regulate insulin delivery on a minute-to-minute basis have shown promise in reducing both hyperglycemia and hypoglycemia and improving overall diabetes control.
- Intranasal glucagon to treat hypoglycemia is effective and simpler to administer than currently commercially available intramuscular glucagon. An aqueous glucagon formulation has been developed and has the potential for use in a dual hormone closed-loop system.

Introduction

The dawn of the era of intensive treatment of type 1 diabetes mellitus (T1DM) in the late 1970s and early 1980s was brought about by the nearly simultaneous introduction of improved methods of monitoring glycemic control (i.e. blood glucose meter monitoring and HbA_{1c} assays) and more physiological approaches to insulin replacement (i.e. insulin pumps and multiple daily injection regimens). It was more than 10 years later that the Diabetes Control and Complications Trial (DCCT) was able to demonstrate finally the benefits of intensive treatment in delaying or preventing the early microvascular and neuropathic complications of the disease [1, 2].

There have been a number of advances in the treatment of T1DM in the more than 20 years since the end of the DCCT that include further improvements in monitoring glycemic control with continuous glucose monitoring (CGM) systems [3] and the introduction of rapid- and long-acting insulin analogs. Nevertheless, too many individuals with T1DM do not achieve target HbA_{1c} levels, while acute complications of severe hypoglycemia and diabetic ketoacidosis remain ever-present dangers [4], and the devastating long-term vascular complications can be delayed by current therapies but may not be prevented [5].

Owing to the failure of a number of clinical trials that utilized a variety of immunologically active agents to preserve residual β-cell function in new-onset diabetes and to prevent the development of T1DM in high-risk individuals, and also the limited availability of pancreas and islet transplants to cure T1DM, clinicians and people with T1DM continue to follow the same insulin-based treatment regimens, albeit with somewhat better methods. Although strict metabolic control has long been known to slow the loss of β-cell function early in the course of diabetes [6], the recent Metabolic Control Study of the DirecNet and TrialNet study groups demonstrated convincingly that we have already reached the maximum benefit from current intensive insulin treatment methods [7].

As we describe in this chapter, there has been a spate of new biosynthetic insulin analogs whose time–action profiles are faster than those of the current rapid-acting insulins and flatter and longer acting than current basal insulins. It is particularly exciting that we also appear to be on the verge of truly transformational changes in the treatment paradigms for adults and children with

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T1DM that move beyond newer insulin preparations. Specifically, new classes of drugs for the treatment of type 2 diabetes (T2DM) in adults, such as dipeptidyl peptidase 4 (DPP-4) inhibitors, glucagon-like peptide-1 (GLP-1) receptor agonists, and sodium–glucose co-transporter (SGLT) inhibitors, are currently being tested for use as adjunctive treatment of T1DM. Although new insulins with better pharmacokinetic and pharmacodynamic characteristics with or without concomitant use of adjunctive therapies may allow more people with T1DM to achieve target HbA_{1c} levels more safely, no treatment of T1DM will be optimal until there is feedback control of insulin delivery. In this chapter, the great advances in the development of closed-loop insulin delivery systems for outpatient treatment of T1DM since the last edition of this book are summarized. New preparations of glucagon, such as intransasal delivery and stable liquid preparations for use in continuous subcutaneous delivery, are important for optimal treatment of severe hypoglycemia and integral to the development of dual-hormone closed-loop systems, which infuse both glucagon and insulin.

New biosynthetic human insulin analogs

One of the limitations of insulin therapy is the use of preparations that do not adequately reproduce the patterns of physiological insulin secretion. Insulin therapy has evolved greatly in the last 50 years, with the introduction of purified insulin analogs that are manufactured by recombinant DNA technology with improved time–action profiles. The synthesis of insulin analogs became possible by rearranging human insulin amino acid positions to modify insulin bioavailability (pharmacokinetics) and glucose-lowering action (pharmacodynamics) in a favorable way compared with human insulin. The ongoing challenge in insulin therapy is to discover new and improved insulin analogs or methods to improve time–action profiles of conventional insulin analogs. A major goal of future insulin therapy is to provide insulin coverage that more closely mimics endogenous insulin secretion while reducing hypoglycemia and postprandial hyperglycemia and improving adherence. Consequently, the essential need for improvement appears to be for insulin analogs with extended-release basal insulin analogs and ultrafast-acting insulin analogs with faster absorption and action. The following section summarizes developments in the field under three main topics: the ultralong-acting basal insulin analogs, the ultrafast-acting insulin analogs, and methods to accelerate insulin action, with a focus on the safety and the efficacy results for each group.

Ultralong-acting insulins

Basal insulin coverage to control fasting blood glucose is an important component of diabetes management. An ideal basal insulin should achieve an equilibrium between the rate of endogenous glucose production and use during the fasting state. It should provide a more physiological pharmacokinetic/pharmacodynamic profile with longer duration, low intra- and inter-patient variability, reduced day-to-day variability, and less pronounced peaks in time–action profiles. Important drawbacks of currently available basal insulin therapy, including dose-to-dose variability resulting in unanticipated blood glucose fluctuations and the need for once or twice per day therapy, have led to the search for ultralong-acting insulins with less variability and longer duration of action to improve adherence. Another important goal for the development of new ultralong-acting insulins has been the reduction or elimination of peaks of insulin action, in order to reduce late hypoglycemia, which has been partially achieved with insulin glargine and detemir. The development of new long-acting basal insulin analogs, including glargine insulin U300 and insulin degludec, offers the promise of improved opportunities for intensive insulin therapy.

Insulin degludec

Insulin degludec is produced by the removal of threonine at position of 30 of the β chain (B30) and the attachment of a 16-carbon fatty diacid to lysine at position 29 of the β chain (B29) via a glutamic spacer linker to change the human insulin amino acid sequence [8]. The phenol solution in the formulation keeps the molecule in a stable dihexameric form *in vitro*. The phenol diffuses once insulin degludec has been injected into the subcutaneous tissue, exposing free ends of the dihexameric structure, which then transforms into a soluble multihexameric structure (zinc and fatty acid side-chains). Similarly to physiological insulin synthesis and storage in the secretory granules, the presence of zinc ions promotes self-association of insulin molecules from dimers into hexamers, increases stability and prolongs insulin's absorption into the circulation. Once the zinc on the terminal ends of the molecule has diffused, the insulin slowly dissociates, resulting in slow and steady absorption of monomers, conferring an ultralong-acting profile. The presence of resorcinol with zinc determines the formation of hexamers and the presence of phenol with zinc promotes dihexamer formation. Linear multihexamers are formed by self-association of dihexamers promoted by phenol depletion after subcutaneous injection [9]. The acylation of lysine B29 contributes to albumin binding similarly to insulin detemir; however, unlike insulin detemir, this feature does not contribute to insulin degludecs prolonged time–action profile [9]. The maximum plasma concentration for insulin degludec is achieved 10–12 h after subcutaneous injection and the mean-terminal half-life is 17–25 h. The steady state is achieved after 2–3 days with once-daily administration during which the daily injected dose is equivalent to the daily eliminated amount of insulin. The pharmacokinetic profile constitutes a similar pattern in persons with T2DM. Pharmacodynamics studies employing the euglycemic clamp technique reported glycemic control that was both stable (evenly distributed across the 24–26-h evaluative periods) and reproducible, with an inter-day within-subject coefficient of variation of 20% compared with 82% for insulin glargine [10–12].

Insulin degludec has been shown to be non-inferior with regard to glycemic control compared with insulin glargine U100 in phase III studies for individuals with T1DM and T2DM.

The risk of nocturnal hypoglycemia was lower for insulin degludec based on meta-analysis of pooled data in T1DM and T2DM in comparison with insulin glargine U100 basal insulin therapy [13].

More recently, a 52-week randomized phase III trial evaluated the clinical efficacy of combining insulin degludec with liraglutide, a glucagon-like protein-1 (GLP-1) receptor agonist that decreases fasting and postprandial glucose levels, compared with insulin degludec or liraglutide separately among people with insulin-naïve T2DM [14]. IDegLir a achieved superior glycemic control to insulin degludec or liraglutide alone, indicating a synergistic effect, and also mitigated weight gain (2.1 kg) and risk of hypoglycemia (38%) compared with insulin degludec. Subsequent 26-week phase III trials among adults with insulin-naïve T2DM also reported that IDegLir a yielded superior glycemic control when tested as an add-on to previous GLP-1 receptor agonist treatment compared with unchanged GLP-1 receptor treatment [15], and also compared with placebo [16]. Notably, IDegLir a led to a 1.5–3.0 kg weight gain compared with the other treatments. Two other 26-week phase III trials tested IDegLir a among insulin-experienced participants with T2DM, and found that it yielded superior glycemic control and reduced body weight (2.7–3.2 kg) compared with both add-on insulin degludec therapy [17] and continued insulin glargine therapy [17]. Overall, the combination of insulin degludec with liraglutide appears beneficial for glycemic control, weight control, and reducing the risk of hypoglycemia.

Another agent that has been successfully combined with insulin degludec is the rapid-acting insulin aspart; the combination drug insulin degludec with insulin aspart was approved by the US Food and Drug Administration (FDA) in 2015. In the presence of zinc and phenol, the former exists as dihexamers but the latter as hexamers, thus avoiding the risk of hybrid hexamer formation. IDegAsp has been tested in six 26-week phase III trials against insulin aspart alone or insulin glargine among individuals with T1DM and T2DM, in all cases yielding equal or superior glycemic control and equal or lower rates of nocturnal hypoglycemia [18]. Despite these favorable outcomes, a meta-analysis of 16 phase III trials testing either insulin degludec or IDegAsp revealed an increased risk of major cardiovascular events versus comparator drugs [14]. The magnitude of increased risk ranged from 13 to 67% depending on the definition of the major cardiovascular event utilized. These data led to the initiation of a post-marketing evaluation dedicated to cardiovascular outcomes for insulin degludec and IDegAsp.

Insulin glargine U300

Insulin glargine is synthesized by exchanging asparagine at position 21 of human insulin for glycine, and adding two arginine residues to the B chain. Insulin glargine is a diarginylinsulin analog with an acidic isoelectric point of 5.4 that shifts to a neutral pH and precipitates once it is injected into the subcutaneous site, thereby delaying its absorption and prolonging its action. Insulin glargine U300 is a concentrated form of insulin glargine with a slower absorption profile secondary to reduction of volume and depot surface. U300 is released more gradually into the circulation with a less pronounced peak action and fluctuation (peak-to-trough ratio 1.8) and a longer duration of action extending beyond 24 h [19]. Insulin glargine U300 has lower within- and between-day variability than insulin glargine U100, with comparable risk of hypoglycemia and a similar safety profile [20]. Steady-state clamp studies of U300 demonstrated an increase in the glucose infusion rate from 2 to 16 h post-dose, followed by a slight decline at around 18 h post-dose, and then stable activity up to 36 h post-dose. Clinical trials of U300 showed a 10% reduction in nocturnal hypoglycemia and 10–17% increased insulin requirement [21]. A small attenuation of weight gain (0.2–0.6 kg) with U300 compared with U100 has been observed in some of the clinical studies, and no trial has reported differences in adverse events between groups [22, 23]. In summary the flatter, more prolonged, and more predictable pharmacokinetic profile of U300 compared with U100 appears to lead to a reduced risk of hypoglycemia and possibly reduced weight gain, although at the expense of a slightly higher dosage to achieve glycemic control.

Peglispro

Basal insulin peglispro comprises insulin lispro covalently bound to a 20-kDa poly(ethylene glycol) (PEG) at lysine B28. The attachment of a PEG chain to a protein (PEGylation) reduces degradation, prolongs exposure, and reduces immunogenicity [24]. The resulting PEGylated insulin lispro's duration of action is ~24 h [25, 26]. Peglispro has demonstrated slightly superior glycemic benefits along with a reduction in nocturnal hypoglycemia and a weight advantage compared with insulin glargine in clinical studies [27, 28]. Peglispro preferential hepatic versus peripherally binds tissue [29], which could mitigate weight gain and possibly lower dose requirements. The main side effect of peglispro of concern has been liver enzyme alanine aminotransferase (ALT) elevation among those taking peglispro in clinical trials [30, 31]. These levels decreased towards baseline about 4 weeks after discontinuation. Participants on peglispro showed elevation of triglycerides and low-density lipoprotein cholesterol and a reduction in high-density lipoprotein cholesterol, which also raised some concern [32]. Clinical studies revealed no significant differences in rates of severe hypoglycemia between the peglispro group and the insulin glargine group for people with T2DM, but those with T1DM taking peglispro had higher rates of severe hypoglycemia than those taking insulin glargine in a clinical study at 26 weeks (39.0 vs. 16.2 events per 100 patient-years) and similar rates of severe hypoglycemia in a subsequent clinical study at 52 weeks (19.7 vs. 22.5 events per 100 patient-years) [30, 33]. Additionally, liver fat as measured by MRI has been noted to be higher among a subset of participants treated with basal insulin peglispro versus insulin glargine in two clinical trials [32, 34]. The mechanism of the increased liver fat content with peglispro is unknown [30, 31, 35, 36] but these abnormalities led Lilly to announce it was ceasing development of peglispro in December 2015.

Ultrafast-acting insulins

One of the limitations of currently available rapid-acting insulins is the insufficiently rapid absorption and onset of action from the subcutaneous compartment, resulting in excessive postprandial glucose excursions. Molecular genetic techniques have allowed the synthesis of rapid acting insulin analogs with faster insulin absorption after subcutaneous injection, achieved by amino acid substitutions in the distal end of the β chain of insulin that allow for more rapid disassociation of hexamers to dimers and monomers in the subcutaneous depot. Rapid-acting insulin analogs produce higher plasma insulin levels earlier and have a shorter duration of action compared with regular insulin but behave like human insulin with regard to both insulin- and insulin-like growth factor-receptor binding. The faster onset of rapid-acting analogs facilitates greater adherence by reducing the interval between the injection and ingestion of a meal, allowing people with diabetes to inject 15 min before the meal or even immediately before the meal rather than the recommended 35 min prior.

Although current rapid-acting insulin analogs have major advantages over regular human insulin, the time–action profiles of Rapid-acting insulin analogs still do not match the rapid absorption and onset of action observed with physiological insulin secretion, which is essential to suppress the rise in postprandial blood glucose [37, 38]. The concept of ultrafast-acting insulin analogs was introduced in order to fulfill a need for faster onset and shorter duration of action than rapid acting analogs [37, 38]. Novel ultrafast-acting insulin and methods to accelerate insulin action represent promising strategies to overcome some of the shortcomings of conventional insulin therapy for optimizing glycemic control [39, 40]. Moreover, the combination of new, ultrafast-acting insulins and automated or semiautomated closed-loop artificial pancreas systems offers the potential of a new era in the treatment of T1DM, in which target glucose and HbA_{1c} levels can be achieved with greater safety and a much reduced burden on patients and clinicians [41].

Faster-acting insulin aspart

Faster-acting insulin aspart is insulin aspart in a new formulation that contains two new excipients (nicotinamide and arginine) to stabilize the insulin formulation. Both of the excipients are generally recognized as safe by the FDA [42], and result in faster initial absorption after subcutaneous injection [43]. Compared with insulin aspart, faster-acting insulin aspart is associated with a faster onset of action and increased early exposure that, in turn, leads to a significantly greater early glucose-lowering effect [43]. Furthermore, increased early exposure with faster-acting insulin aspart, compared with insulin aspart, led to improved glycemic control following a postprandial challenge in both the subcutaneous injection and continuous subcutaneous insulin infusion (CSII) settings [44].

VIAject

VIAject (Linjeta; Biodel Inc.) is an ultrafast insulin formulation with significantly faster absorption than either regular human insulin or insulin lispro [45]. VIAject uses ethylenediaminetetraacetic acid (EDTA) to chelate zinc and, therefore, destabilize insulin hexamers. Glycemic excursions were reduced with VIAject treatment compared with either regular human insulin or insulin lispro [46]. A pH-neutral formulation of this compound has since been developed that has demonstrated bioequivalence with the previous formulation and has also been shown to reduce absorption and onset of action significantly compared with insulin lispro [47]. People experienced less injection-site pain with the pH-neutral formulation than the previous formulation; however, greater discomfort with VIAject than with insulin lispro was reported by participants during the study [45]. The current formulation under development is BIOD-531, which is a U400 formulation containing EDTA, citrate, and magnesium sulfate with an intention to improve injection-site tolerability [48]. BIOD-531 is associated with a significantly faster rapid absorption and onset of effect than concentrated regular human insulin (U500) or insulin lispro.

Technosphere insulin

The search for alternative routes of insulin delivery has been driven by the desire to eliminate the discomfort and inconvenience of insulin injections. The vast surface area of the alveolar surfaces in the lung allows rapid absorption of inhaled drugs. Inhalation as a novel route of administration for insulin delivery has demonstrated faster absorption and onset of action of insulin compared with traditional subcutaneous injection. Additionally, it provides an alternative mode of insulin delivery for those who are reluctant to take injections. The ability to design insulin particles that can reach the lung and be absorbed into the circulation made inhaled insulin a possibility.

Technosphere insulin (Afrezza; MannKind Corp.) is an inhaled preparation consisting of insulin adsorbed on to highly porous microparticles [49]. It consists of recombinant human insulin and fumaryldiketopiperazine (FDKP) that self-assembles into Technosphere particles. The Technosphere particles dissolve immediately at the physiological pH of the lung, and insulin and FDKP are absorbed systemically. The systemic absorption of insulin produces rapid and high peak serum insulin concentrations that fall between the concentration times of intravenous insulin and subcutaneous regular insulin or rapid-acting insulin analog [50]. The glucose-lowering action of Afrezza peaks approximately 30 min after administration and mimics the physiological first-phase insulin response after a meal that is characteristically absent in people with diabetes. Published studies of Technosphere insulin have primarily involved individuals with T2DM and have demonstrated effective control of postprandial blood glucose levels [51]. A phase II study showed that Technosphere insulin plus basal insulin glargine multiple daily injection treatment led to dose-dependent reductions in glucose and HbA_{1c} levels [52]. A subsequent phase III study showed there was no significant difference in HbA_{1c} between treatment with Technosphere insulin plus glargine and treatment with biphasic insulin aspart 30 [53]. However, weight gain and hypoglycemic episodes were

reduced in the Technosphere insulin group. Technosphere insulin was approved for treating individuals with T1DM and T2DM by the FDA in 2014 [54]. However, Technosphere insulin carries a black-box warning advising that acute bronchospasm has been observed in persons with asthma and chronic obstructive pulmonary disease; this product should therefore not be used in such people, or cigarette smokers, because of this risk.

BioChaperone insulin

The BioChaperone platform constitutes a library of polysaccharides modified with naturally occurring molecules. The BioChaperone technology to accelerate insulin absorption relies on a polymer that forms a molecular complex with insulin to speed up insulin delivery into the circulation. The formulation of human insulin and a polymer of the BioChaperone platform, known as HinsBet, has been proven to be absorbed faster than regular human insulin from the subcutaneous tissue. As for rapid acting insulin analogs, BioChaperone Lispro demonstrated an earlier onset of action, earlier maximum action, and stronger glucodynamic effect in the first 2 h after dosing compared with insulin lispro during clamp studies in people with T1DM [55]. New studies are under way to investigate the BioChaperone polymer technology to deliver high-concentration human insulins and compound long-acting- rapid acting insulin mixtures [56].

Alternative means of accelerating insulin absorption and action

Insulin infusion and injection site-warming devices

Insulin absorption may be accelerated by increasing blood flow to a localized area by warming the skin. A pilot study showed that a site-warming device (InsuPatch; Insuline Medical Ltd.) significantly increased the maximum concentration and decreased the time to reach maximum concentration of serum insulin levels in people with T1DM receiving insulin aspart or lispro via insulin pump therapy [57]. The use of a similar device designed to warm insulin injection sites (InsuPad; Insuline Medical Ltd.) has been shown to decrease prandial bolus insulin requirements by 19% in obese individuals with T1DM and T2DM, suggesting that site warming enhances insulin bioavailability [58]. Subsequent studies have confirmed that site warming accelerates absorption and increases the action of rapid acting insulin analogs, and may enhance the performance of open- and closed-loop insulin delivery systems [39, 40].

Administration via intradermal microneedles

Intradermal administration could permit faster insulin absorption because of the skin's greater vascularity in comparison with the subcutaneous space. Studies comparing delivery of insulin lispro via conventional subcutaneous catheters and intradermal microneedles have found that intradermal delivery significantly decreased time to onset and offset of metabolic effect [59, 60]. Intradermal needles are generally well tolerated and may be less painful than subcutaneous injections or catheters; however, transient, localized wheal formation and redness have been observed at injection sites. Currently, no intradermal microneedles are commercially available.

Pretreatment of new infusion sites with hyaluronidase

Recombinant human hyaluronidase (rHuPH20) is an FDA-approved enzyme that is used to increase the absorption and dispersion of other injected drugs by breaking down the connective tissue that acts as a barrier to fluid dispersion [61]. In phase I studies of healthy volunteers, coadministration of rHuPH20 (Hylenex; Halozyme Therapeutics, Inc.) with rapid acting insulin analogs significantly reduced intra-subject variability in the pharmacokinetic response to insulin, and accelerated insulin exposure to insulin aspart, lispro, or glulisine with a faster onset and offset of action [62, 63]. In people with T1DM, rHuPH20 coadministered with either regular insulin or insulin lispro produced earlier and greater peak serum concentrations of insulin and improved postprandial glycemic control [64]. Pretreatment also reduced the rate of hypoglycemic episodes over CSII use alone. Co-mixtures or co-formulations of commercial rapid acting insulin analogs with rHuPH20 have also demonstrated benefits over insulin use alone. Although postprandial glycemic excursions did not differ between coadministered recombinant human insulin and rHuPH20 versus insulin lispro alone in individuals with T1DM [65], a separate study showed that coadministration of rHuPH20 with insulin lispro improved postprandial glycemic control in those with T2DM [66].

New generation of insulins in development

Smart insulins

The rationale behind the discovery of smart insulins is to release insulin into the circulation depending on the ambient blood glucose level, to maintain tight glycemic control. Smart insulins are small molecules containing both an aliphatic moiety and a phenylboronic acid (PBA) moiety [67]. The incorporation of PBA provides a glucose-sensing element within the conjugate. The end product is a glucose-sensing, soluble, and circulating modified insulin molecule. Animal studies have demonstrated enhanced responsiveness to glucose challenge in mice with diabetes and a reduction in hypoglycemic index in healthy mice [67]. There are plans to investigate smart insulins in human trials that can lead to their integration with insulin pumps, infusion devices, or controlled release materials to improve performance further.

Adjunctive therapies

Although insulin therapy is the cornerstone of diabetes treatment, the investigation and application of adjunctive therapies, primarily developed for T2DM, has recently allowed a multipronged

approach to afford targeted glycemic control in the T1DM population. Benefits of adjunctive therapy include the potential to achieve more targeted glycemic control, often in the setting of reduced insulin doses and weight loss. Below, the mechanism of action, currently available preparations, relevant side effects, and preliminary studies of these adjunctive agents in persons with T1DM are summarized for metformin, GLP-1 agonists, DPP-4 inhibitors, and SGLT inhibitors (see Chapter 31).

Metformin

Metformin is an oral agent commonly used in T2DM that improves glycemia by several mechanisms, including lowering hepatic glucose output and increasing peripheral uptake of glucose, especially in the muscle [68]. A recent meta-analysis showed that metformin treatment significantly reduced insulin doses but had no effect on HbA_{1c} levels in adults with T1DM, but the use of this agent in youth with T1DM has never been adequately studied. Pediatric investigators in the T1DM Exchange recently reported the results of a 6-month, multicenter, placebo-controlled randomized trial to assess the effect of the addition of 2000 mg of metformin per day to basal/bolus insulin treatment in 140 overweight/obese adolescents with T1DM with baseline mean HbA_{1c} levels of 8.8% [69]. Although youth in the metformin treatment group were able to reduce total daily insulin doses by ~0.1 U/kg/day and gained ~2.0 kg less weight than the control group, the results did not support the use of metformin with adolescents to improve glycemic control [69]. Rather than lowering HbA_{1c} levels, there was a modest increase to 9.0% in both the metformin and placebo treatment groups by the end of the 6-month study [69].

GLP-1 receptor agonists

GLP-1 is an incretin hormone released from the L cells of the distal small bowel. It suppresses glucagon, stimulates glucose induced insulin secretion, and inhibits postprandial gastric emptying. Although endogenous GLP-1 has a very short half-life, exogenous GLP-1 administration has shown similar effects, slowing gastric emptying, improving postprandial hyperglycemia, and lowering postprandial glucagon levels in people with T1DM [70–76]. Recently, a 12-week randomized, double-blind, placebo-controlled study of liraglutide, a GLP-1 receptor agonist, showed no benefit with regard to glycemic control despite those treated with liraglutide having a significant reduction in body weight (-3.13 ± 0.58 vs. $+1.12 \pm 0.42$ kg, $p < 0.0001$) with a concomitant reduction in bolus insulin doses ($p = 0.02$).

The role of GLP-1 receptor agonists in the propagation and prolongation of β-cell life is an area of investigation [77]. Additionally, this therapy has been approved for use in the treatment of obesity and studies investigating their utility in the treatment of obese children without diabetes are under way [78].

Currently, GLP-1 receptor agonists are not FDA approved for use in conjunction with insulin therapy in T1DM. Formulations currently on the market for the treatment of adults with T2DM include twice-daily injections of exenatide, daily liraglutide, and weekly albiglutide, dulaglutide, and extended-release exenatide. Common side effects are gastrointestinal symptoms including nausea and vomiting. Although postmarketing reports demonstrated rare cases of fatal and non-fatal hemorrhagic or necrotizing pancreatitis, more recent examination of the data has not borne out this concern [79].

DPP-4 inhibitors

Endogenous DPP-4 swiftly degrades GLP-1, glucose-dependent insulinotropic polypeptide (GIP), and other peptides [80]. DPP-4 inhibitors prolong the action of endogenous GLP-1, leading to multiple favorable glycemic effects; however, they have a smaller effect on weight and gastric emptying than GLP-1 receptor agonists [80].

Currently, FDA-approved DPP-4 inhibitors include sitagliptin, saxagliptin, linagliptin, and alogliptin, and comparison of these agents in people with T2DM has shown similar benefits and safety data across the different DPP-4 inhibitors [81]. Notably, these medications are oral agents and tend to have fewer gastrointestinal side effects than GLP-1 receptor agonists.

Application of DPP-4 inhibitors in addition to insulin therapy in persons with T1DM has been explored. Ellis et al. investigated the use of sitagliptin in addition to subcutaneous insulin therapy in persons with T1DM in a double-blind, placebo-controlled trial over an 8-week period [82]. They demonstrated that mean 24-h sensor glucose and postprandial glycemic control based on blinded continuous glucose monitor data were significantly improved with sitagliptin despite a reduction in prandial insulin doses. In a mechanistic study, Garg et al. examined sitagliptin in a double-blind, placebo-controlled trial in 141 participants with T1DM and demonstrated that the use of sitagliptin increased endogenous GLP-1 levels, while suppressing both GIP and glucagon [83]. However, this did not lead to a difference in HbA_{1c} levels, insulin dose, or weight after 16 weeks of treatment.

Additionally, the Restore Pancreatic Beta-Cell Function in Recent-Onset T1D Trial (REPAIR-T1D) explored whether the use of sitagliptin in conjunction with lansoprazole could lead to β-cell preservation in individuals with recent-onset T1DM based on promising findings in the non-obese diabetic (NOD) mouse [84]. However, no improvement in endogenous insulin production, as measured by C-peptide area under the curve (AUC) during a 2-h mixed-meal tolerance test, was demonstrated [84].

SGLT inhibitors

SGLT inhibitors transfer sodium down its concentration gradient while transferring glucose against its concentration gradient by acting as a cell-membrane symporter [85]. SGLT-2 is responsible for reabsorption of 90% of filtered glucose in the proximal renal tubule; whereas SGLT-1 has similar activity in the kidney, but also acts in the enterocytes of the small intestine to absorb glucose [85]. Orally active SGLT-2 inhibitors lower the renal threshold for glucose and thereby increase urinary glucose excretion [86], a mechanism for lowering glucose that is independent of insulin [86, 87].

Phase III clinical trials of SGLT-2 inhibitors in adults with T2DM have shown glucosuria of at least 50 g per day [85]. Decreases in fasting plasma glucose, postprandial glucose, and HbA_{1c} have been observed with SGLT-2 inhibitor treatment in adults with T2DM [85]. SGLT-2 inhibitors are generally well tolerated, with higher rates of genital mycotic infections compared with placebo [88].

Recent investigations have focused on the use of SGLT-2 inhibitors as an adjunct to insulin therapy in individuals with T1DM. In an 8-week proof-of-concept open-label study of empagliflozin, participants showed a lowering of their mean HbA_{1c}, fasting glucose, and total daily insulin dose while experiencing weight loss [89]. Similar results were seen in a study of 75 participants randomized to either once-daily empagliflozin 2.5, 10, or 25 mg or placebo over a 4-week period [90]. Moreover, a 24-week study of dapagliflozin in 12 participants confirmed the lowering of mean HbA_{1c} and fasting glucose; however, neither weight loss nor insulin dose reduction was observed [91].

To date, the FDA has approved the use of canagliflozin, dapagliflozin, and empagliflozin as oral SGLT-2 inhibitors for the treatment of T2DM in adults. Although the use of SGLT-2 inhibitors as agents for treatment of T2DM and T1DM is promising, total daily insulin doses may have to be reduced by 20–30% during treatment. Such decreases in insulin requirements may, in turn, increase rates of lipolysis and make insulin-requiring subjects prone to more rapid development of diabetic ketoacidosis (DKA). Indeed, the FDA has recently published a warning that people with T2DM treated with insulin may be at greater risk for DKA when treated with SGLT-2 inhibitors [17]. Further exploration of the metabolic decompensation that may occur with these agents is warranted.

Exploration of a dual SGLT-1/SGLT-2 inhibitor, sotagliflozin (LX4211), has been explored in persons with T1DM. Initial investigation of this agent demonstrated decreased fasting plasma glucose, postprandial glucose, HbA_{1c}, and insulin dose, and a reduction in body weight [92]. Additionally, sotagliflozin may have beneficial effects on increasing endogenous incretin secretion [93].

Artificial pancreas development

Despite the now widespread use of small, precise, and reliable continuous subcutaneous insulin pumps, and increasingly popular and accurate continuous subcutaneous real-time glucose sensors, the majority of people with T1DM still suffer from average glucose levels above recommended targets and/or unacceptably high rates of severe hypoglycemia [4]. Although the initial studies of an artificial pancreas began over 40 years ago with a feedback-controlled intravenous glucose sensing and insulin delivery device [94, 95], it is only recently that the accuracy, precision, miniaturization, and wireless communication of these devices have made the dream of developing truly portable, closed-loop systems to control glucose levels automatically in persons with diabetes a possibility. This section highlights some of the important studies along the pathway to a fully-automated, closed-loop treatment for people with T1DM.

Limitations of sensor-augmented pump therapy

Large-scale studies evaluating the efficacy of continuous glucose sensors (Juvenile Diabetes Research Foundation [JDRF] Continuous Glucose Monitoring Trial) and combination sensor-augmented pump therapy (Sensor Augmented Pump Therapy for A_{1c} Reduction [STAR-3]) demonstrated the benefits and also the limitations of these devices when used in an open-loop format. In the JDRF CGM trial, 322 adults and children aged 8 years and older with T1DM were randomized either to add a continuous glucose sensor to their usual diabetes management or to remain on their usual regimen of self-monitoring of blood glucose (SMBG). Whereas HbA_{1c} levels decreased by 0.5% in the adult cohort, no significant benefit of CGM over routine SMBG was seen in the child and adolescent cohorts [3]. This disappointing finding can best be explained by the inability of the two younger groups to wear the sensors effectively on a near-continuous basis: a post hoc analysis of the primary data illuminated that in every age group, those who used CGM on an average of six or more days per week had significant reductions in HbA_{1c} levels compared with control participants [96]. In the Medtronic-sponsored STAR-3 trial, which compared the use of sensor-augmented insulin pump therapy with basal-bolus regimens and SMBG, significant treatment group differences were seen at 1 year in all age groups: a 0.6% difference in the entire cohort, 0.5% in the preadolescents, and 0.7% in the adolescents [97, 98]. As in the JDRF CGM trial, the amount of sensor use correlated with the magnitude of HbA_{1c} reduction. Studies of CGM in very young children with diabetes demonstrated high degrees of parent satisfaction but little beneficial effect on HbA_{1c} levels [99, 100].

Taken together, these results suggest that sensor-augmented pump therapy in an open-loop platform has only a limited benefit in individuals with T1DM. Human control of sensor-augmented pump therapy necessitates frequent, almost continuous, surveillance of the system in order to optimize control, and human decisions regarding insulin dose administration are subject to both human judgment error and neglect. The true power of continuous glucose sensors can only be fully realized in a closed-loop platform, in which real-time feedback of current glucose levels allows for minute-to-minute modulation of insulin delivery, thereby removing (or at least relegating to the background) the attention of the user. Such systems depend on control algorithms, which determine the insulin delivery at any given point in time. Systems may be considered *completely* closed-loop if insulin delivery is determined solely by the algorithm based on the glucose levels, without any manual user interaction to the system. *Hybrid* or *partial* closed-loop systems allow for additional information to be provided to the controller algorithm based on the current activity of the user, such as initiation of a meal, exercise, or addition of manual insulin administration. The potential of closed-loop systems to improve diabetes control lies in its ability to perform the necessary functions precisely, accurately, and continuously,

allowing the user the relatively limited responsibility of ensuring the proper calibration of the sensor, patency of the infusion site, and viability of the wireless communication between devices.

Low-glucose (threshold) suspend

The simplest level of feedback control is to have the pump automatically suspend basal insulin infusion in the setting of hypoglycemia. Such a system does not require a sophisticated control algorithm to determine insulin delivery, or even to predict hypoglycemia, only to trigger a suspension of the pump when the sensor reads below a certain predetermined threshold value. These "low-glucose suspend" systems have been compared to an automobile's airbag: although the airbag does not prevent an accident, it at least mitigates the human injury. By the same token, the low-glucose suspend feature does not prevent hypoglycemia, but limits its duration and/or magnitude. Given the greater risk for severe hypoglycemia at night [2, 101, 102], identification that most people fail to wake to respond to alarms at night [103], and that seizures typically occur after a prolonged period of hypoglycemia [104], such a feature could significantly reduce the occurrence of severe nocturnal hypoglycemia and seizures, since pump suspension would be triggered automatically. Sensor-augmented pumps that automatically suspend basal insulin delivery for up to 2 h ("threshold suspend") are now widely available for people with T1DM. An in-clinic study using programmed exercise to induce a drop in blood glucose demonstrated the effectiveness of the threshold-suspend feature to reduce the magnitude and duration of hypoglycemia [105]. A subsequent 3-month in-home clinical trial involving 247 adults with T1DM demonstrated a 38% reduction in the AUC for exposure to nocturnal hypoglycemia and a 31% reduction in nocturnal hypoglycemia events with the use of a threshold-suspend system, without a deterioration in HbA_{1c} [106].

Predictive low-glucose suspend

Whereas the aforementioned low-glucose suspend systems are activated only after a hypoglycemic threshold has been achieved, a more desirable feature would be to suspend insulin delivery *before* the threshold is reached, thereby averting hypoglycemia altogether. A *predictive* pump suspension algorithm has been evaluated in several adult and pediatric studies and shown to reduce the magnitude and duration of hypoglycemia. Initial inpatient studies by Buckingham et al. with a bedside system utilizing a series of parallel prediction algorithms, a hypoglycemia threshold of 80 mg/dL, and an alarm horizon of 35 min, showed that such a system could prevent up to 75% of induced hypoglycemia [107]. More recent in-home studies incorporating a simpler hypoglycemia prediction scheme with a glucose threshold of 80 mg/dL and an alarm horizon of 30 min randomized 45 adolescents/adults and 82 children to have the predictive suspend feature randomly engaged or disengaged for up to 6 weeks of wear. It was found that episodes of sensor glucose levels <60 mg/dL were lower on suspend nights than control nights (21% compared with 33%), and that the median hypoglycemia AUC was reduced by 81% on suspend nights [108]. In children, time spent with night-time sensor glucose levels <70 mg/dL were reduced from 10.1 to 4.6% in the 11–14-year-old cohort and from 6.2 to 3.1% in the 4–10-year-old cohort (p <0.001) [109].

Closed-loop algorithm considerations

All of the studies discussed so far were conducted within an open-loop platform, with varying degrees of closed-loop intervention based on the achievement of certain clinical conditions, such as actual or predicted low sensor glucose levels. In a "true" closed-loop platform, the default condition would be automated insulin delivery based on the sensor glucose input and the control algorithm, with manual intervention at certain points to inform the controller of behavioral conditions, such as meals or exercise.

The key component of a closed-loop system is the algorithm controller; the two most commonly utilized algorithms are proportional integral derivative (PID) and model predictive control (MPC). PID algorithms determine insulin delivery solely on three components: deviation of the current glucose level from the set point (proportional); the integrated AUC between the current glucose and set point (integral); and the rate of change of the current glucose from the prior measurement (derivative) [110, 111]. PID algorithms are essentially *reactive*, responding only to glucose levels. Modifications to strict PID algorithms to account for the amount of insulin already delivered at any given moment have been incorporated into PID systems to improve performance [112–114]. MPC algorithms, on the other hand, attempt to account for many clinical variables in addition to the glucose levels, such as the delays between previously administered insulin, the rate of carbohydrate absorption, and effect of physical activity [115–118]. Insulin delivery in an MPC algorithm is iterative; calculated to achieve a target in the future based on a series of controller "moves" in a prediction window. Other algorithmic approaches to closed-loop control include "fuzzy logic" control [119], fuzzy logic combined with individualized learning algorithms [120], fading memory proportional derivative control [121], and combinations of PID and MPC controllers for dual hormonal systems [122].

Early-phase/inpatient closed-loop studies

The first human study of a closed-loop system utilizing subcutaneous glucose sensing and subcutaneous insulin delivery was performed by Steil et al. at Medtronic and UCLA [123]. In 10 adult with T1DM studied over 30 h of fully closed-loop control, 75% of glucose levels were controlled within target (70–180 mg/dL), but late postprandial hypoglycemia was common. Similar findings were observed in a follow-up pediatric study at Yale University, conducted in 17 adolescents over 36 h of closed-loop control [124]. Glucose control was excellent overall: 85% of glucose values were within the target range of 70–180 mg/dL. This study also described the effect of "hybrid" control, in which at least part of the meal insulin requirements were provided with a manual insulin bolus. Hybrid control resulted in improved postprandial glycemia,

undoubtedly due to the more rapid delivery of insulin to cover ingested carbohydrates. Most closed-loop systems in development today utilize a hybrid approach to glucose control.

Other early approaches to closed-loop control focused entirely on overnight control only. Hovorka's group at the University of Cambridge has extensively characterized the efficacy and safety of an MPC-based closed-loop system, demonstrating improved time-in-target and reduced exposure to hypoglycemia in children [125] and adults [126], and preliminary efficacy was demonstrated in studies of pregnant women [127, 128]. In a multinational study, Kovatchev et al. at the Universities of Virginia, Padova, Montpellier, and Pavia also used an MPC-based algorithm to demonstrate improved overnight blood glucose levels and reduced frequency of hypoglycemia in 20 adult with T1DM during closed-loop control compared with open-loop pump treatment [129]. Phillip et al. and the DREAM Project team used a fuzzy logic controller with an individualized learning module to control safely blood glucose levels overnight, nearly tripling the time in the target range without hypoglycemia [130, 131].

All of the systems discussed up to this point utilized only insulin. Several groups have investigated the feasibility of dual hormonal closed-loop systems employing insulin and glucagon in separate pumps, under individual algorithmic control: Damiano et al. [132], employing an MPC-based algorithm for insulin and a PID-based algorithm for glucagon; Castle et al. [133], using a fading memory proportional derivative algorithm for both insulin and glucagon; Haidar et al. [134], using a fuzzy logic model-based predictive technique; and Van Bon et al. [135], using a proportional derivative algorithm. Our group has explored the use of pramlintide and liraglutide as a means to mitigate prandial glycemic excursions in a fully automated closed-loop insulin delivery system without manual meal announcement and found reductions in prandial glucose peaks and AUC [114, 136].

Outpatient studies

The success of these inpatient feasibility studies and the development of technologies to allow for portability of the controller devices (e.g. moving the algorithms from a laptop to smartphone or tablet) have enabled closed-loop research studies to escape the confines of the clinical research facility and undergo testing in more challenging environments such as home or camp, in which meals and physical activity are less regulated and predictable.

One of the first outpatient studies of a closed-loop system was conducted by Phillip et al. in 56 children in three centers during two consecutive nights at a summer camp. Hypoglycemic episodes were reduced by 30%, without deterioration of overnight mean glucose [137]. Use of this system for up to 6 weeks in the home setting was associated with a 22% increase in time in target range, a 40% reduction in hypoglycemia, and a 50% reduction in time spent with glucose >240 mg/dL [138, 139]. Similarly, a closed-loop system developed by Kovatchev et al. and tested initially in short feasibility studies [140, 141] was also shown, in a six-night camp study, to improve time in target range from 52 to 73% and a reduction of nocturnal hypoglycemia in a cohort of 20 children and adolescents randomized to overnight closed-loop versus open-loop sensor-augmented pump therapy comparator [142].

The longest studies of closed-loop control were conducted by Hovorka's group at the University of Cambridge. Randomized controlled crossover trials of overnight closed-loop compared with sensor-augmented open-loop pump therapy were conducted in 24 adults for 4 weeks and in 16 adolescents for 3 weeks and showed an 18% increase in time in target range, lower mean glucose levels, and reduced exposure to hypoglycemia [143, 144]. Most recently, this group has demonstrated the safety and effectiveness of day *and* night closed-loop control in 33 adults and 25 adolescents over 12 weeks [145]. The adult cohort utilized closed-loop control for day- and night-time periods, with full manual meal boluses, whereas the adolescent cohort used closed-loop control at night only and open-loop sensor-augmented pump therapy during the day. In both cohorts, time in the target range was significantly improved for both overnight and full-day periods, despite the fact that adolescents were on open-loop control during day, highlighting the importance of nocturnal control in optimizing control on the subsequent day. As expected, closed-loop control also reduced hypoglycemia in both cohorts, and in the adult group it also reduced HbA_{1c} [145].

Outpatient bihormonal control with insulin and glucagon was studied by Russell et al. in two parallel studies in 20 adults and 32 adolescents in supervised hotel and camp environments, respectively, over 5-day periods. An alternative approach to meals was used in these studies, using a semiquantitative announcement that did not require exact carbohydrate counting. In both cohorts, both mean glucose and time in range were significantly improved and, in the adult cohort only, time spent in hypoglycemia was significantly reduced [146]. For these studies, aqueous glucagon was prepared fresh daily for delivery in the pump. Future studies of this system will benefit from stable liquid forms of glucagon that will not form amyloid fibrils and insoluble gels, which would occlude insulin pump catheters, after prolonged reconstitution [147].

Extended large-scale multicenter home-use studies of closed-loop systems are now being conducted by industry and academic centers across the world, which will provide the necessary safety and efficacy data for regulatory approval of these devices in the coming years. Regardless of the particular system under study, further research into human factors and long-term effects on complications and quality of life will be needed to optimize the potential of the artificial pancreas in improving the health outcomes of people with T1DM.

Improved glucagon preparations

Unlike insulin therapy, which has evolved since its discovery nearly a century ago, therapeutics directed towards correction of severe hypoglycemia have remained stagnant since injected

glucagon for treatment of severe hypoglycemia was introduced in the 1950s [148]. Current commercially available glucagon emergency kits require an eight-step process to reconstitute the lyophilized powder in a diluent immediately prior to injection given the propensity for fibril formation once the solution is mixed [149]. Recently, explorations of new formulations and modalities to deliver glucagon therapy have been explored.

Stable liquid preparations

With the development of dual hormone closed-loop delivery systems as described above, the need for a soluble formulation of glucagon for use in such systems for commercial application of this product is necessary. Recent studies have demonstrated the stability of aqueous formulations of glucagon, which show no fibril formulation after 7 days [150, 151]. Indeed, further studies have demonstrated that a stable non-aqueous glucagon formulation shows minimal chemical degradation and no fibril formulation for >18 months while stored at room temperature [152], and the use of this preparation compared with a commercially available glucagon kit in healthy people without diabetes showed therapeutic equivalence [152].

Administration of mini-dose injected glucagon has been used for the management of sick days and is being explored as an alternative to oral carbohydrate intake for the treatment of mild hypoglycemia [153, 154]. Recent evaluation of non-aqueous, mini-dose glucagon has been conducted in adults with T1DM, demonstrating beneficial effects of 75, 150, and 300 μg, and supports the development of this therapeutic agent for treatment of impending or mild hypoglycemia [155].

Dry powder intranasal preparations

Investigation of the nasal route for glucagon delivery was first reported in 1983 [156]. However, although a number of small studies yielded positive results in healthy volunteers in both adults and children with T1DM, the product was never commercialized [156–164]. Recently, this mode of glucagon delivery has made a resurgence with the development of a novel dry powder glucagon formulation. Delivery of glucagon to the nasal mucosa occurs with a single-use one-step dispensing device that discharges the powder by depressing a plunger connected to a piston. Importantly, individuals who require this therapy would not need to cooperate with its administration or inhale, as the powder is absorbed passively. Rickels et al. investigated the use of this formulation of glucagon in adults with T1DM in whom a 3 mg of dose of intranasal glucagon was found to be as effective as intramuscular glucagon in reversing insulin-induced hypoglycemia [165]. Additionally, examination of intranasal glucagon in the pediatric population has demonstrated it to have similar pharmacokinetic and safety profiles to those seen in intramuscular therapy [166]. Most importantly, based on the studies conducted, it has been concluded that a single 3 mg intranasal glucagon dose can be used in children as young as 4 years old, with no weight- or age-based dose adjustments required [166].

A recent human factors study compared the ability of 16 trained caregivers of persons with insulin treated diabetes to use intramuscular and intranasal devices to treat a simulated episode of severe hypoglycemia [167]. Intranasal glucagon was successfully administered by 94% of caregivers (average time 16 s) whereas injectable glucagon was administered by only half of the caregivers (average time more than seven times that required for intranasal administration) [167]. Two of the caregivers mistakenly injected insulin and only 12% of participants were able to administer the full injectable dose correctly [167]. These data highlight the potential benefit of a glucagon rescue therapy that does not have the same mode of delivery as insulin.

Conclusion

The care of individuals with T1DM is on the precipice of radical change. From improved insulins to the addition of adjunctive therapies, the medications used to treat this condition will better replicate physiological processes, providing people with the opportunity to reach targeted glycemic control. Mechanical solutions in the form of closed-loop delivery systems will provide the means to reach targeted glycemic control while additionally reducing the burden of the disease on the individual. New formulations of glucagon hold the potential to transform how severe hypoglycemia is managed, making the treatment of these episodes less complicated.

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67 Future Drug Treatments for Type 2 Diabetes

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Key points

- Despite a variety of differently acting glucose-lowering agents, many people with type 2 diabetes do not achieve or maintain adequate glycemic control. Hence there is a continued need for new agents.
- The variable etiology and pathogenesis of type 2 diabetes requires a diversity of therapies that can be used in combination.
- Fixed-ratio combinations of glucagon-like peptide 1 (GLP-1) receptor agonists with insulin, and potential hybrid peptides of incretins and other gluco-regulatory hormones, offer the opportunity to interact with several target receptors via a single injection.
- Further incretin-based therapies in development include depot injections of GLP-1 receptor agonists, orally active GLP-1 receptor agonists, and long-acting dipeptidyl peptidase 4 (DPP-4) inhibitors.
- Novel insulin-releasing agents such as fatty acid receptor agonists could improve pancreatic β-cell responses to rising glycemia.
- Proof of principle has been shown for small molecules to mimic and potentiate insulin action.
- Glucagon receptor antagonists, selective peroxisome proliferator-activated receptor (PPAR) modulators, cellular glucocorticoid inhibitors, adiponectin receptor agonists, and fibroblast growth factor 21 analogs have been reported at various stages of development.
- Agents that directly enhance glucose metabolism or suppress glucose production have been described.
- New inhibitors of sodium-glucose co-transporters SGLT-1 and SGLT-2 are advancing in development.
- Emerging pharmacogenomics and proteomics could offer novel therapeutic opportunities.

Introduction

Despite many initiatives to prevent type 2 diabetes mellitus (T2DM), its prevalence continues to rise, accounting for ~95% of the global totality of people with diabetes (~410 million now and projected to be ~640 million by 2040) [1]. Current treatment strategies are reviewed in earlier chapters of this book, and the importance of an early, effective, individualized therapeutic approach to glycemic control is emphasized to defer the onset and reduce the severity of complications. Although many differently acting classes of glucose-lowering agents are already available (Figure 67.1), a sustained return to normal glucose homeostasis is rarely achieved, and more than one-third of people with T2DM do not attain or maintain an acceptable level of glycemic control [2–4]. This chapter reviews some of the new therapeutic approaches under consideration to improve glycemic control in T2DM, including innovative concepts in preclinical investigation through to agents advanced in clinical development.

Development of new antidiabetes agents

The highly variable etiology and pathogenesis of T2DM, which typically involves disturbances in multiple tissues and organ systems, opens the possibility of many potential approaches to blood glucose control [5]. Some of these approaches directly target underlying pathophysiological defects such as insulin resistance and pancreatic β-cell dysfunction, but interventions that improve glycemic control by any safe means should reduce the risk of complications. Because treatments are often life-long and contemporaneous with comorbidities, frailty, multiple pharmacotherapies, and lifestyle challenges, it is important that new agents offer a commendable safety profile, are well tolerated, and are compatible with a broad selection of other medications. Ideally, they will provide durable and additive glucose-lowering efficacy to existing agents through different but complementary modes of action, while carrying minimal risk of serious hypoglycemia. Additional capability to reduce adiposity and improve other modifiable cardiovascular

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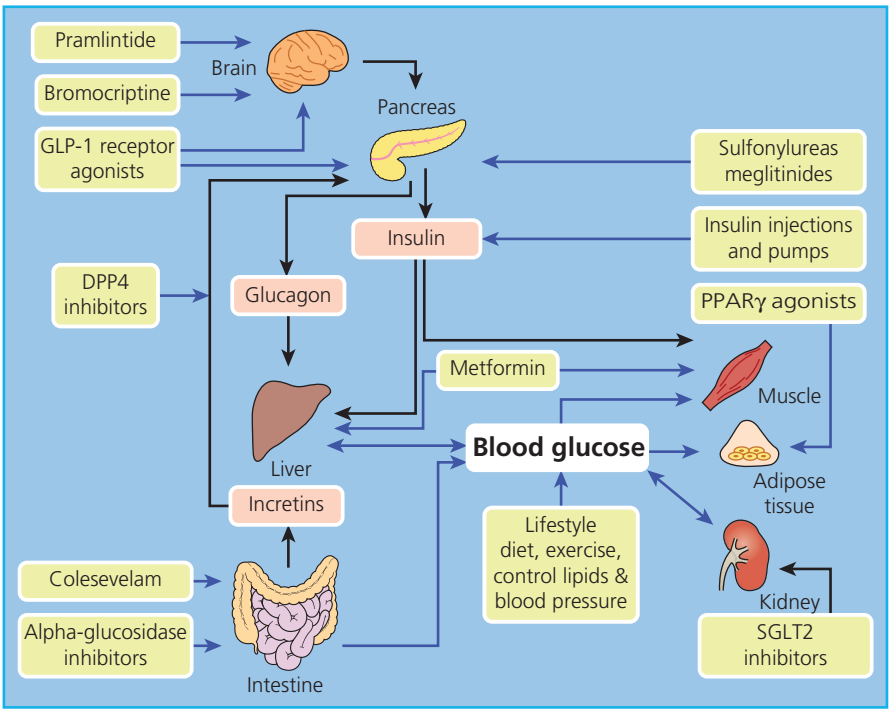

Figure 67.1 Current glucose-lowering therapies showing their main sites of action. Not all classes of therapies are indicated for the treatment of T2DM in all regions. GLP-1, glucagon-like peptide-1; PPAR, peroxisome proliferator-activated receptor; SGLT2, sodium–glucose co-transporter 2.

risk factors such as dyslipidemia and hypertension would also be preferred.

Identifying a new chemical entity and progressing it through the preclinical and clinical phases of development to marketing approval are likely to take at least 10 years (Table 67.1). The cost is expected to exceed US$1 billion, and an average cost was recently estimated to be US$2.6 billion [6]. For glucose-lowering drugs, post-authorization safety studies to monitor cardiovascular outcomes and other events may be required. Further development may be undertaken for additional indications and to produce new formulations, including single-tablet fixed-dose combinations or fixed-ratio injection combinations [7].

Modifiers of carbohydrate digestion and absorption

Dietary fiber supplements to delay the digestion and absorption of carbohydrates have generally achieved only modest reductions of postprandial hyperglycemia with small "carry-over" reductions in basal glycemia [8]. These mostly comprise soluble and/or insoluble plant polysaccharides that are not digested and form either bulky viscous gels and gums or a coarse insoluble matrix (Table 67.2). By reducing diffusion within the lumen of the small intestine. they entrap carbohydrates, impeding entry of digestive enzymes and restricting access of saccharides to the intestinal epithelium. Fiber supplements are conveniently used in conjunction with most other classes of glucose-lowering pharmacotherapies, including insulin, and the extended period of digestion can usefully reduce interprandial hypoglycemia in insulin-treated individuals.

Inhibitors of α-amylases to slow the hydrolysis of starch have not given predictable effects, and supplements containing "active" bacteria or fungal products that might modify carbohydrate digestion and absorption have not shown consistent efficacy in the limited studies to date [9]. Competitive inhibitors of brush-border α-glucosidases such as acarbose, miglitol, and voglibose are well established therapies to slow the last stages of carbohydrate digestion [10]. They require dose titration against the amount of complex carbohydrate in the diet to prevent undigested sugars from entering the large bowel, where bacterial fermentation can produce various gases, fatty acids, and osmotically active glucose, causing flatulence and diarrhea as side effects. Inhibition of sodium–glucose co-transporter 1 (SGLT-1) in the intestinal brush border provides another option to slow the absorption of glucose. This is considered further in a later section.

Supporting pancreatic β-cell function

Disturbances of pancreatic β-cell function occur early in the pathogenesis of T2DM and β-cell failure is a prominent feature of advanced stages of T2DM, making the β cell a key therapeutic target. Agents that initiate insulin secretion (sulfonylureas and meglitinides) or potentiate nutrient-induced insulin secretion (dipeptidyl peptidase 4 [DPP-4] inhibitors and glucagon-like peptide 1 [GLP-1] receptor agonists) are widely used in the treatment of T2DM (see Chapters 31 and 32). These agents partially compensate for the loss of an adequate first-phase insulin response in T2DM, while enhancing the second phase of secretion and improving the secreted proportion of insulin relative to proinsulin. However, risks of hypoglycemia and weight gain are

Table 67.1 Stages in the development of a new drug.

Preclinical stages

New chemical entity

- Identification, extraction/synthesis, chemical characterization, and patenting of compounds
- Genotoxicity testing: screening for biological activity *in vitro* and *in vivo* in animals
- Preclinical pharmacology, mode of action, pharmacodynamics (activity, safety, tolerance), pharmacokinetics (bioavailability, distribution, metabolism, elimination) and toxicity in ≥2 mammalian species

Clinical stages

Investigational new drug application: permission to begin clinical studies

Phase I

- First administration to a small number of healthy human volunteers
- Dose ranging, vital signs, pharmacodynamics, pharmacokinetics, drug interactions, safety

Phase II

- First trials in small numbers of people with the condition
- Dose ranging, efficacy, further pharmacodynamics, pharmacokinetics, and safety

Phase III

- Trials in larger numbers of people with the condition
- Multicenter trials, comparative trials with other treatments, efficacy, further pharmacodynamics and safety (including meta-analysis of cardiovascular outcomes)

New drug application: permission to market as a drug

Phase IV

- Use in medical practice
- Additional trials (similar to phase III) for long-term efficacy and safety, and use in special subgroups (e.g. elderly people), postmarketing surveillance and adverse drug reactions

frequently cited limitations of sulfonylureas and meglitinides. For DPP-4 inhibitors, the magnitude of the glucose-lowering effect may be initially less than for sulfonylureas, but there is low risk of hypoglycemia or weight gain. GLP-1 receptor agonists offer efficacy, durability, weight loss, and low risk of hypoglycemia, but present agents require subcutaneous injection and some individuals do not respond or experience nausea. Although there is preclinical evidence of β-cell preservation and increased insulin biosynthesis with GLP-1 receptor agonists, these properties have yet to be demonstrated equivocally in T2DM [4].

Table 67.2 Soluble and insoluble fiber supplements.

Soluble fiber	Insoluble fiber
Gums	Celluloses
Pectins	Wheat bran
Hemicelluloses	
Mucilages	

Many compounds with insulin-releasing properties have received preclinical and early clinical investigation, but targeting the pancreatic β cells to the exclusion of other cell types has been particularly challenging, and few lead compounds have proceeded further in development [11]. Included here are agents that increase adenosine triphosphate (ATP) production, close K^+ATP channels, depolarize the β-cell membrane, increase cytosolic calcium, enhance cyclic adenosine monophosphate (cAMP) or protein kinase C (PKC), activate imidazoline receptors, or suppress α_2-adrenergic receptors.

Glucokinase activators

Agents that allosterically activate the glucose phosphorylating enzyme glucokinase (GK) (EC 2.7.1.1) continue to attract interest as a means of initiating insulin secretion by increasing β-cell glucose metabolism (Figure 67.2). Despite many promising preclinical accounts, this approach is prone to precipitate hypoglycemia and often incurs loss of efficacy after several months of treatment in human T2DM [12, 13]. Glucokinase is also expressed in the liver, where it is regulated differently to pancreatic β cells, being activated when the influx of glucose dissociates the enzyme from a regulatory binding protein. GK in the liver does not require such rapid activation and deactivation as GK in pancreatic β-cells, and can be chronically upregulated by agents that prevent its association with or cause its dissociation from the inhibitory binding protein [14]. Several such hepato-selective GK activators are under investigation to increase hepatic glucose uptake while avoiding hypoglycemia, but the risk of excess glycogen deposition and increased lipogenesis in the liver has yet to be evaluated in human T2DM.

Fatty acid receptor agonists

Pancreatic β cells express G protein-coupled receptors for various fatty acids, notably GPR40 (FFAR1) and GPR119. Small-molecule agonists of these receptors can enhance insulin secretion in different ways [15] (Figure 67.2). Activation of GPR40 generates intracellular signals via phospholipase C, which raises cytosolic Ca^{2+} by redistribution from endoplasmic stores, and also increases isoforms of PKC that augment insulin exocytosis. Thus GPR40 agonists can partially initiate insulin secretion and also potentiate the release of insulin initiated by nutrients. Although a GPR40 agonist (TAK-875) was recently discontinued owing to hepatic side effects, the glucose-lowering efficacy of this approach was confirmed in human T2DM, and other GPR40 agonists continue in development [16]. Activation of GPR119 signals via adenylate cyclase to increase cAMP and potentiate nutrient-induced insulin secretion in a similar way to GLP-1 [17]. Both GPR40 and GPR119 are expressed by several types of enteroendocrine cells (e.g. K cells, L cells, and I cells), hence agonists for these receptors can increase the secretion of glucose-dependent insulinotropic peptide (GIP), GLP-1, polypeptide YY (PYY), oxyntomodulin, and cholecystokinin, potentially enhancing the incretin effect and promoting satiety [18]. Also, the activation of GPR40 receptors expressed by

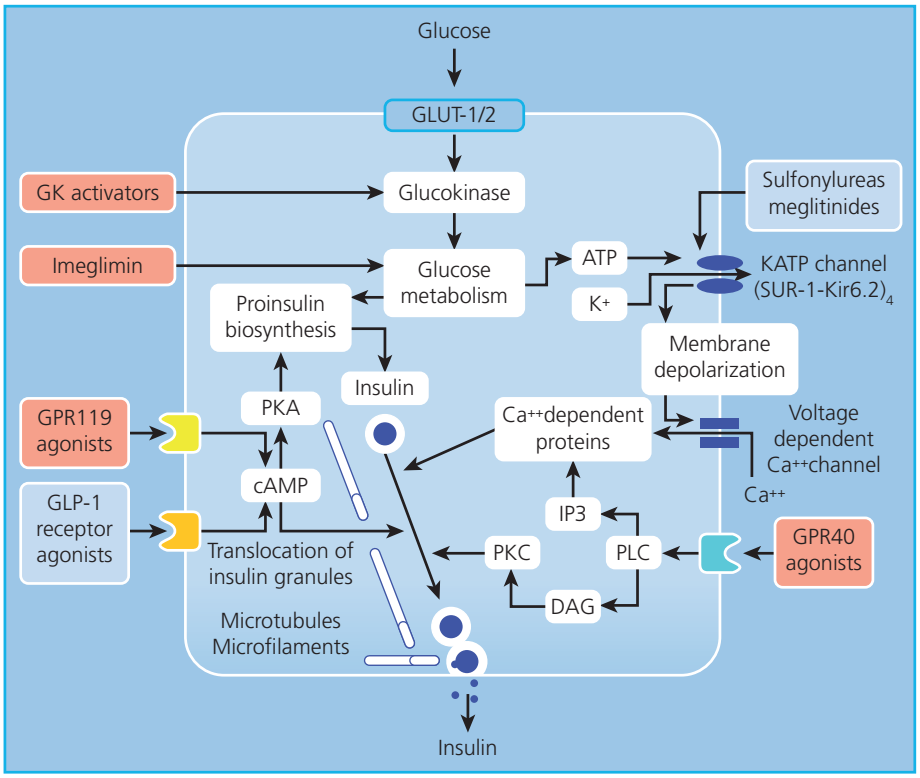

Figure 67.2 Mechanisms of action of insulin-releasing agents on pancreatic β cells. Glucose is taken up by the pancreatic β cells in proportion to the circulating concentration. The glucose is metabolized to produce ATP, which closes the Kir6.2 pores of ATP-sensitive potassium channels (K_{ATP} channels). This prevents elimination of potassium from the cell, causing localized membrane depolarization that opens voltage-dependent calcium channels. The influx of Ca^{2+} raises the cytosolic Ca^{2+} concentration, which activates calcium-dependent proteins that promote the translocation of insulin granules to the plasma membrane for exocytosis. Sulfonylureas and meglitinides initiate insulin release mainly by binding to sites on the sulfonylurea receptor-1 (SUR1), which forms part of the Kir6.2 complex. Activated GLP-1 receptors and GPR119 receptors increase adenylate cyclase activity, which raises cAMP concentrations while GPR40 receptors agonists are functionally linked to PLC. GK activators increase glucose flux into glycolysis and imeglimin acts on mitochondria. ATP, adenosine triphosphate; cAMP, cyclic adenosine monophosphate; DAG, diacylglycerol; GK, glucokinase; GLUT, glucose transporter isoform; GLP-1, glucagon-like peptide 1; GPR, G-protein-coupled receptor; IP3, inositol trisphosphate; K_{ATP}, ATP-sensitive potassium channel; Kir, inwardly rectifying potassium channel; PKA, protein kinase A; PKC, protein kinase C; PLC, phospholipase C; SUR, sulfonylurea receptor.

pancreatic α cells has been reported to reduce glucagon secretion, whereas GPR119 agonists may raise glucagon levels [19, 20]. Another fatty acid receptor, GPR120 (FFAR4), is expressed mainly by adipose tissue. Agonists of GPR120 promote adipogenesis and appear to improve glucose tolerance by increasing insulin sensitivity and reducing ectopic fat [21].

Imeglimin

Imeglimin is a triazine compound that alters mitochondrial energetics, possibly by delaying the opening of mitochondrial permeability transition pores. Studies in individuals with T2DM have shown it to assist glucose-induced insulin secretion and also improve insulin sensitivity and reduce hepatic glucose production [22].

Incretins

The main incretin hormone, GLP-1, potentiates nutrient-induced insulin secretion, suppresses glucagon secretion at raised glucose concentrations, delays gastric emptying, and exerts a satiety effect that assists weight control (Figure 67.3). GLP-1 is rapidly inactivated by the enzyme DPP-4, hence therapeutic GLP-1 receptor agonists are designed to protect against degradation by DPP-4. Currently available GLP-1 receptor agonists are administered by subcutaneous injection: exenatide (twice daily and weekly), liraglutide and lixisenatide (once daily), and dulaglutide and albiglutide (weekly).

Since continuously raised GLP-1 levels achieved with once-weekly administered GLP-1 receptor agonists permit substantial lowering of HbA_{1c}, a subcutaneously implanted miniature (matchstick-sized) osmotic pump has been developed to deliver exenatide continuously at up to 80 μg/day for up to 48 weeks. Trials in people with T2DM indicated that doses of ≥40 μg /day typically reduced HbA_{1c} by >1% and weight >3 kg from baseline values of ~8% and ~93 kg, respectively. Nausea was mostly transient, and antibodies that were identified in about 10% of participants did not appear to interfere with efficacy [23]. Other modes of delivery of GLP-1 receptor agonists in development include an oral tablet formulation of semaglutide: this agent

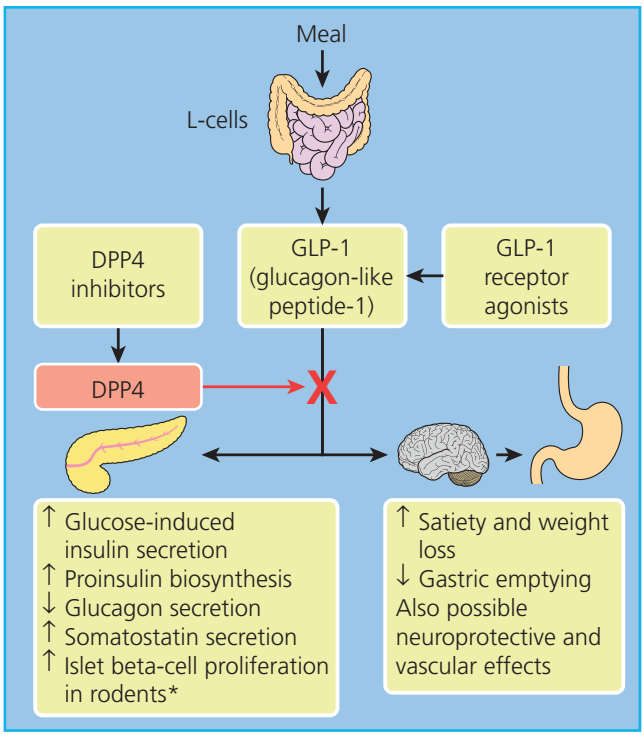

Figure 67.3 Actions of glucagon-like peptide 1 (GLP-1). GLP-1 is the main hormone responsible for the incretin effect (enhanced insulin response to enteral versus intravenous glucose). Intestinal glucose stimulates secretion of GLP-1 by L cells. The effects of GLP-1 on glucose homeostasis include pancreatic effects (increased insulin release and reduced glucagon release, each in a glucose-dependent manner), increased satiety and delayed gastric emptying. GLP-1 is rapidly inactivated by the enzyme dipeptidyl peptidase 4 (DPP-4). DPP-4 inhibitors prolong the activity of endogenous GLP-1. GLP-1 receptor agonists are analogs that are altered to protect against degradation by DPP-4. *Effect seen in preclinical studies but not confirmed in human T2DM.

is already in phase III trials as a once-weekly subcutaneous injection [24]. The GLP-1 receptor can also be activated by various non-peptide molecules that are undergoing preclinical investigation as templates for potential tablet formulations [25].

In view of the complementary actions of GLP-1 receptor agonists (mainly targeting postprandial hyperglycemia) and basal insulin (mainly targeting basal hyperglycemia), mixtures of the two peptides ("fixed-ratio" combinations) have been formulated into the same subcutaneous injection. The first of these combinations (IDegLira) contains liraglutide with insulin degludec in the proportions 3.6 mg : 100 units. The combination is titrated as for basal insulin, and randomized studies in people with T2DM have noted greater reductions in HbA_{1c} with the combination than with either agent alone (e.g. an average fall of 1.8% from a baseline of ~8.3%, compared with a 1.2% fall for liraglutide alone and a 1.4% fall for insulin alone) [26]. Less insulin was required with the combination (mean dose 39 units) than degludec alone (62 units), risk of hypoglycemia was reduced, and weight gain was avoided. Another "fixed-ratio" combination in development (Lixilan) contains lixisenatide with glargine in the proportions 50 μg : 100 units [27].

Hybrid peptides

The substantial improvements in glycemic control and weight reduction after bariatric surgery are associated with changes in the secretion of several gastrointestinal hormones, including increases in postprandial concentrations of hormones from intestinal L cells (GLP-1, $PYY_{3–36}$, and oxyntomodulin), a decrease in ghrelin, and inconsistent changes in GIP and gastrin [28]. In principle, therefore, it should be possible to generate similar effects by administering a comparable mix of these peptides with or without receptor antagonists for those peptides to be suppressed. The possibility of adding other peptides that affect gluco-regulation, food intake, and energy expenditure, such as glucagon and leptin, has also been considered. To avoid the problems associated with mixtures of peptides or giant combinatorial peptides, several hybrid peptides have been synthesized and tested [29, 30]. To date, these have mostly comprised selected epitopes from two or three peptides, introducing modifications to prevent degradation by DPP-4 and to provide stability. For example, hybrid peptides with agonist effects at the GLP-1, GIP, and glucagon receptors have shown glucose-lowering and weight-lowering activity in preclinical studies, and adjustments to the design may be envisaged to modify receptor binding affinities and potencies mediated through these receptors to amplify desired effects (Figure 67.4) [31, 32]. Parenthetically, to account for the inclusion of glucagon epitopes in these hybrids, it is noted that although glucagon raises blood glucose by increasing hepatic glucose output, it also affects nutrient homeostasis by increasing lipolysis, decreasing appetite, and increasing thermogenic energy expenditure [33]. Thus a hybrid might take advantage of the weight-lowering effects of glucagon if, for example, the effects of the GLP-1 moiety within the hybrid can increase insulin release and suppress endogenous glucagon secretion sufficiently to more than compensate for the hyperglycemic effect of the glucagon. Although subject to considerable physicochemical and immunological restrictions, the concept of hybrid peptides with highly selective agonist and antagonist effects at multiple receptors in a single administration offers an appealing approach to address the multiple pathogenic factors in T2DM.

GLP-1	HAEGTFTSDVSSYLEGQAAKEFIAWLVKGRG
GIP	YAEGTFISDYSIAMDKIHQQDFVNWLLAQKGKKNDWKHNIT
Glucagon	HSQGTFTSDYSKYLDSRRAQDFVQWLMNT
Triagonist	HXQGTFTSD*K*SKYLDERAAQDFVQWLLDGGPSSGAPPPS–NH_2

Figure 67.4 Example of a hybrid peptide. The "triagonist" is a hybrid peptide with functional epitopes that act as agonists for GLP-1, GIP, and glucagon receptors. GLP-1, glucagon-like peptide-1; GIP, glucose-dependent insulinotropic polypeptide. See [32].

DPP-4 inhibitors

Inhibitors of the enzyme DPP-4 (EC 3.4.14.5) are widely used in the treatment of T2DM to prevent the breakdown of endogenous incretins [34]. They include sitagliptin, vildagliptin, saxagliptin, linagliptin, and alogliptin, taken as once-daily (or twice-daily for vildagliptin) tablets. Although these agents extend the biological half-lives of many peptides in addition to incretins, they have been associated with relatively few adverse events, and this has encouraged the development of longer-acting DPP-4 inhibitors [35]. Omarigliptin is advanced in development as a once-weekly DPP-4 inhibitor showing similar efficacy and tolerability to sitagliptin [36]. Trelagliptin is another once-weekly DPP-4 inhibitor in development.

Bile acid receptor agonists

TGR5 (GP-BAR1) bile acid receptors are strongly expressed by intestinal L cells and brown adipose tissue, and stimulation of these receptors can enhance GLP-1 secretion, increase energy expenditure, and lower blood glucose [37]. However, excess TGR5 agonism can exert unwanted effects on gallbladder smooth muscle relaxation, causing over-filling. This has prompted studies with poorly absorbed TGR5 agonists intended to stimulate GLP-1 secretion by L cells located distally along the intestinal tract [38]. Because the TGR5 receptors are mostly located in the basolateral membranes of L cells, activation by agonists in the intestinal lumen may require large doses of these agents.

Inhibitors of glucagon secretion and action

Preclinical studies dating from the 1970s have demonstrated the glucose-lowering efficacy of glucagon antibodies, and later preclinical and clinical studies have assessed the therapeutic potential of peptide glucagon antagonists, glucagon receptor antisense oligonucleotides, and various inhibitors of α-cell glucagon secretion (e.g. somatostatin analogs and non-peptide molecules) [11]. However, none has progressed fully in development, mainly owing to an impaired counter-regulatory response to hypoglycemia. A considerable catalog of small-molecule glucagon receptor antagonists has also emerged, but compensatory hyperglucagonemia, rebound hyperglycemia if therapy is stopped, and unwanted liver effects have complicated therapeutic application [39, 40]. Although it is recognized that glucagon mediates a wide range of biological effects beyond glucose homeostasis, the suppression of glucagon action remains an interesting approach to address the relative hyperglucagonemia of T2DM [41].

Insulin mimetic agents

Insulin resistance is a prominent feature of most forms of T2DM, typically reflecting the cumulative detrimental impact of multiple pathogenic factors that disrupt the signaling activity of insulin receptors and various intermediates along the post-receptor pathways. In most presentations of T2DM other than monogenic forms, the mix of pathogenic factors will vary in make-up and severity between individuals and, during disease progression, complicating the search for agents to override or circumvent the "pinch points" [42]. The binding of insulin to extracellular regions of its receptor involves distant sites on the α subunits of the receptor, which are difficult to replicate using a small molecule [43]. However, the conformational changes produced by insulin binding may be achieved in other ways, as indicated by a monoclonal antibody that interacts with the insulin receptor at different sites to insulin but creates a conformational adjustment to the receptor that initiates some of the metabolic effects of insulin and improves glucose homeostasis in insulin-resistant diabetic animals [44]. Recently, a fungal metabolite (chaetochromin A) has been shown to interact with the extracellular portion of the insulin receptor and initiate insulin action independently of insulin binding to the receptor [45]. The metabolite was also able to synergize insulin-induced phosphorylation of the insulin receptor and reduce blood glucose in diabetic animals. This raises the possibility that small molecules might be able to elicit conformational changes at extracellular sites of the receptor other than those bound by insulin and at least partially mimic the effects of insulin. It may also be possible to by-pass the extracellular part of the receptor. For example, another fungal metabolite (demethylasterriquinone) has been reported to interact with the cytosolic region of the β subunit of the insulin receptor, activate receptor signaling without insulin binding, and control the hyperglycemia of diabetic animals [46]. This provides a further proof of concept for developing orally active small molecules to replace insulin [47].

Insulin potentiating agents

Many studies have described agents that potentiate insulin action after insulin has initiated a conformational change to the receptor and enabled tyrosine phosphorylation of the β subunit. Phosphatase enzymes normally terminate receptor signaling through receptor tyrosine dephosphorylation, and agents that inhibit these phosphatases have received special attention [46–48]. Included here are inhibitors of protein tyrosine phosphatase 1B (PTP1B) and less specific phosphatase inhibitors, notably vanadium compounds (Figure 67.5). Although some of these agents have shown efficacy during initial clinical studies, off-target effects have so far precluded their development [48–50]. Several molecules have been reported to increase tyrosine phosphorylation of insulin receptors and insulin receptor substrate (IRS) proteins, but their mechanisms are unclear and they have not been developed as glucose-lowering agents, such as the antioxidant α-lipoic acid, which is used in some regions to treat diabetic neuropathy [11].

Another approach to extend the signaling time of activated insulin receptors and IRS proteins has been to interrupt the

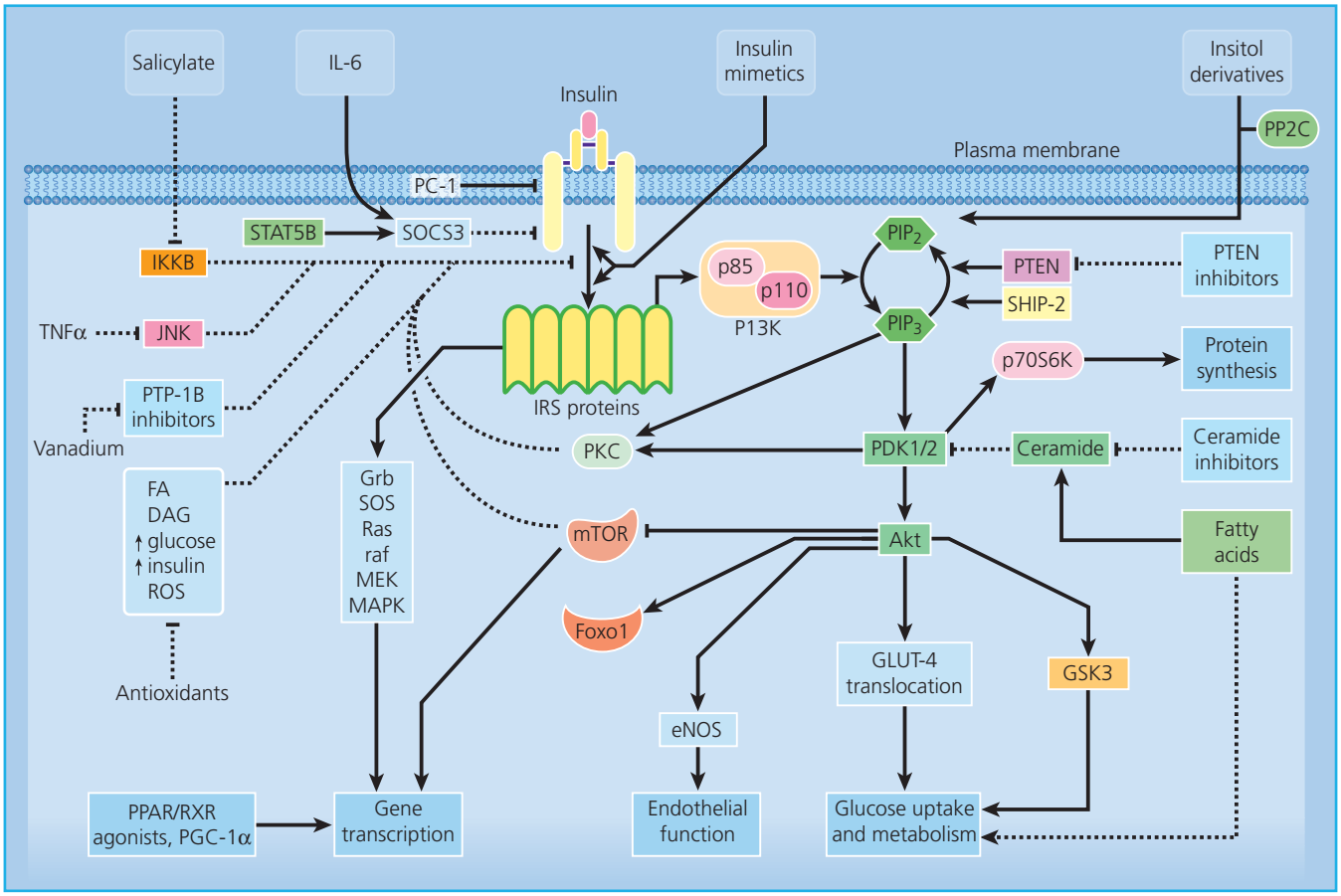

Figure 67.5 Pathways of intracellular insulin signaling illustrating potential sites for therapeutic intervention. Insulin binds to the α subunits of the extracellular region of the insulin receptor, producing a conformational change that extends to the intracellular regions and alters the conformation of the β subunits of the receptor. This allows the β subunits to be phosphorylated on tyrosine residues, which enables the β subunits to act as tyrosine kinase enzymes to phosphorylate a collection of insulin receptor substrate (IRS) proteins. The phosphorylated IRS proteins initiate signaling along the intracellular pathways that control the diverse biological effects of insulin. Many of the signaling steps are restricted ("pinch-points") by factors contributing to insulin resistance, and these steps are potential targets for therapeutic interventions. AKT, protein kinase B (PKB); AMPK, adenosine monophosphate-activated protein kinase; DAG, diacylglycerol; eNOS, endothelial nitric oxide synthase; FOXO1, forkhead box protein O1A; GLUT, glucose transporter isoform; Grb, growth factor receptor binding protein; GSK3, glycogen synthase kinase 3; IKKB, inhibitor κB kinase-β; IL6, interleukin 6; IRS, insulin receptor substrate; JNK, c-Jun N-terminal kinase; MAPK, mitogen-activated protein kinase; MEK, mitogen-activated protein kinase kinase; mTOR, mammalian target of rapamycin; PC-1/NNP1, glycoprotein 1; PDK, phosphoinositide-dependent protein kinase; PGC-1α, PPAR co-activator 1α; PI3K, phosphatidylinositol 3-kinase; PIP2, phosphatidylinositol-3,4-bisphosphate; PIP3, phosphatidylinositol-3,4,5-trisphosphate; PKC, protein kinase C; PPAR, peroxisome proliferator-activated receptor; PP2C, pyruvate dehydrogenase phosphatase (protein phosphatase 2C); PTEN, phosphatase and tensin homolog; PTP-1B, protein tyrosine phosphatase 1B; Raf, a serine-threonine protein kinase; Ras, a guanosine triphosphatase; ROS, reactive oxygen species; RXR, retinoid X receptor; SHIP-2, src homology-2-inositol phosphatase; SOCS-3, suppressor of cytokine signaling-3; SOS, sons of sevenless; STAT, signal transducer and activator of transcription; TNF-α, tumor necrosis factor α; ↑, increase.

negative feedback effects of more distal intermediates within the insulin action pathways. Certain isoforms of PKC mediate the negative effects of excess fatty acids, diacylglycerol, and products of glucotoxicity, in part by phosphorylation of the receptor and IRS proteins at serine or threonine sites [51]. Although some PKC inhibitors have increased insulin action and shown promise in the treatment of diabetic retinopathy and neuropathy, this approach has yet to prove sufficiently effective for the control of hyperglycemia in T2DM. Other signaling intermediates that inhibit the activity of insulin receptors or IRS proteins by serine phosphorylation have also been considered as potential therapeutic targets. These include inhibitor κB kinase-β (IKKβ) and c-Jun N-terminal kinase (JNK), which mediate the insulin resistance produced by certain cytokines such as tumor necrosis factor α (TNF-α), and the mammalian target of rapamycin (mTOR), which mediates a negative feedback from AKT (protein kinase B) [42]. Supplementing the availability of substrates for post-receptor steps is a further intervention to enhance insulin action, as illustrated by the administration of methylchiroinositol (pinitol), which facilitates signaling through phosphatidylinositol 3-kinase and has improved glycemic control in animal models of insulin resistance and insulin deficiency [11].

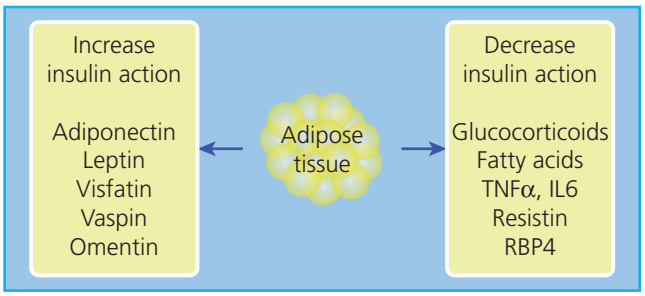

Figure 67.6 Proteins secreted from adipose tissue that can increase or decrease insulin action. These proteins or their receptors are potential targets or templates for therapeutic agents to improve glycemic control. IL6, interleukin-6; RBP4, retinol-binding protein-4; TNF-α, tumor necrosis factor α.

Adipokines

Several peptides and other substances produced by adipose tissue can affect the endocrine pancreas, insulin action, food intake, and/or energy expenditure, and some have been explored as potential therapeutic leads (Figure 67.6). For example, leptin exerts centrally mediated satiety and thermogenic effects, acts directly on tissues to improve insulin action and suppress glucagon, and facilitates weight loss. However, therapeutic doses of leptin and leptin analogs generate leptin resistance, which severely compromises long-term efficacy [52].

Adiponectin offers a range of potentially advantageous effects, including increased insulin sensitivity, improved endothelial function, and reduced inflammation, but the amounts of adiponectin released by adipose tissue are reduced in overweight and obese persons with T2DM. Supplementary adiponectin itself may not be a realistic intervention, but small-molecule agonists of the adiponectin receptors AdipoR1 and AdipoR2 could provide a suitable alternative, and initial preclinical studies have indicated that this approach can reduce insulin resistance and improve glycemic control [53, 54]. Several other adipocyte hormones have been implicated in the pathogenesis of T2DM, but their therapeutic potential remains to be determined [55–58]. For example, resistin and retinol-binding protein 4 reduce insulin sensitivity, whereas omentin and visfatin appear to improve insulin sensitivity. Many of the adipocyte peptides influence inflammatory processes, and the major proinflammatory adipokines, TNF-α, and interleukin-6 (IL-6) have been implicated in insulin resistance, but it is unclear whether these are appropriate targets for glucose-lowering purposes [59].

Fibroblast growth factors

Amongst the fibroblast growth factor (FGF) proteins, FGF21 and its analogs have been assessed as possible treatments in T2DM. FGF21 is secreted by the liver, adipose tissue, and muscle, and in preclinical studies it has improved insulin sensitivity and β-cell survival, in addition to promoting fatty acid oxidation and hepatic gluconeogenesis during fasting. However, T2DM in obese individuals appears to be associated with resistance to FGF21, and plasma concentrations of FGF21 are often raised. Nevertheless, clinical studies with FGF21 analogs have shown improvements in insulin sensitivity, glycemic control, and the blood lipid profile, and evidence is emerging that the metabolic effects of FGF21 are mediated at least in part through increased production of adiponectin [60, 61].

Peroxisome proliferator-activated receptor γ agonists

The insulin-sensitizing and other potentially beneficial metabolic effects of currently available thiazolidinediones (pioglitazone and rosiglitazone) are mostly mediated by activation of the nuclear transcription factor peroxisome proliferator-activated receptor γ (PPARγ). Other thiazolidinediones and non-thiazolidinedione PPARγ agonists have been developed, but unwanted side effects such as fluid retention, excess adiposity, and bone resorption have impinged [62]. Dual agonists of PPARγ and PPARα (known as glitazars) have also been developed to incorporate the lipid-lowering and anti-inflammatory effects of PPARα, but side effects have again precluded routine clinical use [62]. Additionally, triple PPARγ/α/δ agonists (pan-PPARs) have been studied in preclinical models to incorporate the increased energy expenditure and weight loss offered with PPARδ (Figure 67.7). However, based on structure–activity studies, it has become evident that alterations to PPAR agonist molecules can modify their receptor binding properties sufficiently to retain desired therapeutic effects and reduce side effects by altering the recruitment of coactivators and repressors [62]. This concept of selective PPAR modulators has given rise to agents in development with similar glucose-lowering efficacy but reduced side effects compared with current PPARγ agonists [63, 64].

Vitamins and minerals

Debate continues over the use of vitamins and mineral supplements as adjunct treatments in T2DM, and it is stressed that potential benefits of correcting deficiencies are very different to massive doses in individuals who already have adequate levels. Deficiencies in vitamin D are associated with insulin resistance and β-cell dysfunction and supplementation in deficient individuals has shown benefit. Low concentrations of antioxidant vitamins, notably vitamins C (ascorbic acid) and E (α-tocopherol) and β-carotene, are not uncommon in T2DM, but the value of supplements in improving glycemic control or reducing cardiovascular risk remains uncertain [11]. Thiamine (vitamin B_1) and biotin (vitamin H) have also been considered as possible supplements to improve glucose metabolism.

Reduced levels of magnesium, chromium, and zinc are frequently encountered in T2DM and supplements have been shown to improve glycemic control in deficient individuals [11]. Selenium, molybdenum, tungsten, mercury, and cadmium have also been reported to improve glucose metabolism in preclinical

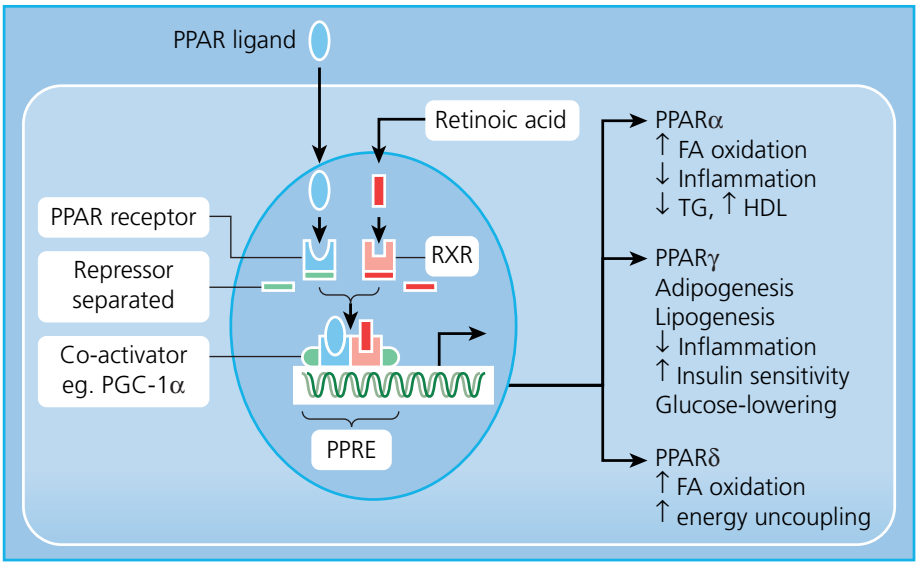

Figure 67.7 Cellular mechanism of action of a peroxisome proliferator-activated receptor (PPAR) ligand. The PPAR ligand binds to its nuclear PPAR receptor, which forms a heterodimer with the retinoid X receptor (RXR). Ligand binding releases repressors, attracts coactivators, and exposes the active site of the receptor which binds with its specific DNA nucleotide sequence—peroxisome proliferator response element (PPRE). RNA polymerase is recruited for transcription of mRNA from genes that carry the PPRE sequence in a promoter region. The mRNA is translated into the enzymes and transporters responsible for the biological effects. There are three types of the PPAR agonist: PPARγ, PPARα, and PPARδ. Each type of agonist offers a range of effects. PPARγ agonists enhance lipogenesis, adipogenesis, insulin sensitivity, and glucose lowering, PPARα agonists have lipid-lowering and anti-inflammatory effects, and PPARδ agonists promote energy expenditure. Selective structural modifications to agonist molecules provide an opportunity to retain and accentuate desired effects while reducing unwanted effects.

models, but the mechanisms are unclear, the therapeutic index is generally narrow, and toxicity risks are high. Lithium can improve insulin sensitivity, but may also decrease insulin secretion with unpredictable effects [11].

Hydroxysteroid dehydrogenase 1 inhibitors

Raised glucocorticoid concentrations can precipitate and aggravate truncal obesity, insulin resistance, and hyperglycemia, whereas interventions to reduce glucocorticoid action can prevent and reverse these effects. The enzyme 11β-hydroxysteroid dehydrogenase 1 converts cortisone to active cortisol mostly within liver and adipose tissue; hence in principle, agents that specifically inhibit this enzyme could reduce cortisol production within these tissues without substantially affecting circulating cortisol [65]. Trials with such inhibitors have shown improvements in insulin sensitivity, glycemic control, and the lipid profile of people with T2DM while enabling some weight loss, but reduction of circulating cortisol has also occurred, prompting a compensatory increase in ACTH [66, 67].

Sodium–glucose co-transporter inhibitors

SGLT activity plays an important role in the intake and elimination of glucose. Intestinal absorption of glucose is via SGLT-1 in the brush border of enterocytes, and glucose that is filtered in the kidney is reabsorbed mostly (~90%) via SGLT-2 in the initial part of the proximal tubules and the remainder by SGLT-1 in the more distal part of the proximal tubules (Figure 67.8). SGLT inhibitors in current clinical use (e.g. canagliflozin, dapagliflozin, and empagliflozin) predominantly inhibit SGLT2, lowering the renal threshold for glucose and eliminating excess glucose in the urine (glucosuria). This provides an insulin-independent mechanism to lower blood glucose and dispose of calories, thereby assisting weight loss [68]. The osmotic diuresis that accompanies the glucosuria may contribute at least in part to a lowering of blood pressure at the same time. Several additional SGLT-2 inhibitors are being developed, and there are also variants that exert a significant inhibitory effect against both SGLT2 and SGLT1 (e.g. sotagliflozin). The latter type of agent can defer glucose absorption more distally along the intestinal tract and slow the appearance of glucose in the portal circulation. However, the agent itself must either be fully absorbed, denatured along the intestinal tract, or dose adjusted to avoid unabsorbed glucose passing into the large bowel. If the passage of extra glucose along the proximal tubules leads to upregulation of SGLT-1, the inhibition of SGLT-1 may also increase glucosuric efficacy [69, 70].

Suppression of glucose production

Any intervention that suppresses hepatic gluconeogenesis and/or glycogenolysis should reduce blood glucose, but the effect must be partial and promptly reversed in hypoglycemia to avoid interference with counter-regulatory mechanisms [71]. Reducing the

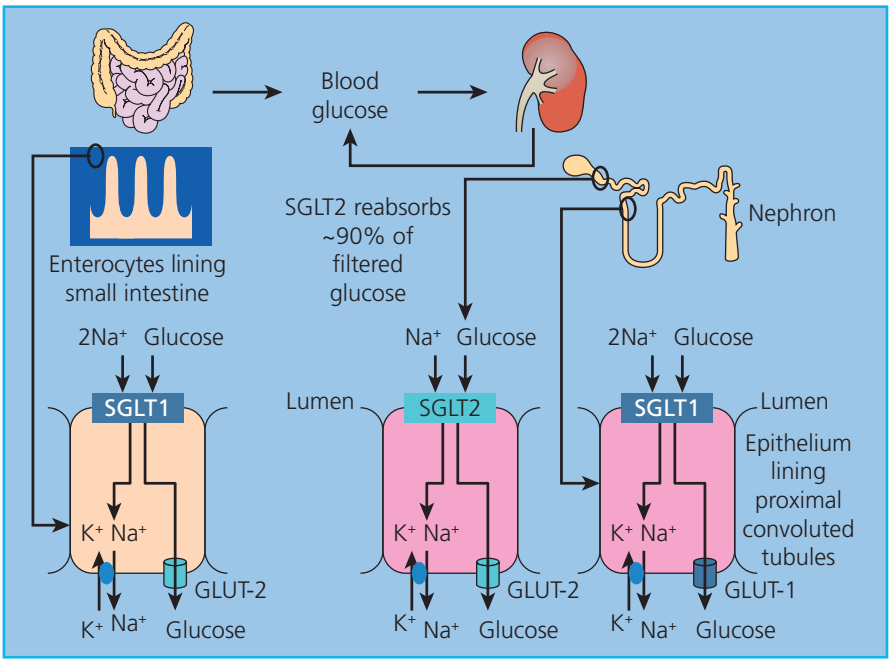

Figure 67.8 Sites of action of sodium–glucose co-transporters SGLT1 and SGLT2. SGLT1 is responsible for intestinal glucose absorption and SGLT2 is the main transporter responsible for glucose reabsorption from renal proximal convoluted tubules. SGLT1 also contributes to glucose reabsorption from the renal proximal convoluted tubules. GLUT, glucose transporter.

breakdown of glycogen stores by using inhibitors of glycogen phosphorylase has lowered blood glucose in preclinical studies. However, despite employing several different inhibitory mechanisms, clinical efficacy has been modest or not sustained. Glucose 6-phosphatase inhibitors prevent the last step in glucose output from both glycogenolysis and gluconeogenesis. Although such inhibitors can effectively lower blood glucose, their activity is not easily terminated and the risk of hypoglycemia is increased. Inhibitors of fructose 1,6-bisphosphatase prevent the dephosphorylation of fructose 1,6-bisphosphate to fructose 6-phosphate, which is the penultimate step in gluconeogenesis before glucose 6-phosphate. Studies with these inhibitors has indicated that it is possible to maintain a partial reduction of hepatic glucose output due to increased compensatory glycogenolysis, and clinical studies are ongoing [72].

Direct enhancers of glucose metabolism

Many substances are known to stimulate directly glucose uptake and utilization by muscle and adipose tissue, but few have been considered for a therapeutic application in T2DM as the magnitude of their effects is difficult to control and their side effect profiles are not suitable. Examples of agents with such effects are dichloroacetate, spermine, diamides, various peroxides, vitamin K_5, deoxyfrenolicin, okadaic acid, and several phorbol esters [11]. Inhibitors of glycogen synthase kinase have increased glycogenesis and lowered blood glucose in insulin-resistant diabetic animals, but potential adverse effects on the control of cellular division have deterred development for T2DM.

Agents that activate adenosine 5′-monophosphate-activated protein kinase (AMPK) have attracted interest as therapies for T2DM. AMPK is a key energy-regulating enzyme that appears to be one of several targets for metformin and probably PPARγ agonists and adiponectin receptor agonists. It is activated when cellular energy status declines and AMP concentrations rise, promoting the uptake and oxidation of glucose and fatty acids to restore ATP production. AMPK also reduces gluconeogenesis and lipogenesis, and may have a tumor suppressor effect [73]. Analogs of AMP such as AICAR (5-aminoimidazole-4-carboxamide-1β-D-ribofuranoside) have been shown to activate AMPK and improve glycemic control in animals with insulin-resistant diabetes. In addition, α-lipoic acid, various polyphenols, salicylates, and other small molecules have been identified as activators of AMPK [74].

Antiobesity agents

It is well recognized that the act of losing weight by reducing food intake or increasing energy dissipation, and also the longer-term achievement of reduced adiposity, improve insulin sensitivity and improve glycemic control in overweight and obese individuals with T2DM. Indeed, bariatric surgery has produced laudable results in this respect. However, there seems to have been a reluctance to approach glycemic control through pharmacological interventions primarily designed for weight loss. The intestinal lipase inhibitor orlistat is an established weight-reducing therapy, and the satiety-inducing agent phentermine is used in some regions. Several new satiety-inducing agents include a high-dose GLP-1 receptor agonist (liraglutide), a 5HT2c serotonin receptor agonist (lorcaserin), a phentermine–topiramate combination (Qsymia), and a bupropion–naltrexone combination (Contrave) [75–77]. Studies in obese individuals with T2DM indicate that these can improve glycemic control, often with results approaching comparability with some established glucose-lowering agents.

Although GLP-1 receptor agonists and SGLT-2 inhibitors already combine glucose-lowering and weight-reducing properties, it would highly advantageous if future attention could strongly target the coexisting problems of obesity and diabetes (diabesity).

Sirtuins

Sirtuins are nicotinamide adenine dinucleotide (NAD)-dependent histone deacetylases and adenosine diphosphate (ADP) ribosyltransferases that serve as epigenetic mediators. They alter histone structure and chromatin stability, enabling transcription of genes that increase mitochondrial biogenesis and energy expenditure, modulate insulin secretion and nutrient metabolism, mimic caloric restriction, and protect against weight gain, diabetes, and cardiovascular disease in animal models [78]. Several small-molecule sirtuin activators with initially encouraging effects in animal models of diabetes have been described, but these effects have not been consistently observed [79, 80].

Pharmacogenomics

Associations between gene variants and responses to glucose-lowering medications are under investigation to predict the efficacy, tolerability, and risk of adverse effects of a particular agent for the individual. Gene variants for transporter proteins that affect the absorption, cellular distribution, and elimination of drugs, and also variants encoding the enzymes involved in their metabolism, have been shown to influence responses to these drugs within the genetic constraints of the disease process itself [81, 82]. Pharmacogenomic testing for personalized medicine is in its infancy, but offers future opportunities to improve drug–patient compatibility and avoid ineffective or harmful interventions.

Using pharmacogenomics to design new drug therapies presents a particular challenge for the treatment of T2DM owing to the multivariable etiology and heterogeneous, progressive natural history of the disease [83, 84]. There is seldom a single rate-limiting protein that can be pharmacologically manipulated to reset normal glucose homeostasis, but studies are under way to map the diabetes proteome and identify prime contenders for future pharmacological intervention, especially to address the defects of β-cell function and survival as T2DM advances [85].

Safety

The long-term use of diabetes medications requires particular attention to long-term safety, and regulatory processes for the approval and subsequent surveillance of new glucose-lowering agents take thorough account of this requirement [86–88]. As noted at the start of this chapter, individuals with T2DM are prone to develop comorbidities that contraindicate some medicines, lead to drug interactions, or introduce other safety concerns. Some safety issues can take many years to emerge and necessitate revision to the label in accordance with the change in risk–benefit balance. If new medicines are to become available in a timely manner, such revisions will need to be accepted without prejudice as part of the lifespan of a medicine [89].

Conclusion

This chapter has considered glucose-lowering medications in development and potential novel therapeutic targets for T2DM. Novel insulin therapy and interventions specifically directed against type 1 diabetes are reviewed in Chapter 66. It is noted that T2DM involves such a variable mix of defects that effective management usually needs to exploit a selection of differently acting agents that can be used in combination as the disease progresses. For the future, attention to adiposity, hunger–satiety discord, energy expenditure, and inflammation may acquire greater precedence alongside more conventional approaches directed towards the secretion and actions of insulin, glucagon, and incretins. Futuristic mechanisms might incorporate very different forms of intervention such as antisense oligonucleotides and short interference RNA to modify the proteome, or pre- and probiotics to modify the microbiome. Cell-based therapies, especially glucose-sensing surrogate endocrine cells, could deliver more than insulin, and so-called "smart" drugs that are activated in accordance with the prevailing glucose concentration could obviate the problems of dose titration and hypoglycemia.

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68 Stem Cell Therapy in Diabetes

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Key points

- Stem cells divide asymmetrically to produce self-renewing cells and daughter cells that differentiate; they can also divide symmetrically to expand the stem cell pool.
- A β cell can be formed by an α cell following allocation towards the pancreatic lineage.
- A functional β cell can be reprogrammed from adult cell types through an inducible pluripotent stem cell (iPSC).
- Myocyte apoptosis in the normal human heart involves at least 1 in 100,000 cells at any time, which corresponds to a decrease of 2.2% of myocytes per year.
- Angiogenesis occurs as sprouting of small endothelial tubes from pre-existing capillary beds in response to local hypoxia whereas arteriogenesis is the transformation of pre-existing collateral arterioles into functional collateral arteries.

Why use stem cells in individuals with diabetes?

Major unmet clinical needs in diabetes care include the following: (1) to cure the disease by recreating physiological insulin secretion and normal blood glucose in order to avoid long-term complications; and (2) to reverse long-term complications in persons already suffering from these disabilities. The primary treatment for type 1 diabetes mellitus (T1DM) is daily intensive insulin therapy, and many individuals with type 2 diabetes mellitus (T2DM) will also require insulin therapy with time. Although multifactorial interventions have significantly decreased the incidence of complications, many people with diabetes die prematurely despite optimal medical therapy. For instance, revascularization procedures have improved in recent years, but diabetes is still an independent predictor of worse outcomes after an acute coronary syndrome. Interest in the therapeutic role of stem cells has progressively increased, especially for their potential ability to reconstruct blood vessel cells and to restore insulin secretion [1].

What is a stem cell?

Stem cells divide asymmetrically to produce self-renewing cells and daughter cells that differentiate; they can also divide symmetrically to expand the stem cell pool [2]. Stem cells usually reside in a particular environment called the niche, which controls stemness by providing short-range signals. In terms of the potential to differentiate, stem cells can be categorized into (1) totipotent, typically derived from the early embryo, which can form all tissues and organs of the body, including extraembryonic membranes (e.g. placenta); (2) pluripotent, which can form almost all tissue or cell types in the body; and (3) multipotent, which form a limited number of cellular phenotypes. Stem cell potency is recognized by typical surface or intracellular markers, and is regulated by the expression of pluripotency genes. Human embryonic stem cells (ESCs) show long-term self-renewal, while retaining a normal karyotype, and are pluripotent, as they can generate cells derived from all three germ layers. Adult stem cells can generate identical copies of themselves in a long-term self-renewal fashion; they are probably set aside during fetal development and restrained from differentiating. Before they achieve their fully differentiated state, stem cells generate intermediate cell types, called precursor or progenitor cells. Progenitor cells in fetal or adult tissues are unspecialized or partially specialized cells capable of generating specialized cells. Such cells are usually regarded as "committed" to differentiating along a particular cellular development pathway, although this characteristic may not be definitive. Mesenchymal stem cells (MSCs) give rise to bone, cartilage, muscle, tendon, and connective tissue cells. Hematopoietic stem cells (HSC) differentiate into oligo-lineage progenitor cells and gives rise to mature blood cells. Inducible pluripotent stem cells (iPSCs) are adult cells that have been reprogrammed to an embryonic stem cell-like state. Mouse iPSCs show characteristics of pluripotent stem cells, including stem cell markers, and forming tumors containing cells from all three germ layers. Several groups have shown that iPSCs can be generated from different cell types, although many obstacles remain to be resolved before being able to take full advantage of this technology in therapy [3].

Textbook of Diabetes, Fifth Edition. Edited by R. Holt, C. Cockram, A. Flyvbjerg and B. Goldstein.

Stem cells for insulin replacement

A considerable number of protocols for efficient differentiation of stem cells into functional endocrine cells have been developed [4], but most have not been able to generate fully functional β cells [5]. Nonetheless, cells generated with these protocols secrete human C-peptide in response to glucose, and can rescue hyperglycemia in mice with streptozotocin-induced diabetes [6]. A new approach is to microencapsulate progenitor cells in an immunoisolation devise, where maturation to functional β cells would take place [7, 8]. Several studies have shown that ESCs can differentiate towards a β-cell-like phenotype (Figure 68.1). However, this approach has various limitations, such as inefficiency of differentiation, low insulin content, generation of insulin-producing neural cell lineages, and ethical concerns. D'Amour et al. developed a differentiation process that converts human ESCs into endocrine cells capable of synthesizing pancreatic hormones [9]. MSCs have also been used to generate insulin-producing cells [10], to enhance islet engraftment and survival, and to improve metabolic control in experimental diabetes [11].

Trials performed in T2DM suggest a positive impact of bone marrow–derived mononuclear cells on metabolic control in the absence of adverse events following intra-arterial injection by selective cannulation of the pancreatic vasculature [12]. Rezania et al. demonstrated that pancreatic progenitor cells can produce glucose-responsive, insulin-secreting cells and prevent or reverse diabetes in mice [13]. An alternative strategy is the reprogramming of terminally differentiated cell types into β cells. Zhou and Melton showed a direct conversion of mouse acinar cells to β cells *in vivo* via viral expression of given genes; these induced cells were able to improve glycemic control in mice with diabetes [14]. A further example of adult cell reprogramming to β cells has been described for adult mouse α cells. Following allocation towards the pancreatic lineage, the endocrine differentiation program is initiated through the expression of neurogenin3 (Ngn3), and $Ngn3^+$ cells can become α cells or bipotential β/δ precursors [15]. Combining several lineage-tracing approaches, it was demonstrated that pancreatic duct-lining precursor cells are continuously mobilized, re-express the developmental gene *Ngn3*, and successively adopt a glucagon-expressing and a β-like cell identity through mechanisms involving the reawakening of the epithelial-to-mesenchymal transition [16]. The restoration of insulin-producing cells from non-β-cell origins is enabled throughout life via spontaneous reprogramming of δ or α cells, suggesting a condition with multiple intra-islet cell interconversion events. A further approach to making functional β cells is to reprogram adult cell types towards β cells: any tissue could be reprogrammed to an inducible pluripotent state (iPSCs). Differentiation protocols can be applied to human iPSCs: cell lines derived from reprogrammed human fibroblasts have been successfully differentiated to insulin-producing cells *in vitro* [17, 18]. Maehr et al. have shown that fibroblasts obtained from skin biopsies from two people with T1DM were reprogrammed to pluripotency and differentiated to insulin-producing cells, although their functionality needs further validation [19]. In this context, Hua et al. generated iPSCs from people with maturity-onset diabetes of the young type 2 (MODY-2), which is characterized by heterozygous loss of function of the gene encoding glucokinase (GCK) [20]. These stem cells differentiated into β cells with an efficiency comparable to that of people without diabetes and expressed markers of mature β cells.

Healing the heart

During an acute myocardial infarction (MI), billions of cardiomyocytes are lost and, unfortunately, current therapies are unable to re-establish such loss. Aging also causes cardiomyocyte loss.

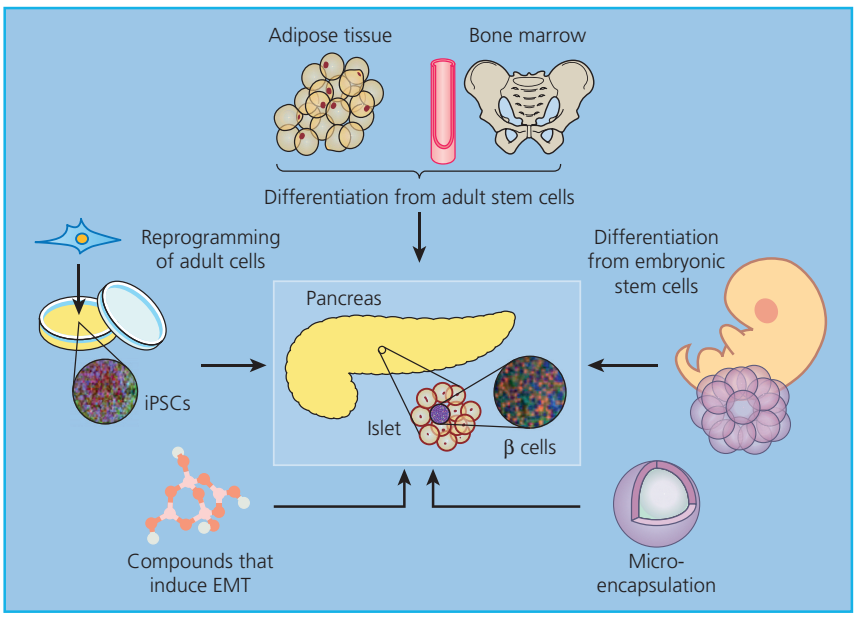

Figure 68.1 Approaches to creating insulin-producing cells. iPSCs, inducible pluripotent stem cells; EMT, endothelial-to-mesenchymal transition.

Myocyte apoptosis in the normal human heart involves at least 1 in 100,000 cells at any time, which corresponds to a decrease of 2.2% of myocytes per year.

The recognition that the adult heart harbors a compartment of multipotent c-kit$^+$ cardiac stem cells (CSCs) and other progenitor cells capable of differentiating into cardiomyocytes and coronary vessels has sparked interest in cardiac regeneration. CSCs are stored in interstitial structures with the characteristics of stem cell niches and can divide symmetrically or asymmetrically, with the ability to self-renew and form a committed progeny [21]. Recent results favor the hypothesis that cardiac development is controlled mainly by growth and differentiation of c-kit$^+$ CSCs [22]. However, the possibility that bone marrow-derived HSCs are involved in the restoration of damaged myocardium and contribute to the cardiac repair process cannot be excluded. Such cells may secrete a variety of cytokines that activate endogenous progenitors, which are actually responsible for the repair process and the restoration or preservation of ventricular function.

In 2001, Menasché et al. described the successful implantation of autologous skeletal myoblasts into the postinfarction scar of a patient with severe congestive heart failure who was undergoing coronary artery bypass surgery [23]. Five months after treatment, they concluded that treated hearts pumped blood more efficiently. Several phase I and phase II clinical trials have been conducted to test the hypothesis that cell therapy may represent a potential resource for treating heart failure. However, the mechanisms whereby stem cells promote cardiac repair remain controversial. Several cell phenotypes have been used to implement stem cell-based therapy to treat ischemic heart disease, namely unselected CD133$^+$ or CD34$^+$, circulating stem/progenitor cells, MSCs, adipose tissue-derived stem cells, resident cardiac/stem cells, and iPSCs. Intracoronary infusion of CD133$^+$ cells, an immature HSC phenotype, after recent MI was evaluated in a small, non-randomized clinical study that reported improved left ventricular ejection fraction (LVEF) with a concomitant reduction in myocardial perfusion defect after 4 months [24]. However, more coronary events, such as stent occlusion and in-stent restenosis, were observed after CD133$^+$ cell therapy. CD34$^+$ cells represent a subpopulation of cells with more endothelial-determined cells. In the randomized controlled REGENT trial, unselected and CD34$^+$CXCR4$^+$-selected bone marrow (BM) cells were administered to people with MI with reduced left ventricular (LV) function (LVEF 40%) [25]. After 6 months, the LVEF increased by 3% in individuals treated with unselected BM cells and 3% in those receiving CD34$^+$CXCR4^{+-}selected BM cells, and remained unchanged in the control group, but the differences in absolute changes of LVEF were not significant among the groups.

The intracoronary application of MSCs was assessed in two non-randomized early-phase studies by Chen et al. [26]. High-dose administration of BM-derived MSCs (6×10^{10}) resulted in a significant improvement in LVEF, whereas a lower dose (5×10^6) did not improve LV function in heart failure. Notably, MSC treatment resulted in an improved exercise capability and heart failure symptoms after 3 months. It has been proposed that expanded CSCs from self-adherent clusters, denoted cardiosphere-derived stem cells (CDCs), may represent a valid cell phenotype to rescue infarcted areas [27]. Preliminary results indicated that, in individuals with ischemic cardiomyopathy, the administration of CDCs decreased scar size, increased viable myocardium, and improved regional function of infarcted myocardium at 1 year post-treatment. In contrast to exogenous cell transfer, adult stem/progenitor cells can be mobilized from the bone marrow by systemic administration of selected cytokines (e.g. granulocyte colony-stimulating factor [G-CSF]) to augment their circulating levels in order to increase the possibility of ischemic tissue repair. However, in the MAGIC trial, G-CSF mobilization after MI was associated with a higher rate of in-stent restenosis at the culprit lesion. In a controlled, non-randomized study by Ince et al., G-CSF mobilization of CD34$^+$ BM cells shortly after angioplasty in MI improved LV function and metabolic activity and attenuated LV remodeling for up to 12 months without increasing the restenosis rate [28]. Similarly, Valgimigli et al. showed a fair safety profile for G-CSF in people with MI, although LV perfusion or function was unchanged 6 months after treatment [29]. G-CSF did not improve LV wall motion or perfusion over a period of 1 month in people with stable coronary artery disease. A meta-analysis of stem cell mobilization by G-CSF from 10 trials, including 445 participants with MI, indicated that cumulatively the data do not support efficacy of endogenous stem cell mobilization by G-CSF [30].

As an alternative to cell therapy, the use of drugs to modulate stem/progenitor cell availability and homing is being considered. Zaruba et al. proposed a combined strategy of G-CSF plus dipeptidyl peptidase 4 (DPP-4) inhibition to improve cardiac homing of mobilized stem/progenitor cells, which is currently under clinical investigation in the SITAGRAMI trial in people after MI [31]. This approach stems from the concept that inhibition of DPP-4, which cleaves the main stem cell-attracting chemokine, stromal-derived factor 1α (SDF-1α), will improve homing of mobilized stem/progenitor cells. Endogenous stem cell mobilization can be achieved also using the CXCR4 antagonist plerixafor. The cardiac stem/progenitor cell (CSPC) compartment is involved in the occurrence of diabetic cardiac dysfunction through activation of the cell death pathways and inhibition of cell replication [32]. Glucose-induced dysfunction of the pool of cardiac progenitor cells (CPCs) leads to insufficient replacement of old, dying cells, and the acquisition of the heart senescent phenotype. A protein that appears to be implicated in CPC poll damage is p66shc, an adaptor protein, which is linked to premature aging, oxidative stress, and apoptosis. Exposure of human CPCs to hydrogen peroxide results in increased caspase-3 cleavage and apoptosis, mediated by the activation of the c-jun N-terminal kinase (JNK) pathway [33]. Regarding cells bioenergetics, CSPCs exposed to a diabetic environment show remarkably reduced activity of key enzymes of the pentose phosphate pathway (glucose-6-phosphate dehydrogenase [G6PD] and transketolase), resulting in decreased antioxidant defense mechanisms and activation of apoptosis [34]. Inflammation has also been implicated [35].

Creating new vessels

Peripheral arterial disease is highly prevalent among persons with diabetes and is associated with significant morbidity and mortality. Peripheral arterial disease can lead to critical limb ischemia, resulting in major amputations and death. In people with peripheral vascular disease, both angiogenesis and arteriogenesis should represent compensatory mechanisms to increase vessel growth. Angiogenesis occurs as sprouting of small endothelial tubes from pre-existing capillary beds in response to local hypoxia; it is mainly mediated by vascular epithelial growth factor with no need for non-tissue resident cells. The resulting capillaries are small, and cannot compensate for the large occluded conduit artery. Arteriogenesis is the transformation of pre-existing collateral arterioles into functional collateral arteries; this implies an increase in diameter of existing arterial vessels capable of compensating for the loss of function of occluded arteries. Ischemia itself induces elevation of plasma stem and progenitor cell-activating cytokines, including sKitL (soluble Kit ligand) thrombopoietin, and G-CSF. Together with hypoxia, these in turn induce the release of SDF-1, thereby stimulating mobilization of proangiogenic cells that accelerate revascularization of the ischemic site. Traditional circulating endothelial progenitor cells (EPCs), as identified by Asahara et al. [36], were recently found to originate from the monocyte–macrophage lineage. Traditional cardiovascular risk factors have been associated with decreased circulating progenitor cell number and function. A number of studies have reported dysfunction of endogenous EPCs in the setting of hypertension, dyslipidemia, smoking, and diabetes. Reversal of these risk factors may overcome intrinsic deficiencies of autologous EPCs. Attention should be paid to the application of EPCs in advanced cardiovascular states, with special effort to optimize the metabolic and mechanical context of cell therapy. Standard treatment for severe cases of peripheral arterial disease is surgical or endovascular revascularization. Nonetheless, up to 30% of individuals are not candidates for such interventions, owing to the high operative risk or adverse vascular anatomy. BM-derived stem and progenitor cells have been identified as a potential new therapeutic option to induce angiogenesis. In humans, two different approaches have been proposed, based on (i) unselected autologous mononuclear BM-derived stem cells (BM-MNCs) directly sampled from BM, or (ii) autologous $CD34^+$ or $CD133^+$ BM-MNCs sampled from the peripheral circulation after G-CSF stimulation of the BM. Cells can be administered either intramuscularly, intra-arterially, or topically (Figure 68.2). The intramuscular approach is easily performed and allows a large amount of cells to be injected in the proximity of the ischemic area; theoretically, this approach may result in a cell depot, which would allow local paracrine activity.

The first clinical trial of stem cell therapy in peripheral arterial disease was the TACT (Therapeutic Angiogenesis using Cell Transplantation) study, with unselected BM-MNCs injected intramuscularly into the ischemic limbs of people with critical limb ischemia: it proved safe and able to improve rest pain, perfusion, oxygen pressure, and pain-free walking distance at 24 weeks' follow-up compared with placebo [37]. One clinical trial using

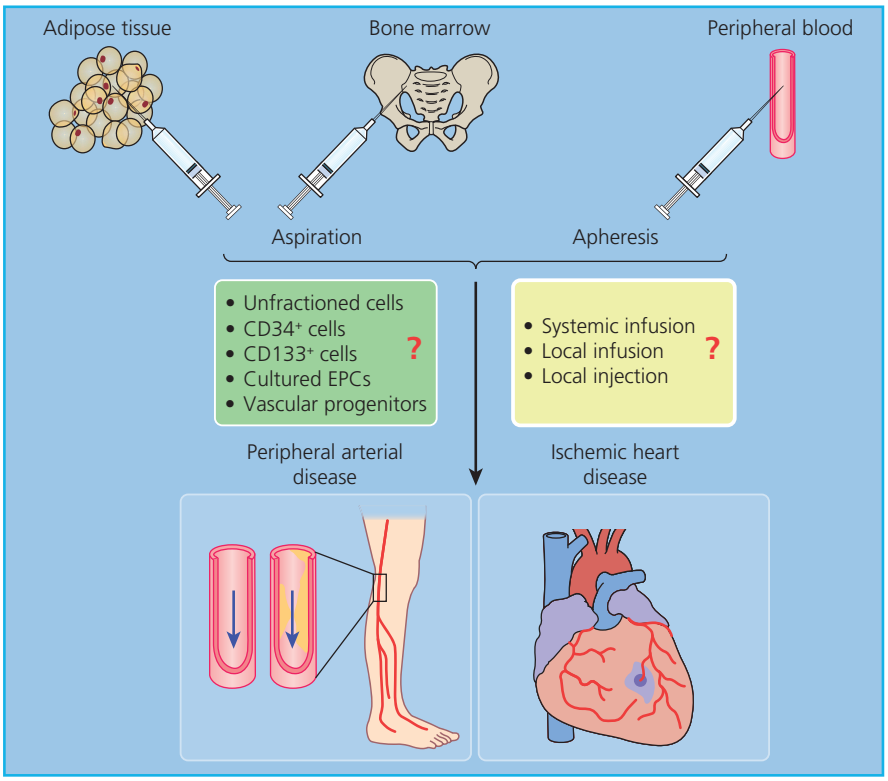

Figure 68.2 Technical approaches for the administration of stem cells to treat critical limb ischemia and heart failure.

unselected BM-MNCs delivered intra-arterially demonstrated a similar improvement in ankle brachial index (ABI) compared with previous trials of intramuscular BM-MNC administration [38]. Notably, an intra-arterial study in individuals with diabetes suggested much greater ABI improvements, and also improvements in wound healing and blood flow. The Intraarterial Progenitor Cell Transplantation of Bone Marrow Mononuclear Cells for Induction of Neovascularization in Patients with Peripheral Arterial Occlusive Disease study was a multicenter randomized trial of intra-arterial BM-MNC therapy in persons with critical limb ischemia [39]. The study reported improvements in wound healing and reductions in rest pain, despite no effect on ABI and limb salvage rates. Both intramuscular and intra-arterial injection of G-CSF-mobilized peripheral MNCs have been shown to result in a >0.1-point improvement in ABI and a twofold increase in maximum walking distance in small clinical series. A meta-analysis by Fadini et al. of 37 trials of cell therapy indicated that cell therapy is able to improve significantly ABI, total carbon dioxide (TCO_2), rest pain, pain-free walking distance, ulcer healing, and limb salvage [40]. In contrast, G-CSF monotherapy was not associated with significant improvements of these endpoints, albeit final conclusions should be deferred because the number of G-CSF testing trials was limited.

Conclusions

Important advances have been made recently in the field of stem cell biology and in the therapeutic application of stem cells in the treatment of diabetes and its complications. However, a tremendous amount of work still lies ahead in the endeavor to apply stem cell therapy to people with diabetes. Common to therapeutic strategies for the replacement of β cells, and for the rescue of blood vessels and myocardium, is the need for totally safe cellular approaches. This is particularly relevant to the deployment of the iPSC approach. However, considerable uncertainties still remain regarding which is the precise lineage to employ, and the proper conditions that need to be created to yield the optimal therapeutic approach. This is of importance for new vessel formation since, as described in detail by Fadini et al., the endothelial progenitor is a dynamic phenotype in space and time [41]. Furthermore, other phenomena such as the endothelial-to-hematopoietic or the epithelial-to-mesenchymal transitions should also be taken into account, underlying, needless to say, the major challenges that lie ahead before the definitive application of cellular treatment to persons with diabetes.

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69 Islet Transplantation

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Key points

- Islet transplantation is a promising treatment for people with type 1 diabetes (T1DM) with severe hypoglycemia, hypoglycemia unawareness and/or glycemic lability.
- Successful islet transplantation can lead to insulin independence, but this is often not maintained in the long term.
- Graft function is preserved for several years beyond the loss of insulin independence, which results in a better glycemic control in spite of a return to insulin use.
- Current immunosuppression protocols include the use of more potent induction agents, which lead to better long-term outcomes, and improved safety and tolerability profiles.
- The side effects of maintenance immunosuppression are now clearly understood, and with appropriate dose titration, side effects are generally well tolerated.
- The long-term impact of islet transplantation on diabetes-related complications is incompletely elucidated, but there appears to be stabilization of microvascular and macrovascular disease.

Introduction

The discovery of insulin revolutionized outcomes for people with type 1 diabetes (T1DM), and the acute lethal complications of diabetes such as diabetic ketoacidosis were effectively treated. However, improved survival allowed development of secondary complications of diabetes [1]. Typically, the person with T1DM develops retinopathy, nephropathy, neuropathy, or vascular disease over time. It was not until 1993 that definitive proof for the value of good glycemic control was established. The landmark Diabetes Control and Complications Trial (DCCT) study showed that the microvascular complications of diabetes could be delayed or avoided by good glycemic control, which required intensive insulin therapy [2]. Such therapy was associated with an HbA_{1c} that was 1.9% lower than the control group. It should be noted that the HbA_{1c} was not normalized, but remained at least 1% above the upper limit of normal in the intensively treated group. Similar evidence was provided by the United Kingdom Prospective Diabetes Study (UKPDS) in type 2 diabetes (T2DM) with microvascular disease, showing significant improvement for a decline of 0.9% in the HbA_{1c} [3]. Thus, glycemic control is essential if the microvascular complications of diabetes are to be prevented.

Controlling glycemia with exogenous insulin remains a challenge. Given the non-physiological subcutaneous route of insulin administration, its inherent delay in absorption, the variability of serum levels obtained, and the systemic versus portal venous delivery, it is perhaps remarkable how well the glucose levels are actually controlled. The newer insulin analogs have removed some of the variability and delay in absorption but even with intensive therapy, it is difficult to achieve normoglycemia. Continuous subcutaneous insulin administration helps further but neither earlier nor more recent studies have managed to normalize glucose values [4, 5]. Carbohydrate counting and attention to diet aids the quest for normoglycemia but is not the complete solution. The largest study using all available tools to optimize therapy was still associated with an increased risk of hypoglycemia [2]. In the DCCT, the risk for severe hypoglycemia (defined as needing third-party assistance) was increased threefold. Concern about hypoglycemia remains the limiting factor in attempts to achieve optimal glycemic control.

Many efforts have been made to generate a closed-loop system for glucose control. The first successful efforts were with the Biostator®, which involved continuous monitoring of blood glucose and then an insulin infusion using a computer-derived algorithm [6]. Although effective for a short period, it was impractical being bulky and plagued with flow problems from the double lumen catheter used for sensing the glucose level. Insulin infusion pumps have helped (especially those using insulin analogs such as insulin lispro or aspart), but they are not closed-loop systems. Frequent glucose monitoring is required and this rarely results in normal glycemia without severe hypoglycemia. The goal of any closed-loop system is to have reliable glucose sensing linked to appropriate insulin delivery on a continuous basis. Considerable progress has been made recently with the so-called

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"bionic pancreas" which is a wearable dual insulin and glucagon pump system. Russell and colleagues reported in 2014 that the bihormonal approach significantly improved glycemic control and protected against hypoglycemic episodes [7]. Furthermore, Ly and colleagues demonstrated that a glucose sensor-augmented insulin pump fitted with an automated low glucose suspend feature effectively reduced the incidence of severe and moderate hypoglycemic reactions [8].

Transplantation of islets of Langerhans or of the whole pancreas can achieve a biological-based and even more physiological closed-loop system, but requires life-long immunosuppression to achieve this. Choudhary et al. have recently discussed in detail the first-, second-, third-, and fourth-line current recommended options for people with T1DM with refractory glycemic control [9]. Islet or pancreas transplantation is reserved as a final step once structured education, continuous glucose monitoring, consideration of low-glucose suspend pumps, and other options have been explored and exhausted.

Background history

Transplantation of pancreatic tissue was first tried in 1890 when a surgeon in England transplanted fragments of a sheep's pancreas into a boy with diabetic ketoacidosis [10]. The immune barriers, unknown at the time, were insurmountable, especially for a xenograft. The modern era of transplantation began in the 1960s when the use of steroids, especially when combined with azathioprine, allowed successful renal transplantation [11]. The steroids block several cytokines and act as inhibitors of antigen presentation; azathioprine is an inhibitor of purine synthesis and thus impedes the generation of active T cells. Cyclosporin A, a calcineurin inhibitor, which is associated with an impaired transcription in active T cells and thus blocks interleukin 2 activation, greatly improved transplantation graft survival [8]. In 1972, Ballinger and Lacy demonstrated that chemical diabetes could be "cured" in mice with islet transplantation [12].

Many groups had been working on rodent and canine models to perfect islet isolation and maintain demonstrable β-cell insulin secretion [13, 14]. Experiments in rats and mice showed that success in transplantation of islets could be obtained in rodents and the transplanted islets had a biphasic insulin secretory response to glucose [15]. Islet allotransplantation in animals was also successfully performed [16, 17] and it has been possible to isolate human islets that would function in diabetic nude mice [18, 19]. The results of these studies highlighted the need for purified islets and the importance of the site of transplantation. Multicellular islet tissue comprises 1.5% by weight of the whole pancreas [20]. Careful digestion is necessary to achieve a purified preparation, and collagenase became the mainstay in the digestion [13]. Success with isolation from human pancreases was more problematic than in animal studies [21, 22]. Methods used for the dissociation of islets from the exocrine tissue required a combination of mechanical and enzymatic techniques.

The site of transplantation was also an issue. The pancreatic bed, because of the risk of inducing acute pancreatitis, was not a preferred option. Liver, spleen, renal subcapsule, and an omental pouch have been the primary locations tried [17, 23–25]. Work with immune privileged sites, such as the testes, has been ongoing but has not been routinely adapted [26]. A site with portal drainage has the natural advantage of mimicking the normal route of insulin delivery and is most commonly used for human islet transplantation [27]. The splenic site was associated with infarction [28] and so the liver, renal, and omental pouch have been the preferred areas for islet transplantation. All sites have disadvantages compared to the native islet bed in that oxygenation is lower [29] and the intra-islet blood pressure is elevated [30]. The vascularization of the liver gives it an advantage and may help in angiogenesis of the islets while an advantage of the omental pouch or renal site is the ability to remove the islets for histologic examination. When the liver is used, an unresolved question is whether the venous drainage of the islets is into the portal sinusoids or the systemic circulation. A possible drawback of the portal site is that it allows more exposure to high levels of immunosuppressive drugs and their potential toxicity as they are absorbed [31].

Early human studies

The first human islet transplants, were performed in the 1970s [32], with insulin independence rarely reported [33]. Up to 1998, approximately 260 people with T1DM had received an islet transplant, with only 12% remaining insulin-independent for more than 1 week [27]. The first two patients transplanted as part of an early cohort transplanted in Edmonton in 1989 [34] received approximately 260,000 islets at the same time as a renal transplantation. Exogenous insulin was used intravenously for 14 days with intensive glucose monitoring in order to maintain euglycemia, which may help preserve β-cell function [35]. The immunosuppression therapy included corticosteroids, azathioprine, cyclosporin A, and Minnesota antilymphocyte globulin. Both patients demonstrated positive C-peptide status posttransplant but both developed cytomegalovirus infection and lost islet mass, never having achieved insulin independence. The subsequent five patients had transplants using both fresh and cryopreserved islets so that the total islet mass given exceeded 10,000 islet equivalents/kg. One patient obtained insulin independence for 2 years [36]. One patient who was transplanted at this time had a liver transplant with partially purified islets infused. Complete portal vein thrombosis ensued necessitating an urgent repeat liver transplant [37]. One other patient attained insulin independence for a period but eventually all patients required insulin again. On long-term follow-up, two of these patients have continued C-peptide production, the longest being more than 9 years since her transplant. However, subsequent technical problems arose in Edmonton, particularly with the collagenase, and so purified islets could not be obtained and thus islet transplantation lapsed as an avenue for treating diabetes. Other major centers, particularly

Miami/Pittsburg, St. Louis, and Milan, also reported early success [38–41] and demonstrated that the transplanted cells may survive for a prolonged time [42, 43].

Pancreas transplantation

With improved immunosuppression the possibility of performing whole pancreas transplants, particularly at the time of renal transplantation, for end-stage diabetic nephropathy, became a possibility [44]. Initial efforts were associated with peritonitis from exocrine drainage of the pancreatic duct. These problems were surmounted by using bladder drainage [45] such that success rates reached over 80% for 1-year graft survival accompanied by low mortality rates [46–49]. With newer techniques of anastomosis connecting the transplanted duodenum to an enteric drainage site [50], fewer problems were encountered (especially with the acidosis secondary to bicarbonate loss in the urine associated with the bladder anastomosis [51]). More than 25,000 whole pancreas transplants have been carried out worldwide. The 1-year graft survival rate has improved due to reduction in technical and immunological failure rates [52]. However, the overall 10-year graft survival rate for deceased donor pancreas transplants has not substantially improved over time and was 48% for transplants between 1995–1999 [53]. Graft survival is better for simultaneous pancreas–kidney transplantation than for either pancreas transplant alone, or pancreas transplantation after kidney transplantation. The side effects are diminishing but it remains a technically challenging surgical procedure [54–56] with some morbidity and mortality. The excellent glycemic control [54] can lead to reversal of diabetic renal lesions [55], stabilization or improvement in neuropathy [57, 58], vascular status [59, 60], and stabilization but not necessarily improvement of retinopathy [61, 62].

Islet transplantation and the Edmonton Protocol in the year 2000

The unimpressive results of islet transplantation in the late 1990s, as illustrated by low rates of insulin independence [42, 63, 64], were related to the islet preparation (purity of preparations and adequate islet numbers) [65] and immunosuppression (potency and toxicity especially in terms of glucose tolerance) as has been reviewed by Hering and Ricordi [66]. The field of islet transplantation was rejuvenated with our report of seven consecutive cases who achieved insulin independence after islet transplantation, using a steroid-free immunosuppression regimen (Edmonton Protocol) [67]. Some of the factors associated with this success are discussed below.

Islet isolation

Islet mass availability remained a central issue for success. An adequate islet mass contributed to the success of the Edmonton Protocol, with >11,000 islet equivalents/kg recipient body weight being transplanted.

The normal pancreas has 1.0–1.7 million islets [68, 69] yet early studies showed only 250,000 islets being recovered for allotransplantation. Minimizing warm and cold ischemia time and other donor issues are important [70, 71]. The use of University of Wisconsin perfusate solution at the time of organ retrieval [72] enhanced the yield. In addition, the intraductal delivery of collagenase [21, 22, 73], particularly with improved collagenase preparations [74, 75], further enhanced the number of islets obtained. Great strides were made in characterizing the collagenase necessary for purified islet isolation, resulting in much better preparations. The enzyme preparation Liberase was widely used for islet isolation and is a blend of primarily collagenase type 1 and 2, but also has collagenase 3 and 4, clostripain, thermolysin, and proteases (trypsin, chymotrypsin, and elastase), and is associated with a low endotoxin load [75].

Another major advance was the development of a metal chamber by Ricordi et al. that allowed disassociation of islets with mechanical digestion and the continuous removal and harvesting of the liberated islets [76, 77]. Purification of islets using a refrigerated COBE centrifuge and Ficoll gradient is also important; while it leads to some loss of cells, it reduces the otherwise substantial risk of intraportal hypertension associated with the infusion of unpurified preparations [37, 78]. The increased purification may also have a negative effect in that ductal elements, which may be important as a source for islet neogenesis, are removed [79].

Short-term culture of the islets may lead to enhanced purity without excessive loss of islets. In addition, the newer methods of islet isolation have removed all xenoproteins from the process, and this could further reduce the risk of rejection.

Immunosuppression

The importance of the appropriate immunosuppression regimen is demonstrated by the fact that with autotransplantation once 2500 islet equivalents/kg are provided then insulin independence can usually be achieved, but three or four times this number of cells are required for insulin independence in the allotransplant environment [80]. In the Edmonton Protocol, daclizumab was used for induction, followed by maintenance immunosuppression therapy with sirolimus (target trough levels of 12–15 μg/L for first 3 months, then 10–12 μg/L) and low-dose tacrolimus (target trough levels of 3–6 μg/L) [67]. Such a combination allowed the omission of steroids from the regimen, which was a major advantage in the setting of borderline islet mass by reducing β-cell toxicity. Effective blockade of interleukin 2 with sirolimus, which inhibits T-cell expression and activation, and daclizumab, an antibody to interleukin 2 receptors, allows inhibition of T-cell activation and provides potent immunosuppression. Sirolimus can result in lipid abnormalities but was not known to affect glucose tolerance [81, 82]. Tacrolimus, a more potent calcineurin inhibitor than cyclosporin A, is associated with some diabetogenicity [12, 83–85] by inhibiting insulin release [86] in a dose-dependent manner [87], a problem shared by its predecessor cyclosporin A

[88, 89]. Hence, part of the rationale for using sirolimus as the mainstay of immunosuppression with low-dose tacrolimus was to reduce diabetogenicity of the maintenance immunosuppresion regimen.

Islet transplantation current state-of-the-art

Following this initial success, more than 1800 islet transplants have been performed worldwide using the Edmonton Protocol or variants of it, and incorporating newer advances. Indeed, islet transplantation today is quite different from 15 years ago.

Islet preparation

Pancreas preservation

The University of Wisconsin solution (UW) was effective in pancreas preservation, but prolonged storage before islet isolation led to reduced recovery of viable islets [90]. The two-layer system using perflurodecalin (PFC) and UW for whole pancreas preservation was thus advocated for rescuing ischemically damaged pancreases [88]. This was due to the ability to ensure adequate oxygenation to the pancreas during preservation, and the reduction of cold ischemic injury by promoting adenosine triphosphate production [91]. It was also found that preservation in PFC resulted in the upregulation of anti-apoptotic genes and the downregulation of pro-apoptotic genes [89].

Indeed, islet recovery from pancreases preserved with the two-layer system was double that of UW alone [91, 92]. Furthermore, PFC preservation resulted in an islet yield from pancreases procured from marginal donors that were sufficient for clinical transplantation in more cases than with UW alone [92]. However, more recently, it was shown that there was no significant difference in islet yield or transplantation outcome regardless of whether the two-layer method or UW alone was used [93]. We currently use histidine-tryptophan-ketoglutarate (HTK) solution alone for pancreas preservation, which appears to be equally effective as UW for islet isolation. However, outcomes in clinical pancreas transplantation have been reportedly inferior where HTK is used in place of UW solution.

Islet culture

Previously, islets were infused into recipients within 2 hours of isolation [67], to reduce the risk of ischemic injury to the islets. However, this gave little time for appropriate quality control measures to be completed and potential recipients had to live near the transplant center. Our current practice is to culture islets for up to 72 hours prior to transplantation. This has numerous advantages since the additional time when the islets are in culture allows for the administration of conditioning or other immunosuppressive therapies, can result in improved safety because transplants can be carried out when the entire transplant team is present, and allows for better islet characterization before transplant [94]. In addition, the decrease in total tissue volume with culture may reduce the risk of portal vein thrombosis. Furthermore, the use of regional islet processing centers has been advocated as a means of standardizing the islet product, and hence, improving transplant outcomes. Islet culture can result in better islet recovery after shipment [95], and islet culture has now become standard and routine practice at most islet transplant centers worldwide.

Enzyme preparation and digestion protocols

In 2007, it became apparent that the crude collagenase extract in Liberase, a secretion product of *Clostridium histolyticum* bacteria, could have been contaminated with bovine brain infusion extract, as this extract contains high levels of lipid, carbon and nitrogen, which apparently facilitates the proliferation and secretory capacity of the bacteria. The specific risk to an islet transplant recipient is the possibility of prion transmission from the cow brain extract through the enzyme and into the pancreas organ during digestion of the gland. The estimated risk is currently unknown, but a working number is currently less than one in ten million risk, in other words exceedingly remote. Since then, most islet isolation centers have switched to an alternative enzyme manufactured by Serva. This is a GMP grade enzyme where the potential risk of prion transmission should be dramatically lower as no bovine brain extracts are used in the manufacture process. Using HPLC and collagenase activity assay, we found that the Serva collagenase is less pure and less potent compared to Liberase. However, with modification of our digestion protocols, we have now managed to achieve a high rate of islet isolation success (defined as >300,000 islet equivalents (IEQs), >70% viability and <5 mL packed tissue volume) that is superior to historical outcomes from the Liberase era (unpublished data). Specifically, we use different digestion protocols for younger ($\leq$35 years old) versus older donors. For younger donors, we use collagenase and neutral protease simultaneously, while for older donors, a higher amount of collagenase initially, followed by sequential digestion with a lower amount of neutral protease was found to be optimal. Others have found islet isolation outcomes and islet function are similar with the two enzyme blends [96].

Transplant procedure

Once adequate pure islets are prepared, the patient is brought to radiology and percutaneous access is established under midazolam and fentanyl sedation. After infiltration of local anesthetic, a 22-gauge Cheba needle is advanced under fluoroscopic guidance into the portal vein. Others have used CT guidance or it is possible to gain access by the transjugular route or with laparoscopy [97]. A guidewire is then inserted into the main portal vein and a catheter is positioned with confirmation by portal venogram. Purified islets are then infused with frequent monitoring of portal pressure. If the portal pressure doubles or rises to greater than 22 mmHg, infusion is halted until it resolves and if it does not resolve, the infusion is discontinued. Initially we used a 60 mL syringe but quickly adopted the use of an intravenous bag that is prepared in the laboratory [98]. This aids aseptic technique and

may also pose less shear pressure on the islets and further provides some constant monitoring of portal pressure during islet infusion.

This percutaneous approach can result in the risk of bleeding from the liver, which was seen in the first report. Subsequently, gelfoam pledgets and coils were used to seal the catheter tract, and bleeding was not seen in the next 28 cases [99]. However, in 2003, there was a spate of post-procedural bleeding (defined as an acute fall in hemoglobin of 20%, associated with free fluid on ultrasound, the need for blood transfusion or surgical intervention for control of bleeding) [99, 100]. Since then, the portal tributary cannulation site has been plugged with coils, and the tract ablated using tissue glue (Tisseel) with no further recurrence of bleeds in the next 35 procedures [100]. Over the most recent 10 years, we have found that Avitene powder (1 gram) dissolved in 6 cc of solution made up of radiological contrast media and saline has been the most effective, reliable, simple, and practical sealant approach. The advantage of making this up in contrast media is that deployment can be readily visualized on fluoroscopy, and provides confidence that the entire tract has been ablated. When adequately deployed, this has eliminated bleeding risks and has the practical advantage of being clearly visible during deployment on fluoroscopy.

Before transplant, intravenous insulin and dextrose infusions are started to maintain euglycemia during transplant. Initially, insulin was discontinued after transplantation and was avoided unless hyperglycemia (serum glucose ≥11.1 mmol/L) occurred [67]. Subsequently, this threshold was lowered and insulin was given if pre-meal glucose was >6.0 mmol/L or 2-hour post-meal glucose was >8.0 mmol/L [99]. We previously showed that maintaining euglycemia in the immediate post-transplant period could contribute to better graft survival [101]. Since mid 2005, it has been our policy to maintain euglycemia (serum glucose 4.0–7.0 mmol/L) following transplant by using intravenous insulin (minimum of 1 unit/hour) with dextrose infusions for the first 48 hours, and then subcutaneous insulin thereafter.

Intravenous heparin is also infused to keep the prothombin time between 70–90 seconds for 48 hours after transplantation, to promote engraftment by reducing the immediate blood-mediated inflammatory reaction (IBMIR). Heparin is withheld if there is inadequate tract plugging with Avitene (<3 cm in length) until imaging confirms the absence of bleeding.

After the heparin infusion is discontinued, subcutaneous low molecular weight heparin (enoxaparin 30 mg twice daily) is administered for seven days and aspirin 81 mg daily for 14 days.

In addition, patients receive one tablet of sulfamethozazole 400 mg–trimethoprim 80 mg daily for 6 months; *Pneumocystis* pneumonia prophylaxis, and valganciclovir 900 mg daily for 14 weeks when there is Cytomegalovirus status mismatch between donor and recipient, and in those who have received lymphocyte-depleting induction agents.

Immunosuppression

The immunosuppressive regimen of the original Edmonton Protocol is still being used today, with some modifications. Daclizumab was initially given at a dose of 1 mg/kg every 2 weeks for five doses. After 2003, this was changed to a dose of 2 mg/kg at transplant and at 5 days post-transplant [99]. This was because the latter dosing regimen was found to be efficacious and was more convenient for patients.

Recently, induction with antithymocyte globulin (6 mg/kg) and etanercept, with maintenance immunosuppression with tacrolimus (target trough level 8–10 μg/L) and mycophenolate mofetil (1 g twice daily) is used [100]. Also, a lymphocyte depletion protocol consisting of alemtuzumab (Campath-1H), tacrolimus and mycophenolate mofetil is being evaluated. Preliminary data suggest that the use of these potent induction agents has improved short- to medium-term graft outcomes [101–103].

Many of the initial patients who were on sirolimus and tacrolimus for maintenance immunosuppression have had intolerable side effects that were attributed to sirolimus (see later), necessitating a switch of immunosuppression to tacrolimus and mycophenolate mofetil. This latter combination appears to be as efficacious and better tolerated [104]. Furthermore, sirolimus impairs β-cell regeneration, and could contribute to the observed gradual loss of graft function seen following islet transplantation [105]. Thus, the current combination of tacrolimus and mycophenolate mofetil is now our routine first-line maintenance immunsouppression choice for islet transplantation.

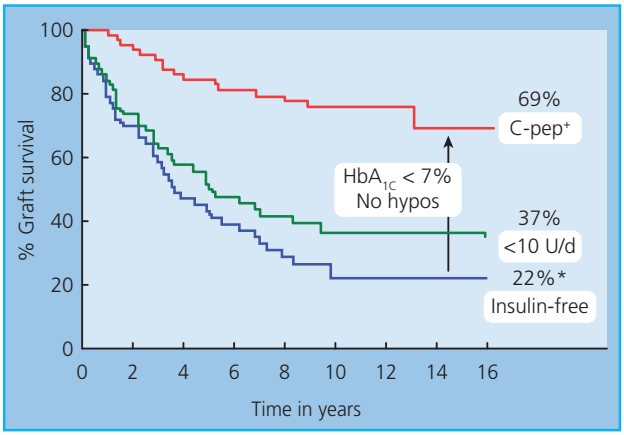
Islet transplantation outcomes

Glycemic control

Insulin independence was achieved in 11 out of the first 12 patients, after a minimum of 9000 IE/kg were transplanted [67]. HbA_{1c} levels improved in all islet recipients, and this was achieved without hypoglycemia and was accompanied by an improved stability of glucose control [67]. Unfortunately, insulin independence was not sustainable in the long term for the majority of patients. From survival analysis, only ~10% of patients remained off insulin at 5 years although most patients (~80%) still had C-peptide present [99] (Figure 69.1).

In terms of overall blood glucose control, those who remained off insulin did the best (median HbA_{1c} 6.2%), similar to the patients who were back on insulin but still had C-peptide (median HbA_{1c} 6.7%). Patients who had lost all graft function had relatively poor glucose control (median HbA_{1c} 9.0%), and required more insulin than before the transplant [96] (Figure 69.2).

The HYPO score and lability index were developed to measure the severity of hypoglycemia and glycemic lability. The HYPO score is generated using a combination of 4 weeks of self glucose monitoring results and self-reported hypoglycemic episodes over the previous year. For every episode of hypoglycemia <3 mmol/L in the 4 weeks, patients are instructed to record all symptoms felt and if assistance was required for recognition or treatment of the hypoglycemia. Higher scores were given for more severe hypoglycemic episodes (i.e. lower glucose values, absence of symptoms or neuroglycopenic symptoms, needing outside help



* Includes late retransplants

Figure 69.1 Kaplan-Meier graft survival curves over 16 years after islet transplantation. The blue line shows the overall proportion remaining completely free of insulin at 16 years, including those receiving late top-up transplant infusions (22% insulin free at 16 years). The green line shows similar survival curves for transplant recipients using less than 10 units of insulin per day, and continuing to enjoy substantial benefit from the islet procedure (37% at 16 years). The red line shows the proportion of individuals with measurable insulin release from their transplanted islets, as measured by human C-peptide release by 16 years (69% of transplant recipients). Importantly, the white box (HbA_{1C} < 7% and no hypos) shows the ongoing substantial benefit of even partially functioning islet transplants, where patients have markedly improved glucose control (HbA_{1C} < 7%) in a manner that cannot be achieved by exogenous insulin therapy, and protection from severe hypoglycemic reactions.

for recognition/treatment), while from the self-reported episodes in the past year, higher points were awarded if an ambulance was called or glucagon given. The lability index was also calculated from the 4 weeks of glucose records, using a formula that takes into the account the number of glucose readings, the glucose values, and the time interval between testing [106]. These scores are now routinely used in the assessment of suitability of a candidate for transplant, as well as for follow-up of transplant recipients. In addition, the Clarke score [107] is also frequently used, with a score of ≥4 indicating hypoglycemia unawareness.

Both the HYPO score and lability index show marked improvement post-transplant. With resumption of insulin use, there was more lability and some episodes of hypoglycemia, but both scores were still better than pre-transplant [99].

A key indication for islet transplantation is hypoglycemia unawareness. People who have received a pancreas transplant have restoration of their counter-regulatory response to hypoglycemia [108, 109]. The autonomic response and hence hypoglycemia awareness is also improved post pancreas transplant [110]. On the other hand, the same restoration in counter-regulatory responses and symptom recognition was not seen following successful islet transplantation [111]. Conversely, others have found that counter-regulatory hormonal and symptom responses to hypoglycemia do improve after islet transplantation [112–114]. The reasons for these differences are unclear, however, there may be a subset of patients who have return of hypoglycemia awareness, and/or the timing of testing could be critical. Indeed, we have noted that 85% of our cohort of islet transplant recipients reported return of symptoms of hypoglycemia, although 62% of them subsequently lost hypoglycemia awareness.

Diabetes complications

Retinopathy

Retinopathy has been reported to remain stable following islet transplantation [115, 116]. The majority of our patients (~80%) showed either no change or an improvement in retinopathy grade compared to baseline 3 years following islet transplantation. However, in our cohort, 18 of 98 (18.4%) islet transplant recipients had either vitreous hemorrhage or need for laser photocoagulation after islet transplantation, suggesting that close ophthalmologic follow-up remains necessary.

Nephropathy

We have previously reported that the estimated glomerular filtration rate (eGFR) (by MDRD study equation) declined with time. The median rate of eGFR decline was -0.39 mL/min/1.73 m^2/month with wide inter-patient variability [117]. This decline in GFR is comparable to that seen in optimally treated people with T1DM and albuminuria [118]. However, for one-third of the islet transplant recipients, the decline in eGFR exceeded that in untreated diabetic nephropathy [119]. In addition, on follow-up, progression in albuminuria was seen in 24% of patients, with regression only in 2.4% [117].

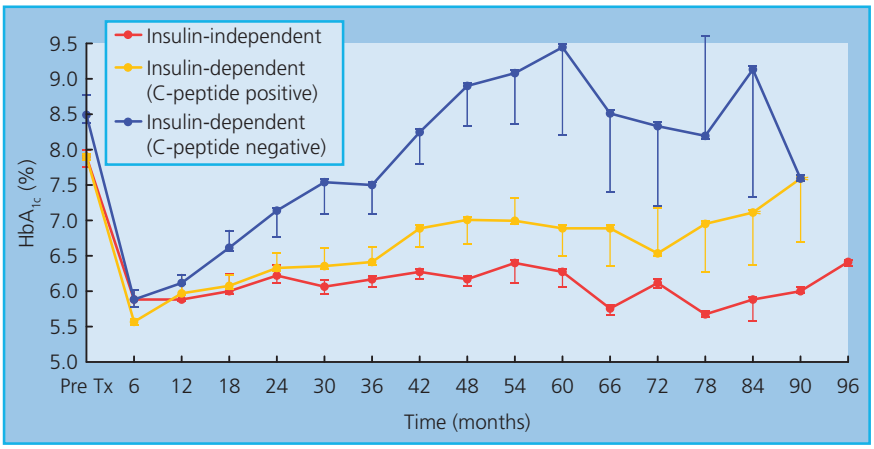


Figure 69.2 Glycemic control is related to islet graft function.

When tacrolimus and mycophenolate mofetil were used for maintenance immunosuppression, no difference in the rate of GFR decline was seen compared to either medically treated controls or the general population; nor was there any progression in albuminuria [120].

It is not clear at present whether the decline in renal function in islet alone transplants is due to progression of diabetic nephropathy or the effects of immunosuppression, in particular the combination of sirolimus and tacrolimus. Nevertheless, care should be taken during the patient selection process with regard to the assessment of renal function.

Neuropathy

There was no change in neuropathy status as assessed by vibration perception threshold or neuropathy disability score in our cohort [121], and others have shown stabilization of neuropathy [115].

Cardiovascular disease

A substantial proportion (30%) of islet transplant recipients at our center have pre-existing coronary artery disease prior to transplantation. In terms of cardiovascular risk factors, triglyceride levels increased (0.82 ± 0.04 mmol/L vs. 1.09 ± 0.06 mmol/L, $p < 0.001$, while there was a reduction in LDL-cholesterol levels (2.53 ± 0.06 mmol/L vs. 2.14 ± 0.06 mmol/L, $p < 0.001$) likely from an increase in statin use following transplantation. Blood pressure remained unchanged. Following islet transplantation, the rate of incident (new or worse) coronary artery disease was similar to the general T1DM population at 8.9 events/1000 patient-years [122].

Procedure-related complications

Complete portal vein thrombosis has not occurred with the use of purified islet allograft preparations, although partial thrombosis (of right or left branch, or peripheral segmental vein) was seen in about 5% of transplant recipients, all of whom were treated with anticoagulation without any long-term clinical sequelae [67, 99]. The risk of portal vein thrombosis has been minimized by: limiting the islet packed cell volume, careful monitoring of portal pressures during islet infusion, and intraportal dosing with heparin followed by systemic anticoagulation.

Other rare complications include gallbladder puncture and arteriovenous fistulae formation.

Liver enzymes (aspartate transaminase, alanine aminotransferase, and alkaline phosphatase) were elevated in >50% of transplants and are generally subclinical. These enzymes peak at around 1 week and normalize spontaneously within a month [123].

Changes consistent with fatty liver have also been observed on imaging post-transplantation [124]. These steatotic changes were confirmed with biopsy in some cases, and may be related to the high insulin levels the hepatocytes are exposed to following intrahepatic transplant [124]. It is unclear currently whether these changes would result in any long-term sequelae.

Side effects of immunosuppression

Most transplant recipients would have some side effects from immunosuppresion, but it is highly variable between patients.

Mouth ulcers previously occured frequently, but was entirely associated with use of sirolimus. These are usually small and self-limiting. Most respond to topical therapy, dose reduction, and switching to the tablet formulation of sirolimus [96]. Elimination of routine use of sirolimus has entirely resolved this problem.

Gastrointestinal disturbances, either constipation or diarrhea, are also common, occurring in 60% of islet transplant recipients, while acne was noted in 52%. Peripheral edema was reported by 43% of patients [100]. Peripheral edema was also closely linked to the high-dose use of sirolimus, and has similarly been largely eliminated through current use of tacrolimus and mycophenolate mofetil.

Ovarian cysts following transplant were previously commonly encountered [99]. It was also found in another small study that among women, ovarian cysts occurred in 62% of islet transplant recipients, and menstrual irregularity developed in all the six women who had regular menstrual cycles before transplant [125]. At our center, new ovarian cysts were found in 33 of 57 (57.9%) women after islet transplantation. Most cysts were asymptomatic but 14 women reported pelvic pain. Sirolimus withdrawal was associated with a reduction in cyst size and resolution of cysts in 80% of women. Also, the use of combined oral contraception appeared to be protective against ovarian cyst development [126]. Again, elimination of sirolimus from the routine regimen has largely resolved this issue.

Other complications related to immunosuppressive therapy include anemia, leukopenia, hypertension, dyslipidemia, weight loss, and fatigue [100].

Tacrolimus was associated in a dose-dependent manner with tremor and nephrotoxicity. The combination of sirolimus and tacrolimus could also worsen renal function. Indeed, two individuals in whom tacrolimus was switched to mycophenolate mofetil (MMF) had stabilization of renal impairment [127]. Also, three patients had resolution of proteinuria after sirolimus was withdrawn and replaced by a combination of cellcept and higher dose tacrolimus [128].

Mycophenolate mofetil is generally well tolerated, with the most commonly reported side effect being gastrointestinal in nature (bloating, diarrhea, abdominal cramps), which usually subside with dose reduction [129].

Pneumonia occurred in 3 patients, of which one was considered fungal in etiology [98].

Cytomegaloviral disease has not occurred, although seroconversion from negative to positive has occurred in 4 of 67 (6%) islet transplant recipients. To date, we have encountered a single incidence of post-transplant lymphoproliferative disorder in now 252 patients treated (risk 0.39%), a risk which is lower than that encountered in other solid organ transplantation.

With experience, we have learned to tailor the immunosuppression regimen and target drug levels to minimize side effects without compromising graft function, such that fewer complications are seen in those transplanted more recently as compared to earlier patients.

Thirty-four patients had undergone immunosuppression change from sirolimus+tacrolimus to tacrolimus+mycophenolate mofetil following islet transplantation. The three most frequent reasons for this change were: peripheral edema (18/34, 53%), gastrointestinal symptoms (11/34, 32%), and ovarian cysts in women (9/26, 35%). These all improved after the immunosuppression change. Importantly, there was no change in graft function or immune status following the change [104].

Immune sensitization

The percentage of panel reactive antibodies (PRA) increased in 13% of patients from levels <15% to ≥15% after transplant [99]. Recently, it has become clear to us that positive PRA does negatively impact islet transplant outcome. Indeed, pre-transplant PRA of >15% in either class I or II is an independent predictor of poor graft survival (in terms of C-peptide) after transplant [130].

For individuals with high PRA, it will be important to determine the specific antibodies causing the positive PRA and a flow cytometry-based crossmatch performed against potential donors before transplant. Our current policy is to perform prospective crossmatches for all recipients with PRA >5% and for those who have received previous transplants.

It has become apparent that high rates of broad PRA sensitization were observed in patients when immunosuppression was slowly and completely withdrawn following complete graft loss [131]. Our current approach is therefore not to withdraw all immunosuppression when a patient loses all islet function, but rather to wean down to single-agent therapy with mycophenolate (Myfortic therapy). We currently plan to continue this for at least 2 years after function is lost in order to reduce the risk of subsequent sensitization. The effectiveness of this strategy is still to be evaluated.

Indications and contraindications for islet transplantation

At our center, islet transplantation is offered to people with T1DM who have severe hypoglycemia and/or hypoglycemia unawareness, or glycemic lability, in spite of optimal medical therapy with frequent blood glucose monitoring and the use of multiple daily insulin injections or continuous subcutaneous insulin infusion. This is largely still based on clinical judgment, although the use of the HYPO score and lability index adds an objective component to the decision. Some individuals have progressive complications despite optimization of medical therapy. Although we originally considered this group, they are now the exception, as we are concerned about the potential for immunosuppression to exacerbate renal impairment.

Diabetes-related complications are not absolute contraindications for islet transplantation. For people with unstable retinopathy, we recommend waiting for 6 months from the last treatment for the disease to stabilize before islet transplantation since there is a risk of worsening following transplantation. The sirolimus and tacrolimus combination is avoided in individuals with macroalbuminuria (>300 mg/day). We prefer not to transplant people with mild to moderate reduction in GFR (<60 mL/min/1.73 m^2). We also recommend waiting for at least 6 months following myocardial infarct, revascularization procedure, or evidence of ischemia on functional cardiac testing. A severely reduced left ventricular ejection fraction <30% is a contraindication for islet transplantation.

The current accepted indications and contraindications for islet transplantation in most centers are listed in Table 69.1.

Patient evaluation

At the assessment visit for islet transplantation the person with diabetes should have a realistic expectation of the outcome. If they have frequent hypoglycemia and glycemic lability problems, then both of these are readily correctable by islet transplantation. The ability to render the person free of the risk of progression of diabetes complications is unproven at this time, although given good glycemic control this may be expected in the longer term. Those who have active infection, a history of cancer, severe vascular disease, or active foot ulceration, who abuse alcohol or drugs, or who are younger than 18 or older than 65 years are not usually considered. Once the individual meets the entry criteria and is willing to accept the risks of the procedure and immunosuppression, a full evaluation is required. This includes a thorough history and physical examination, the latter concentrating on diabetes complications: retinopathy, neuropathy (autonomic and peripheral), and vascular disease. Our laboratory evaluation includes details of these complications with an ophthalmology report required, 24-hour urine for microalbuminuria, protein, and creatinine clearance; together with a serum creatinine, ECG, stress MIBI scan, and a lipid panel. If there is any suggestion of an abnormality either clinically or on vascular testing, coronary angiogram is performed. In addition, the basic transplant screens are required, including blood group, complete blood count, coagulation screen, liver function tests, electrolytes, calcium, magnesium, phosphorus, analysis for HIV, hepatitis, Epstein-Barr virus, syphilis, cytomegalovirus, and urine culture. An ultrasound of the abdomen and liver is required to ensure that no lesions are present in the liver. A hemangioma on the right side of the liver would place a patient at increased risk of bleeding during the procedure if a percutaneous approach was used. In people older than 40 years, mammograms are performed in women and prostate-specific antigen determinations in men. Considerable time is spent reviewing the potential complications with the patients so that each individual can make a personal assessment of the risk–benefit ratio for themselves and decide if they wish to proceed. In most other transplant settings (heart and liver), the issues are life and death but in islet transplantation this is not the case, as continuing to work with other insulin regimens is possible and thus risk–benefit issues are different.

Table 69.1 Indications and contra-indications for islet transplantation.

A. Indications for islet transplantation

Clinical history compatible with T1DM, with stimulated C-peptide <0.3 μg/L on mixed meal tolerance test.

Intensive diabetes management

- Glucose testing ≥3 times/day
- ≥3 insulin injections/day or insulin pump as directed by endocrinologist, diabetologist or diabetes specialist with ≥3 clinical evaluations during the past year.

≥1 severe hypoglycemic event, defined as an event with one of the following symptoms: memory loss; confusion; uncontrollable behavior; irrational behavior; unusual difficulty in awakening; suspected seizure; seizure; loss of consciousness; or visual symptoms, in which the person was unable to treat him/herself and with blood glucose <54 mg/dL (3 mmol/L) or prompt recovery after oral carbohydrate, intravenous glucose or glucagon in the past 1 year.

One of the following:

- Reduced hypoglycemia awareness (Clarke score ≥4 or HYPO score ≥90th percentile or ≥1047) within last 6 months
- Marked glycemic lability with wide swings in glucose levels despite optimal therapy, with glycemic lability index ≥90th percentile or 433 within last 6 months
- Composite Clarke score ≥4 + HYPO score ≥75th percentile (≥423) + lability index ≥75th percentile (≥329)

B. Contraindications for islet transplantation

Glycated hemoglobin ≥10%

Untreated proliferative retinopathy

Blood pressure >160/100 mmHg

Glomerular filtration rate <80 mL/min/1.73 m^2

Presence or history of macroalbuminuria >300 mg/day

Presence or history of panel reactive anti-HLA antibodies (by flow cytometry)

Active infections, including:

- Hepatitis B, hepatitis C or HIV
- Tuberculosis requiring treatment within the previous 3 years
- Invasive aspergillus, histoplasmosis, or coccidiomycosis within 1 year

Severe cardiac disease

- Myocardial infarct within 6 months
- Evidence of ischemia on functional cardiac testing within 1 year
- Left ventricular ejection fraction <30%

Any history of malignancy except for completely resected squamous or basal cell carcinoma of the skin.

Receiving treatment for a medical condition requiring chronic use of systemic steroids except for the use of ≤5 mg prednisolone daily or equivalent.

Any medical condition that could interfere with safe participation in islet transplantation.

Desired pregnancy (female recipient)

Challenges and future directions

Islet shortage

The shortage of donor pancreases for islet transplantation remains a challenge. Most recipients require more than one islet infusion to become insulin-independent. Given the limited supply of organs, the ability to achieve insulin independence after infusion of islets from a single donor is an important goal which has been achieved by Hering et al. in carefully selected recipients given excellent islet preparations, intensive peritransplant management, and alternative induction immunosuppression [101]. Other alternative sources of islets include xenografts (e.g. porcine islets) or stem cells, but these remain in the pre-clinical experimental phase at present [132–134].

Islet engraftment

Defects in insulin secretion soon after transplantation of what should be an adequate islet mass indicates that many islets were lost at the time of engraftment. This could be due to hypoxia early post transplant [135], the toxic effects of the immunosuppressive drugs [136], and the IBMIR which results in immune destruction of islets [137]. It has been estimated that only a third of islets engraft successfully [138].

Various strategies are being tested in attempts to improve engraftment, including the use of vascular growth factors to promote re-vascularization [139], inhibitors of IBMIR [140], and anti-apoptotic peptides (e.g. caspase inhibitors) [141]. The use of low molecular weight dextran sulphate was found to block IBMIR to a greater extent than heparin, possibly by its more potent inhibition of the complement system [142]. The use of islet surface heparinization was also shown to significantly attenuate IBMIR *in vitro* and *in vivo*, without systemic side effects [143].

Monitoring the islet graft

A key barrier to understanding what happens to the islet graft after transplantation is the lack of access to the graft. Current methods of monitoring graft function are based on the measurement of markers of glucose homeostasis, which may not be disrupted in early stages of rejection [144]. Immunological monitoring is limited by the lack of standardized markers for autoimmunity and rejection [145]. Unlike other solid organ transplants, serial protocol liver biopsies may not yield sufficient islet tissue for examination. Several approaches for β-cell imaging have been proposed, but are still in various stages of development [146]. Clearly, it is of vital importance to develop methods to detect graft dysfunction in its early stages or even before it happens, so as to allow intervention in an attempt to rescue the graft.

Promoting graft survival

Islet graft function appears to decline over time, with most islet transplant recipients returning to insulin use. The glucagon-like peptide 1 (GLP-1) receptor agonist, exenatide, when used in islet transplant recipients with failing islet graft function resulted in reduction in insulin requirements, but this could not be sustained when the drug was discontinued, suggesting that there was no trophic effect on β-cell mass [147]. The lack of detectable changes in markers of allo- or auto-immunity in the majority of islet transplant recipients, together with the absence of significant inflammatory infiltrate in histological specimens of islet transplants suggest that non-immunological mechanisms

play an important role in the gradual graft loss [99, 148]. Possible culprits include increased metabolic demand and toxicity of immunosuppressants, and certainly warrant further investigation.

Immunosuppression toxicity

While newer immunosuppressant drug combinations are associated with less toxicity, the ideal situation would be the ability to withdraw immunosuppressive drugs after an initial period of use post transplant. To achieve this, tolerance to the graft must be induced. Co-stimulation blockade has shown promise for tolerance induction. There have been encouraging results with belatacept (LEA29Y), a potent new CTLA4-Ig, in primate models of islet transplants [149], and clinical trials in human are in progress. Indeed, the use of belatacept for ongoing maintenance immunosuppression, thus allowing the avoidance of calcineurin inhibitors, has been used successfully in the renal transplantation setting and may be the basis for future maintenance therapy [150].

Another strategy would be islet encapsulation, but this has been associated with limited success to date [151].

Summary and conclusions

Islet transplantation can correct problems with glycemic lability and recurrent hypoglycemia. Given its technical ease, it is particularly suitable for those with problems with glycemic control and no other major complications. The more technically difficult whole pancreas transplant provides stable glucose control and is ideal in those undergoing simultaneous renal transplant. The islet transplant procedure has some risks both acutely (particularly bleeding, and thrombosis in the portal vein circulation) and in the long term, the unknown but real risk of sepsis and neoplasms. For some people with major problems with diabetes control these risks are acceptable. Whether the good glycemic control attained will prevent complications in the long term will take years to resolve. Using the indication of progressive diabetes complications is less suitable at this time, given the problems encountered. Islet transplantation can free an individual with very difficult diabetes from the risks of frequent hypoglycemia or glycemic lability. The decision whether to proceed can only be made by an informed patient who has to cope with difficult diabetes on a daily basis.

Major steps have been taken in islet transplantation but more needs to be done. Significant changes over the past 10 years have resulted in improved outcomes, but many challenges remain. Islet transplantation has faced hurdles before and overcome them. These new challenges can be met and solved. To quote Sir Winston Churchill, "Now this is not the end. It is not even the beginning of the end. But it is, perhaps, the end of the beginning."

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70 Gene Therapy for Diabetes

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Key points

- The term "gene therapy" defines any therapeutic strategy based on the genetic modification of a cell by introduction of exogenous genetic material in order to prevent, correct or ameliorate the symptoms of a disease.
- The selection of a gene transfer vector over another depends on the indication, the target tissue in case of *in vivo* gene therapy and the period of time during which the expression of the transferred genetic material is required.
- The use of gene transfer technologies has allowed the development of potential therapeutic strategies for the treatment of type 1 (T1DM) and 2 diabetes (T2DM), as well as the performance of proof-of-concept studies in small and large animal models to understand the pathophysiology of these diseases better.
- For T1DM, most gene therapy strategies have focused on restoring insulin production by islets or surrogate cells, enhancing glucose disposal or preventing the destruction of remaining β cells.
- For T2DM, attempts have been directed towards ameliorating insulin resistance in peripheral tissues, enhancing insulin production or increasing the functionality and/or mass of β cells.
- Extensive studies are required to demonstrate the efficacy and safety in large animal models of the approaches that have shown therapeutic potential in small diabetic animals before any of these gene therapies are brought to the clinic to treat diabetes in humans.

Introduction to gene therapy

Gene therapy is a therapeutic strategy based on the genetic modification of a cell by introduction of exogenous genetic material in order to prevent, correct, or ameliorate the symptoms of a disease. Originally, gene therapy was conceived to supplement or replace the function of a defective gene by delivering to the target cell a functional copy that could mediate the production of the desired therapeutic protein. Progress in the field has led to the broadening of gene therapy applications, and nowadays the introduction of genetic material to a cell is not only limited to gene addition but also includes induction, repression, and modulation of gene expression at transcriptional and post-transcriptional level and, more recently, genome editing. To these ends, full-length genes, cDNAs and a variety of modulatory and interfering RNA and DNA molecules, including antisense RNA, short-hairpin RNA (shRNA), microRNA (miRNA) and microRNA target sequences (miRT), have been used. Furthermore, the vast range of technologies that the field has set up over the years for therapeutic purposes are also being exploited in proof-of-concept studies to demonstrate gene function.

On the basis of the strategy used, gene therapy can be classified into the following two subtypes: *ex vivo* gene therapy, in which target cells are genetically modified *in vitro* before transplantation into the patient, and *in vivo* gene transfer, in which cells are genetically modified *in situ* in the individual [1].

The success of gene therapy depends on the existence of gene transfer vehicles capable of safely and efficiently introducing genetic material into target cells either *ex vivo* or *in vivo*. In order to achieve this goal, a wide variety of vectors has been developed over the past few years; these are generally divided in two categories: non-viral and viral vectors. Delivery systems based on non-viral vectors include both the direct administration of naked nucleic acids and the use of physico-chemical means to ferry the genetic material into the target cell, such as electrotransfer or incorporation of nucleic acids into liposomes or cationic polymers. On the other hand, the use of viral vectors exploits the natural ability of viruses to enter cells, transfer their genetic material to the nucleus and express proteins. So far the vast majority

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of gene therapy strategies developed for the treatment of diabetes have been based on the use of viral vectors as gene transfer vehicles.

Viral vectors

Several naturally occurring viruses have been subjected to numerous genetic modifications to allow their use as safe gene transfer vehicles. For example, viral vectors cannot develop a productive infection after delivery to cells or animals due to the genetic deletion of genes essential for the life cycle of the wild-type virus. Therefore, recombinant viral particles contain a genetically modified viral genome that may be partially or completely devoid of viral genes and is unable to generate new virions upon infection. They retain, however, the infectivity of the wild-type virus and its ability to mediate introduction of the genetic material into the cell nucleus (a process known as transduction) because these functions are conferred by the capsid itself [2].

The selection of one vector over another depends on the gene transfer application, the target tissue in case of *in vivo* gene therapy and the period of time during which the expression of the transferred genetic material is required. For example, for proof-of-concept studies or if short-term expression is sufficient, adenoviral vectors (AdV) show great efficiency of transduction *in vitro* and *in vivo*. However, the immunogenicity of these vectors precludes their use for therapeutic purposes [3], particularly in the context of chronic diseases such as diabetes. For therapeutic, *in vivo* approaches in which long-term gene expression is desired, adeno-associated vectors (AAV) stand out as the vectors of choice. The wild-type virus is non-pathogenic and the different serotypes of vectors have ability to transduce a wide variety of cell types, mediating long-term expression of the gene of interest in non-dividing tissues. In addition, the simple composition of AAV vectors, and their low efficiency in transducing professional antigen-presenting cells perhaps contribute to their generally low immunogenicity [4]. These gene transfer vectors have been used in clinical trials since the mid-1990s, and no serious adverse events related to the vectors have been described so far. More than 300 participants have been enrolled in these studies, comprising adults and children affected by different pathologies, generally all serious illnesses, and administered with recombinant AAV at different doses and through different routes to target different organs, mainly liver, skeletal muscle, brain, and eye [5]. Thus, recombinant AAV vectors are regarded as having a strong safety record after both local or systemic administration [6]. Indeed, in 2012 the European Medicines Agency gave marketing approval to the first gene therapy product for the management of lipoprotein lipase deficiency (Glybera®) based on the administration of lipoprotein lipase-expressing AAV vectors of serotype 1 (AAV1) to the muscle. The only limitations to the use of these vectors are their limited cloning capacity, the presence in the general population of pre-existing anti-AAV humoral immunity due to natural infection that may preclude transduction of certain organs, and the subclinical activation of capsid-specific T cells when vectors are administered to peripheral organs that can limit expression of the therapeutic transgene but this has so far been efficiently controlled with short-course immunosuppression [7–9].

The main properties of the viral vectors most commonly used in gene therapy are summarized in Table 70.1.

Gene therapy for diabetes

Both type 1 diabetes (T1DM) and type 2 diabetes (T2DM) are characterized by hyperglycemia, which when not properly controlled, ultimately leads to the development of severe microvascular, macrovascular, and neurological complications with high morbidity and mortality. Although the control of hyperglycemia remains the main target of the strategies developed so far for diabetes, several approaches target other components of the disease pathogenesis, which are different in T1DM and T2DM, as discussed later.

Much less work has been done in the development of gene therapy approaches for diabetes long-term complications. The complexity of the mechanisms underlying the development of these diseases as well as the lack, in most cases, of appropriate animal models of human disease, in particular retinopathy, neuropathy and nephropathy, have hampered this objective.

Gene therapy for T1DM

The hyperglycemia of T1DM results from an absolute deficiency of insulin secretion due to the autoimmune destruction of the β cells of the pancreas. Therefore, the main gene therapy approaches developed for T1DM have focused on restoring insulin production by islets or surrogate cells, enhancing glucose disposal or avoiding the destruction of remaining β cells.

Ex vivo genetic engineering of islets for transplantation

Islet transplantation has demonstrated therapeutic benefit in people with T1DM, particularly with the Edmonton Protocol (see Chapter 69) [10]. However, the scarcity of cadaveric donors and the large quantities of functional islets required for amelioration of diabetes in each single individual have limited the broad clinical application of this approach. Moreover, the processes of islet isolation, purification and transplantation, together with the host's immune response, greatly impair islet function and promote islet apoptosis, limiting the long-term survival of the grafts [10]. To overcome these limitations, several studies have explored gene therapy strategies based on the *ex vivo* genetic engineering of islets prior to transplantation. Adenoviral vectors have been the most extensively used vectors to this end because of their high efficiency for *ex vivo* transduction of islets of different species, including human [11, 12]. The transgenes used to improve the outcome after transplantation can fall within three main categories:

1 Mitogenic and/or prosurvival/anti-apoptotic factors aimed at promoting islet survival, such as hepatocyte growth factor (HGF),

Table 70.1 General characteristics of the most commonly used viral vectors.

Viral vector	Retroviral (RV)	Lentiviral (LV)	Adenoviral (Ad)	Adeno-associated (AAV)	Herpes Simplex (HSV)
Family	*Retroviridae*	*Retroviridae*	*Adenoviridae*	*Parvoviridae*	*Herpesviridae*
Pathogenicity of parental virus	Yes	Yes	Yes	No	Yes
Genome	ssRNA, lineal	ssRNA, lineal	dsDNA, lineal	ssDNA, lineal	dsDNA, lineal
Maximum cloning capacity	8 kb	8 kb	36 kb	4.7 kb	150 kb
Production at high titers	Yes	No	Yes (lower titers with 3rd generation vectors)	Yes	No
Insertion in host genome	Yes, with preference for regulatory elements	Yes, but with no preference for regulatory elements	No	Yes, but randomly and with extremely low frequency Mainly episomal.	No
Innate immunity	Yes	Yes	High for 1st and 2nd generation vectors	Very limited	Yes
Target cells	Infects dividing cells	Infects dividing and quiescent cells	Infects dividing and quiescent cells	Infects dividing and quiescent cells	Infects dividing and quiescent cells
Transgene expression	Long-lasting	Long lasting	Short-lived, except for 3rd generation vectors	Long-lasting	Short-lived, except for late generation vectors
Main advantages	Long-lasting expression in dividing cells Production at high titers	Long-lasting expression in dividing cells	Episomal Production at high titers (except for 3rd generation) High levels of transduction *in vivo* High cloning capacity	Episomal Production at high titers High levels of transduction *in vivo* Non-pathogenic, low immunogenicity Several serotypes with different tissue tropism	Episomal High cloning capacity
Main disadvantages	Infects only dividing cells Limited cloning capacity Risk of insertional mutagenesis	Limited cloning capacity Risk of insertional mutagenesis but lower than for retroviral vectors	Inflammatory and immune responses to the viral proteins limit persistence of transgene expression. Diminished in 3rd generation vectors. Useful only for short-term studies Unselective tropism	Limited cloning capacity	Transient expression of the transgene Non -characterized neurotoxicity

X-linked inhibitor of apoptosis (XIAP), manganese superoxide dismutase (MnSOD), B-cell lymphoma 2 (Bcl-2), and heme oxygenase-1 (HO-1) [13–15].

2 Immunoregulatory genes to counteract the immune response that destroys β cells, such as interleukin-1 receptor antagonist protein (IRAP), interleukin 10 (IL-10), interleukin 4 (IL-4), and transforming growth factor β (TGF-β) [16, 17].

3 Factors that promote vascularization, such as HGF and vascular endothelial growth factor (VEGF), given that hypovascularization has been deemed a likely culprit for the short-term survival of transplanted islets [18, 19].

In general, these strategies enhanced the viability and function of the transplanted islets and attenuated β-cell death, preventing graft failure and reversing hyperglycemia.

In addition to the *ex vivo* genetic manipulation of islets, AAV vectors have been used *in vivo* to deliver immunomodulatory genes, such as the immunosuppressive IL-10 or Epstein-Barr-derived BCRF-1, to the muscle of the recipient of the islet graft prior to the transplant [20, 21]. This strategy has been shown to prevent recurrence of autoimmunity and allogeneic rejection, resulting in prolongation of graft survival and remission of diabetes in mice [20, 21].

Ectopic production of insulin by non β cells

Other gene therapy strategies have focused on the use of surrogate cells to produce insulin. In β cells, proinsulin is processed into mature insulin by the proprotein convertases PC1/3 and PC2, which are absent in the majority of other cells. To solve this problem and enable the processing of proinsulin by surrogate cells not expressing PC1/3 and PC2, new proteolytic sites have been engineered in the proinsulin molecule which are recognized by furin, a protease present in most cells.

Several cell types have been used in *ex vivo* gene transfer approaches to achieve ectopic production of insulin, including mouse pituitary corticotroph cells [22], keratinocytes [23, 24], fibroblasts [25], myotubes [26], hepatocytes [27, 28], and gut K cells [29, 30]. For the last four engineered cell types there is evidence of amelioration of glycemia, ranging from partial to total, when transplanted into diabetic mice [25, 26, 28, 30]. However, in most of these studies the therapeutic effect was short-lived due to loss of transplanted cells [25, 26, 30].

The most noteworthy results in the attempts to achieve ectopic insulin production have been obtained by genetically engineering hepatocytes *in vivo* to produce insulin in a glucose-regulated manner. Hepatocytes are attractive target cells because they express the same glucose-sensing molecules as β cells, such as the glucose transporter type 2 (GLUT-2) that mediates the insulin-independent entry of blood glucose into the cell and the enzyme glucokinase (GK), which phosphorylates the incoming glucose molecule. In addition, hepatocytes are essential regulators of carbohydrate metabolism and several genes expressed in the liver are transcriptionally regulated by glucose or insulin, offering the possibility of engineering glucose/insulin-controlled expression cassettes that mediate the production of insulin as a function of circulating glucose/insulin levels. To this end, naturally occurring promoters such as those from the GLUT-2, phosphoenolpyruvate carboxykinase (PEPCK), glucose-6-phosphatase (G-6-Pase) and liver-pyruvate kinase (L-PK) genes as well as engineered hybrid and synthetic promoters have been used to mediate glucose/insulin-responsive insulin expression following *in vivo* delivery of gene transfer vectors [31–37]. None of these systems, however, managed to mimic the quick response to glucose of the insulin promoter [34], and the slow glucose-mediated transcriptional control of these promoters may result in an inadequate insulin secretory response, with postprandial episodes of hyperglycemia followed by hypoglycemia several hours later.

Enhancement of glucose disposal

As an alternative to ectopic glucose-regulated insulin expression in the liver, gene transfer of the insulin gene can be used to engineer a glucose sensor in skeletal muscle in order to enhance glucose uptake in a glucose-dependent manner in this tissue to lower diabetic hyperglycemia [38]. Several reasons support the choice of skeletal muscle as a target organ for this strategy. First, muscle can efficiently secrete proteins into the bloodstream and has a metabolism highly based on glucose consumption, accounting for about 70% of glucose disposal after a meal. Second, muscle is easily accessible by non-invasive procedures, and gene transfer by AAV vectors leads to minimal systemic biodistribution, limiting biological effects to this organ even if ubiquitous promoters are used to direct therapeutic transgene expression [39]. Moreover, gene delivery to muscle is not limited by the presence of pre-existing neutralizing antibodies against AAV [40], a key aspect given the relatively high prevalence of anti-AAV antibodies in the general population [41].

In normal conditions, insulin stimulates glucose uptake in skeletal muscle by promoting the translocation of the glucose transporter type 4 (GLUT-4) to the plasma membrane [42]. Once inside the muscle cell, glucose is phosphorylated by hexokinase II (HK-II) [43]. HK-II has a low Km for glucose and is inhibited by glucose-6-phosphate, which limits glucose uptake. In contrast to HK-II, the hepatic GK has a high Km for glucose (about 8 mM), is not inhibited by glucose 6-phosphate, and shows kinetic cooperativity with glucose [43]. During diabetes, because of the lack of insulin, the translocation of GLUT-4 to the plasma membrane and mRNA levels and activity of HKII are decreased in muscle cells [44, 45], compromising the ability of the skeletal muscle to dispose of glucose after a meal. To counteract diabetic hyperglycemia, a novel gene therapy approach has been developed based on the co-expression of the insulin and glucokinase genes in muscle cells. The rationale behind this approach is based on the following premises:

1 Expression of constant, low levels of insulin ensures translocation of GLUT-4 to the plasma membrane without the risk of causing hypoglycemia;

2 Low levels of insulin are also sufficient to inhibit lipolysis and prevent ketoacidosis; and

3 The expression of GK draws the uptake of glucose into the muscle cell only when blood glucose levels are high.

Hence, the combination of these two genes generates a "glucose sensor" in the skeletal muscle that uptakes large quantities of glucose only when circulating glucose levels rise, such as in postprandial conditions, but does not cause hypoglycemia because GK activity is shut down at physiological glucose concentrations.

As a proof of concept, this approach was first tested in transgenic animals that overexpressed the insulin and glucokinase genes specifically in skeletal muscle [38]. When made diabetic, these mice were normoglycemic and did not develop secondary complications. Afterwards, AAV1 vectors were used to transfer the insulin and glucokinase (GCK) genes to the skeletal muscle of diabetic mice. In contrast to untreated diabetic mice, in AAV1-Ins and AAV1-GCK-treated mice, long-term restoration of fed and fasted normoglycemia was achieved [38]. AAV1-treated mice also showed increased skeletal muscle glucose uptake, normalization of glucose metabolism in the liver (increased glucose uptake and glycogen synthesis and reduced hepatic glucose production) and improved glucose tolerance [38]. Moreover, these mice had normal food and fluid intake, and the weight of the abdominal fat pad and skeletal muscle was normalized [38]. This study established the proof-of-concept that a gene therapy based on the production of basal levels of insulin and the increased uptake of glucose by the skeletal muscle allowed for a tight regulation of glycemia [38].

As a next step towards the clinical translation of this approach, a pre-clinical study in diabetic dogs was undertaken to investigate feasibility, efficacy, duration of the therapeutic effect as well as safety issues. A single intramuscular administration of AAV1 vectors encoding for insulin and GCK to diabetic dogs resulted in normalization of fasting glycemia and accelerated disposal of glucose after an oral challenge for >4 years after gene transfer,

with no episodes of hypoglycemia, not even during exercise [39]. This normalization of glucose metabolism was associated with recovery of body weight, normal levels of glycated plasma proteins, and long-term survival without secondary complications. In contrast, gene transfer of either the insulin or the GCK genes alone failed to achieve complete correction of diabetes, indicating that the synergistic action of insulin and GK are needed for full therapeutic effect [39].

In vivo reprogramming of surrogate cells into β cells

The concept of β-cell reprogramming implies the transdifferentiation of a surrogate cell into a functional β cell capable of sensing glucose and releasing insulin accordingly. This is generally achieved through the use of transcription factors that are key for the differentiation of progenitor cells into β cells during pancreas development.

Most *in vivo* approaches tested so far have used adenoviral-mediated gene transfer of Pancreatic duodenal homeobox-1 (Pdx-1), NeuroD, MafA, and Neurogenin-3 (Ngn3), individually or in combination, to liver or pancreatic exocrine cells via systemic or intra-pancreatic administration, respectively [46–55]. Although this vector type generally mediates short-term expression of transgenes of interest (Table 70.1), their use here is justified because evidence suggests that, at least in the liver of mice, adenoviral transduction per se is required for efficacy [54]. When the target cells were hepatocytes, oval cells or ductal cells in the liver, hyperglycemia partially ameliorated because of the expression of insulin in these cells, but full phenotypic conversion into functional β cells could not be achieved [46–51, 53, 54]. In contrast, when cells from the exocrine pancreas were reprogrammed, the resulting cells did not exhibit a hybrid or mixed phenotype but closely resembled islet β cells at biochemical and ultrastructural level [52, 55]. Furthermore, reprogrammed cells formed islet-like structures and mediated long-term (>1 year) normalization of hyperglycemia [52]. It is worth mentioning that the formation of islet-like clusters and the acquirement of glucose-responsiveness like the one of endogenous β cells were slow processes, and full physiological maturity of the reprogrammed cells was not accomplished until several months after reprogramming induction [52].

It should be borne in mind that genetically reprogrammed β cells, like endogenous islet β cells, will be susceptible to autoimmunity [56], hence reprogramming gene therapy approaches may require concomitant immunotherapy to avoid destruction of the β-cell surrogates.

β-Cell regeneration

Another approach to restore the β-cell mass considers the regeneration of β cells from those cells that have survived the attack of the immune system. The regenerative potential of the endocrine pancreas seems to be quite high immediately after the onset of the disease [57], but it slows down as the disease progresses [58]. To induce replication of remaining β cells, genes have been transferred *in vivo* to murine and canine β cells mostly by means of adenoviral and AAV vectors, the latter having a much more efficient transduction, via different routes of delivery including intravenous and intraperitoneal systemic administration and local delivery to the pancreas through the bile-pancreatic duct [59–63]. *In vivo* gene transfer of mitogenic and anti-apoptotic/prosurvival factors such as HGF or Sirtuin 1 or downregulation of NADPH oxidase 2 (Nox2) or miR-338-3p reduced apoptosis and induced proliferation of β cells [61, 64–66]. Noticeably, delivery of glucagon-like peptide 1 (GLP-1), β-cellullin or Akt not only mediated β-cell regeneration but also reversal of diabetes [67–69]. Other genes that have been shown to promote β-cell regeneration in transgenic animal models and are therefore promising for gene therapy approaches for T1DM include insulin-like growth factor-I (IGF-I), regenerating gene 1 (Reg1), epidermal growth factor (EGF), gastrin or nerve growth factor (NGF) [70–74].

Immune modulation

The immune system is a key component of the etiopathogenesis of T1DM. The T cell–mediated destruction of β cells arises as a consequence of the breakage of tolerance to β-cell antigens. Consequently, many gene therapy approaches developed for the treatment of T1DM aim at increasing the number and/or activation of regulatory T cells (Tregs) and/or decrease the frequency of autoreactive T cells. Amongst all vectors, AAVs have been the most widely used vectors to transfer immunomodulatory genes to prevent or ameliorate T1DM in mice. AAV-mediated overexpression of the cytokines IL-2, IL-4, IL-10, or the chemokine CCL22 have demonstrated therapeutic efficacy in non-obese diabetic (NOD) mice, an animal model of spontaneous autoimmune diabetes [75–80]. IL-2 is the key cytokine supporting survival and function of Tregs [75]. Treatment with low-dose recombinant IL-2 has been recently reported to safely expand/stimulate Tregs and improve clinical condition in humans with T1DM, but multiple administrations were needed [81]. In contrast, one-time, AAV-mediated, systemic, muscular or β-cell specific delivery of the IL-2 gene increased the frequency and activation of Tregs and prevented diabetes in NOD mice [75, 76, 78]. IL-4 induces the expression of the transcription factor Forkhead box P3 (Foxp3), the defining marker of Tregs [82], in Treg precursor cells [83]. AAV-mediated expression of IL-4 in β cells prevented islet destruction and onset of diabetes in NOD mice [80]. On the other hand, IL-10 plays an important role in the development of Tregs and secretion of IL-10 by Tregs inhibits effector T-cell responses [82]. Gene transfer of IL-10 to murine muscle increased Tregs in a dose-dependent manner and abrogated diabetes development [77]. Finally, CCL22 is the ligand of the chemokine receptor CCR4, highly expressed on Tregs. Overexpression of CCL22 in β cells recruited endogenous Tregs to the islets, limiting expansion and effector activity of autoreactive T cells and conferring long-term protection from autoimmune diabetes [79].

Another strategy is based on the conversion of cytotoxic T cells, including pathogenic, β-cell-specific T cells into Tregs through *ex vivo* lentiviral or retroviral vector-mediated gene transfer of

Foxp3 [84, 85]. In addition, systemic administration of adenoviral vectors encoding a cytotoxic T-lymphocyte associated antigen 4 (CTLA4)-Fas ligand fusion protein stimulated apoptosis and blocked co-stimulation of autoreactive T cells and greatly reduced the incidence of T1DM [86].

Another group of strategies has relied on the active induction of immune tolerance, for example by expression of the preproinsulin II gene in the thymus following intrathymic administration of lentiviral vectors [87], by non-viral gene transfer of the IGF-I gene to the liver [88] or by transient, adenoviral-mediated expression of a soluble form of the immunoadhesin intercellular adhesion molecule 1 (ICAM-1) [89] soon after diabetes onset. All of these approaches resulted in suppression of autoimmune diabetes in NOD mice or transgenic mice overexpressing human interferon β in β cells [71], both of them murine models of human T1DM. Induction of antigen-specific tolerance by retroviral-mediated expression of insulin or glutamic acid decarboxylase 65 (GAD65) in B lymphocytes has also proven to be promising for T1DM (90). Likewise, the administration of viral vector- or plasmid-based gene transfer vaccines encoding the autoreactive antigens insulin, proinsulin or GAD65 has been reported to induce immune tolerance and prevent the development of T1DM in mice [91–93].

Gene therapy for T2DM

Although most of the gene therapy strategies developed so far for diabetes have focused on T1DM, as the scientific understanding of the pathophysiology of T2DM increases, a growing number of proof-of-concept gene transfer studies are being conducted in rodents to gain insight into the molecular mechanisms underlying T2DM as well as to evaluate the therapeutic efficacy of several candidate factors. The results of these studies highlight the tremendous potential of the genetic modification of metabolic tissues for the treatment of T2DM, but further work is warranted for the development of safe gene therapy approaches mediating long-term counteraction of T2DM.

T2DM results from a state of insulin resistance in peripheral tissues (mainly skeletal muscle, adipose tissue, and liver) which is not appropriately compensated by an increased insulin secretory response, likely due to a combination of decreased β-cell mass and function. Therefore, the vast majority of gene transfer studies for T2DM have either focused on ameliorating insulin resistance in peripheral tissues or on stimulating insulin secretion, with the goal of enhancing insulin production or increasing the functionality and/or mass of β cells.

Enhancement of insulin production

The systemic or intra-pancreatic gene transfer of the HGF, GLP-1, heat shock factor, adiponectin, metallothionein, or PPARα genes using adenoviral, lentiviral or AAV vectors has been proven to enhance insulin secretion, decrease endoplasmic reticulum (ER) stress-induced β-cell apoptosis and, in the case of GLP-1 and HGF, increase β-cell mass in mice with T2DM [94–98]. In a completely different approach, the engineering of the liver with adenoviral vectors to mediate glucose-responsive insulin production has been shown to improve glucose tolerance, insulin sensitivity and glycemic control in diabetic obese *db/db* mice [99].

Amelioration of insulin resistance

A growing number of *in vivo* proof-of-concept gene transfer studies have directed their efforts towards amelioration of insulin resistance and glucose intolerance via several different approaches. The systemic administration of adenoviral vectors encoding GLP-1 improved insulin sensitivity through restoration of insulin signaling in peripheral tissues and reduction of hepatic gluconeogenesis in diabetic obese *ob/ob* mice [100]. The attenuation of insulin resistance has also been achieved in T2DM high-fat diet (HFD)-fed rats through systemic AAV-mediated gene transfer of the serine protease kallikrein [101]. Kallikrein converts kininogen to the peptidic hormone bradykinin, which increases insulin sensitivity and stimulates glucose uptake *in vivo* [102]. Similarly, the AAV-mediated local gene transfer of HK-II to white adipose tissue has managed to increase glucose uptake in adipocytes [103], and may also be a promising strategy for improving insulin sensitivity in T2DM [104].

There is strong evidence that individuals with T2DM overexpress phosphoprotein enriched in diabetes/phosphoprotein enriched in astrocytes (PED/PEA-15) in skeletal muscle and adipose tissue [105], a protein that causes insulin resistance by interacting with the D4 domain of phospholipase D1 (PLD1) [106]. The disruption of the association between PLD1 and PED/PEA-15 at tissue level through adenoviral-mediated overexpression of a soluble form of D4 in the liver, pancreas, and skeletal muscle restored glucose homeostasis by improving both insulin sensitivity and secretion in diabetic transgenic mice ubiquitously overexpressing PED/PEA-15 and in obese HFD-fed wild-type mice [107].

On the other hand, recent studies support a role for cholesterol in the development of obesity, insulin resistance, and hepatic steatosis [108]. The ABCG5 ABCG8 (G5G8) sterol transporter promotes cholesterol excretion into the bile and the intestinal lumen. Following adenovirus-mediated delivery of the G5G8 genes to the liver of *db/db* mice, the levels of biliary cholesterol and fecal sterol increased, the levels of plasma glucose and triglycerides decreased and glucose tolerance improved [108]. These changes were associated with reduced expression of lipogenic genes, alleviation of ER stress, and restoration of hepatic insulin signaling [108].

Reduction of adipocity, adipocyte dysfunction, and adipose tissue inflammation

Given the strong association between T2DM and obesity, many proof-of-concept gene transfer studies have targeted adiposity, adipocyte dysfunction, and/or adipose tissue inflammation, with the aim of ultimately improving insulin sensitivity and glucose tolerance. The intra-cerebroventricular administration of AAV vectors encoding the adipokine leptin prevented HFD-induced adiposity, reduced blood glucose and insulin levels, and increased energy expenditure through thermogenesis [109]. It was

demonstrated that the effect was mediated by transduction of hypothalamic cells of the brain [110]. The administration to the muscle of AAV vectors encoding the secreted glycoprotein Wnt10b, a recently described member of the Wnt family reported to inhibit adipogenesis, decreased overall fat mass and improved glucose and energy homeostasis in obese rats [111]. In humans, mutations in Wnt10b are associated with obesity [112], and certain variants of the transcription factor 7-like 2 (*TCF7L2*, formerly *TCF4*) gene, another member of the Wnt signaling pathway, confer increased risk of T2DM [113].

AAV-mediated delivery to subcutaneous white adipose tissue of mitoNEET, a protein residing in the mitochondrial outer membrane and involved in regulation of mitochondrial iron content, resulted in benign expansion of the fat pad, reduced inflammation and preservation of insulin sensitivity in mice subjected to HFD [114]. Likewise, the adenoviral-mediated gene transfer of the secreted frizzled-related protein 5 (Sfrp5) to the liver reduced adiposity and adipose tissue inflammation in different models of obesity and diabetes, improving glucose tolerance and insulin sensitivity [115]. Sfrp5 is an anti-inflammatory adipokine linked to the Wnt signaling pathway whose expression is perturbed in models of obesity and T2DM [115]. Inhibition of macrophage infiltration and inflammation in adipose tissue has also been reported upon intravascular delivery to obese diabetic mice of adenoviral vectors encoding GLP-1 that resulted in increased circulating levels of the protein [116]. This observation suggested that the anti-inflammatory action of GLP-1 on adipose tissue might be the mechanism underlying the reported improvement in insulin sensitivity.

Interferon regulatory factor (IRF) proteins are a family of nine transcription factors involved in the mammalian regulation of type I interferon expression and innate immunity [117, 118]. These proteins also seem to play an important role in metabolism [119, 120]. For example, hepatic expression of IRF3 has been reported to be decreased in animals with diet-induced and genetic obesity [120], making IRF proteins interesting targets for gene therapy approaches to counteract T2DM. In this regard, the adenoviral-mediated liver-specific overexpression of IRF-3 or -9 improved glucose and lipid homeostasis and attenuated systemic and hepatic inflammation in diet-induced diabetic and *ob/ob* mice [119, 120].

Another promising therapeutic candidate for T2DM and obesity is adiponectin, which possesses insulin-sensitizing and anti-inflammatory properties [121]. In humans, adiponectin levels are inversely correlated with the degree of adiposity, insulin resistance and T2DM [122, 123]. Muscular or hepatic gene transfer of adiponectin by means of AAV vectors enhanced insulin sensitivity, lessened insulin-resistance, reduced obesity and downregulated hepatic gluconeogenesis, *de novo* lipogenesis and inflammation in HFD-fed diabetic rats [121, 124]. Similarly, the adenoviral-mediated expression of C1q/TNF-related protein-12, an adipokine sharing partial homology with adiponectin whose expression in adipocytes is increased by the antidiabetes drug rosiglitazone [125], improved glucose tolerance and insulin sensitivity, normalized hyperglycemia and hyperinsulinemia, and lowered postprandial insulin resistance in obese diabetic mice [125]. The effects on insulin sensitivity were mediated by the activation of insulin signaling in adipose tissue and liver [125].

Enhancement of adipose tissue vascularization

It has been postulated that the obesity-associated adipose tissue hypoxia that occurs as a result of insufficient adipose tissue blood flow could trigger insulin resistance by inducing inflammation, altering adipokine expression, and/or affecting adipocyte differentiation [126–128]. In this regard, a recent proof-of-concept study demonstrated that AAV-mediated gene transfer of the potent pro-angiogenic factor VEGF to fat pads can increase tissue vascularization in mice [103]. This may be a promising approach for the treatment of T2DM as VEGF overexpression in adipose tissue of transgenic mice has been proven to protect against obesity and insulin resistance in HFD-fed mice [129].

Conclusions and perspectives

Viral vectors have taken the lead as tools to achieve efficient *ex vivo* and *in vivo* long-term genetic modification of tissues and organs through a single vector delivery. This technological advance has opened the possibility of not only doing gene transfer studies to understand the role of a given gene in disease, but also to the development of new therapeutic strategies. In the case of diabetes there are a number of gene transfer approaches with demonstrated efficacy in lowering blood glucose that could offer an advantage over conventional treatments. Future studies are required to demonstrate the efficacy and safety in large animal models of the approaches that have demonstrated promise in small animals before any of these gene therapies are brought to the clinic to treat diabetes in humans.

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71 Future Models of Diabetes Care

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Key points

- In the United States, recent legislation aims to reward healthcare systems and providers who offer value-based care representing a departure from traditional, volume-oriented fee-for-service models.
- The Chronic Care Model is a well-known framework for organizing diabetes care which has demonstrated effectiveness in a wide variety of clinical settings.
- Delivery system design emphasizing team-based care represents one of the most effective strategies for improving diabetes care.
- Primary care providers will remain central to the reorganization of chronic care, including safe and effective diabetes management.
- Self-management education and support are distinct, but important, components of effective diabetes care.
- Emerging technologies, such as telemedicine, may address important access issues for individuals with diabetes, but their cost-effectiveness warrants further investigation.

Introduction

The future of diabetes care will be shaped by projections of increased incidence, greater prevalence of complications in an aging population, and corresponding escalations in healthcare expenditures. The worldwide diabetes prevalence of 8.3% in 2014 already exceeded the 20-year projected prevalence made in 2010 (7.8%). Furthermore the number of individuals with diabetes are predicted to increase further from 415 million in 2015 to 642 million in 2040 [1]. In the United States (USA) alone, one in three persons will develop diabetes in their lifetime [2]. Current healthcare costs associated with diabetes and its complications now exceed $245 billion in the USA, and worldwide estimates are considerably higher [3]. In addition to promoting diabetes prevention, the millions of people with diabetes will require more cost-effective care models to reduce the burden of diabetes on affected individuals and society in general.

Nearly a decade after the Institute of Medicine's report describing *Crossing the Quality Chasm* [4], momentum continues to build for an implementation of better models of chronic illness care and diabetes is at the forefront of these efforts. In many ways, diabetes is the hallmark disease for studying quality improvement because of the prevalence, cost and strong evidence-base for attaining metabolic control [5]. For persons with diabetes, there is agreement about minimum goals for HbA_{1c} ≤7% (53 mmol/mol) (for youth <18 years, HbA_{1c} ≤7.5% (58 mmol/mol)); blood pressure (BP) <140/90 mmHg (for youth <18 years, BP <90th percentile for age, sex, and height); and low density lipoprotein (LDL) cholesterol <100 mg/dL (2.6 mmol/L). However, fewer than 14% of Americans with diabetes are currently achieving these goals, noting more stringent blood pressure goals (<130/80 mmHg) at the time of publication [6]. Patient, provider, and system-level factors contribute significantly to these suboptimal outcomes. As such, there is need for greater evaluation of real-world outcomes to understand optimal models of diabetes care better across the wide spectrum of care settings and cohorts of people with diabetes.

Diabetes is one of the most psychologically and behaviorally challenging chronic illnesses to manage because as much as 95% of the management relies on the individual's self-care efforts central to a person's livelihood, namely diet, exercise, and stress management [7]. With the onset of diabetes-related complications, the burden and costs increase substantially. Despite this, the current healthcare system often does not have adequate resources to foster a person's self-management. Limitations in the availability of self-management education and the lack of ongoing self-management support impair engagement with self-care. Effective diabetes self-management often requires the expertise, training, and ongoing involvement of a coordinated, multidisciplinary team of medical providers, educators, nutrition counselling, and mental health professionals. Most individuals with diabetes do not have ready access, either geographically or financially, to gain the necessary foundation for improving self-efficacy and ultimately self-management.

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Providers may be similarly constrained to provide high-quality care due to constraints on time and resources. Clinical inertia is defined as the clinician's "recognition of the problem but failure to act" [8]. This refers to the situation where physicians fail to initiate or intensify therapy when faced with people who are not meeting target goals for clinical variables. This inertia certainly has many potential reasons including decreased provider visit time, lack of timely data, inadequate provider attention to patient adherence, and financial barriers. More information is ultimately needed on the basic epidemiology of clinical inertia including a careful analysis of associated patient, physician and clinic characteristics. Additionally, providers may not be up to date on rapidly evolving evidence-based guidelines, optimal approaches to medication management, and adequately trained on delivering effective encounters in time-constrained settings. Compounding these challenges is the plethora of new diabetes management data that are becoming available to the provider. The expanding use of electronic health records (and related regulatory requirements), advanced diabetes technologies such as continuous glucose monitoring devices, and greater connectivity through patient portals present the risk of overwhelming diabetes care providers. Better information technology systems are needed to provide the right information in a timely and efficient manner.

Despite the significant challenges confronting people with diabetes and their providers, it is increasingly clear that healthcare systems bear much of the responsibility for the delivery of suboptimal care and resulting outcomes. Lack of insurance remains a critical barrier to access for 12% of the US population; rates of insurance coverage vary internationally with many developed countries providing a basic level of national health insurance, in particular, coverage for primary care services. Despite the highest cost expenditure in the USA ($7000 per capita versus less than $3500 for Australia, Canada, France, Germany, The Netherlands, New Zealand, and the UK), 12% of the US population is uninsured despite federal regulation requiring health insurance coverage for all citizens [9]. In comparison to these seven high-income nations, the USA had the worst ratings for access, care coordination, and safety experiences [10].

Primary care is an important foundation of care in any health system. Starfield et al. [11, 12] have shown that residents of countries with strong primary care foundations have improved health outcomes and lower mortality, with lower costs and fewer health disparities. For people with diabetes mellitus, primary care physicians are a critical foundation of the healthcare delivery system. In the USA, individuals with diabetes consulting a primary care physician outnumber those consulting an endocrinologist by almost 10 to 1 [13]. There are well-described shortages of endocrinologists to support the management of particularly complex patients. Therefore, any reorganization of care will need to focus on the needs of primary care providers, the effectiveness of primary care settings, and coordination with ancillary support services, such as endocrinologists and community resources.

Overall, the solutions to these issues will require reorganizing and reinventing diabetes care from a systems-level approach that addresses the needs of people with diabetes and providers as well as the broader community in which they live. In the cross-national Diabetes Attitudes Wishes and Needs (DAWN) study, attitudes towards diabetes care were assessed across 13 countries from Asia, Australia, Europe, and North America [14, 15]. Although variation existed among countries in terms of both provider and patient perspectives of diabetes care, all respondents (primary care physicians, nurses, and specialists) noted lack of care coordination and implementation of chronic disease strategies as an area in need of improvement worldwide. As noted above, the payment system was also identified as a barrier in most of the countries surveyed, with the USA, Germany, and Japan leading the way. In the DAWN Study, people with diabetes reported high ease of access to providers, but ratings of team collaboration among their providers were relatively low. Primary care physicians noted a lack of multidisciplinary care and a need for more coordination of care. This chapter focuses on the safe, efficient, and effective organization of diabetes care, provides current examples, and introduces the potential of telemedicine to enhance high-value healthcare delivery.

The Chronic Care Model

Although several approaches have been utilized to translate evidence-based recommendations into clinical practice, the Chronic Care Model (CCM) has been the most widely implemented model to demonstrate effectiveness in a variety of clinical settings in the USA and internationally [16, 17]. The CCM proposes that productive interactions resulting in improved outcomes are more likely to result from prepared, adequately resourced practice teams and an informed and empowered patients (Figure 71.1).

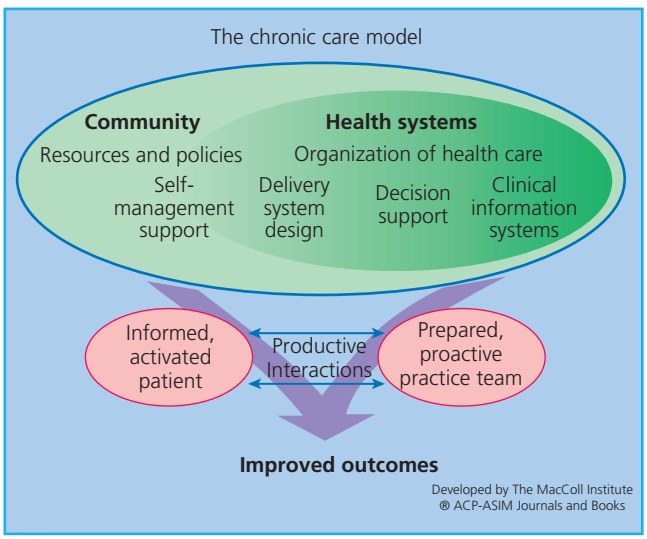

Figure 71.1 The Chronic Care Model. Source: Wagner 1998 [16]. Reproduced with permission of American College of Physicians; permission conveyed through Copyright Clearance Center, Inc.

The CCM conceptual framework highlights the organization of care that would facilitate these productive interactions with the goal of transforming the overall care delivery system from one that is reactive and organized around acute care to one which is proactive and planned around the care of individuals with chronic diseases such as diabetes. Indeed, interventions evaluating the CCM framework have often focused on more cost-effective management of diabetes.

Mounting evidence from randomized intervention trials, and evaluations of large-scale quality improvement efforts, and comparisons of high and lower performing practices have demonstrated that the implementation of the CCM is feasible across a diversity of practice settings with resultant improvements in disease outcomes [18]. The CCM has been employed for diabetes in a number of healthcare settings and has demonstrated improvement in cardiovascular risk factors [19] and reductions in HbA_{1c} [16], along with improvements in care processes, such as complication screening. Although simpler interventions would be attractive, the evidence suggests that high-performing practices do best when they incorporate multiple elements of the CCM [20–24].

The CCM focuses on six core elements summarized below, and followed by more in-depth descriptions:

1 *Health systems.* The success of reorganizing more effective care systems is contingent on the support of senior leadership responsible for setting overall priorities and allocating resources. There is often a need to better inform leadership of the unique burden diabetes places across various ambulatory and inpatient care settings. At a minimum, recognizing the financial opportunities of more cost-effective care strategies for this highly prevalent condition may need to be demonstrated given myriad demands of a health system. Senior leadership can then facilitate interventions and set policies aimed at delivering and promoting high-value diabetes care.

2 *Delivery system design.* The healthcare system must thoughtfully reorganize, and even restructure, staff and resources to deliver high-quality diabetes care. The Institute of Medicine has characterized high-quality care as safe, timely, effective, efficient, equitable, and patient-focused. In the ambulatory care setting, planned visits are more likely to result in proactive and productive patient encounters. In this setting, clinical staff take on specific roles and responsibilities in preparation for each visit. Visits themselves are structured to be efficient and patient-centered. Given time constraints, effective visits will often require targeted goal setting and addressing potential barriers to behavior change with timely follow-up by phone or in person. The delivery system should be organized to ensure that staff are engaged to their full potential to address patient needs before, during and—importantly—following routine encounters. Team-based care may also facilitate higher level care management efforts for more complex or challenging patients.

3 *Decision support.* Once healthcare teams are efficiently organized, they must be empowered to access and deliver evidence-based care in time-constrained settings. Individuals with diabetes often have multiple comorbidities resulting in competing demands for provider attention and knowledge. Given the likelihood of time-constrained encounters, high-quality systems must provide timely, easily accessible, and relevant clinical decision support around diabetes management. Guidelines are best integrated through reminder systems that can be embedded into daily care; periodic feedback and standing orders can be used to empower other practice staff to ensure that evidence-based guidelines are implemented. Embedding evidence-based guidelines into daily clinical practice and sharing those guidelines and information with people with diabetes to encourage their participation are the keys to decision support. For more complex patients (presence of significant comorbidities or diabetes-related complications) or those with more advanced needs (insulin titration, insulin pump initiation), there needs to be an effective approach to accessing support from specialists, such as endocrinologists or diabetes educators. Innovative approaches that incorporate real-time specialist-based decision support are needed.

4 *Clinical information systems.* Health information technology has the capacity to go well beyond meeting rules and regulations around medical documentation to support the delivery of high-value diabetes care. Clinical decision support systems, ideally embedded in electronic health records, may improve both diabetes care delivery and clinical outcomes [25]. These systems can provide timely information and reminders to both providers and people with diabetes and identify high-risk subpopulations for more intensive care. As practices engage with broader population health strategies (e.g. care management and outreach programs), diabetes registries that provide searchable information on diabetes populations are proliferating in many healthcare settings [26]. By tracking key process and outcomes, these registries can also provide important feedback on the overall functioning of the healthcare system.

5 *Self-management support.* Diabetes education has long been recognized as a crucial part of diabetes management, but there is increased recognition of the need for ongoing support. Self-management support goes beyond providing the knowledge needed by the individual to manage their own disease successfully. It emphasizes the person's central role in their care by involving them in establishing health priorities, identifying potential barriers to behavior change, and reflecting on personal goals at follow-up. This helps to foster the individual's personal responsibility and self-efficacy for managing their own health. Given the inadequate supply of diabetes educators, it is incumbent on primary care providers to incorporate these approaches into their daily encounters. The cost-effectiveness of using practice-based health coaches and physician extenders to improve self-management support warrants further evaluation.

6 *Community.* People with diabetes should be encouraged to participate in effective community programs, and this highlights the need of providers to partner with those within the community to fill gaps of care related to access, education, and ongoing support. Partnering becomes even more critical in limited resource environments where extending care beyond the confines of the clinic is essential. Partnerships with community advocates may also be

used to advance laws and policies at the local, state, and national level to improve benefits for those living with diabetes.

Health systems

In suggesting solutions to improve the US healthcare system, Berwick et al. [27] provide insight into important aspects of the healthcare delivery system that translate into improved outcomes. They propose that an effective healthcare system that produces outstanding health outcomes pursues three primary goals, known as the Triple Aim:

1 Improving the patient's experience of health;
2 Improving the health of a defined population;
3 Reducing the costs of care for populations.

In order to accomplish the Triple Aim goals, Berwick et al. define three preconditions. First, the healthcare system must be focused and responsible for the health of a defined population. Second, monetary and related constraints are placed on the system. The system does not have unlimited resources. The USA has experienced unrestrained healthcare costs and spends far more than any other high-income country's health system, yet its health outcomes lag behind other countries [28]. Third, there is an overarching entity that is responsible for the health of the population and pursues the goals of the Triple Aim. Health systems such as those in Canada and the UK already embody these principles. There are also several examples in the USA such as Kaiser Permanente, and Health Partners in Minneapolis and Group Health Cooperative, both closed-panel health maintenance organizations.

Accountable Care Organizations

Medicare expenditures represent 15% of all US federal spending and have risen faster than the gross domestic product for decades. The current, widely used fee-for-service payment structure incentivizes the provision of more services and has largely contributed to the unsustainable growth in healthcare spending in the USA. Perhaps most concerning, the US healthcare system is not achieving higher—or even comparable—quality care when compared to other high-income countries. Earlier efforts to control spending through capitation payments only incentivized cost reduction and risked further deterioration in patient health outcomes [29]. In 2010, the Affordable Care Act (ACA) was signed into law with the broad aims of expanding health insurance coverage and reforming the healthcare delivery system in order to improve access to high-value care [30]. Efforts to redesign care delivery have focused on strengthening the role of primary care providers and coordinating care for Medicare beneficiaries across healthcare settings [31]. This focus on primary care has been central to initiatives in a number of health systems worldwide given the pioneering work demonstrating that robust primary care helps prevent illness and death [32].

The ACA established accountable care organizations (ACOs) under the Medicare Shared Savings program (MSSP) which would serve as the cornerstone of aligning incentives and accountability for providers across the continuum of care [33]. Under these programs, provider-led organizations assume responsibility for a population of Medicare beneficiaries (typically people over the age of 65 years) attributed to it based on their patterns of primary care use [34]. For its designated population, ACOs assume responsibility for the cost and quality of care regardless of where that care is provided. ACOs that deliver high-quality care at costs that are lower than their risk-adjusted projected spending target will share in savings with Medicare [34].

Accountable care organizations continue to evolve, but the early performance of ACOs has been assessed. By the end of 2014, MSSP had 405 participating ACOs serving 14% of the Medicare population. The ACOs demonstrated improvements in healthcare quality across numerous indicators, including some beneficial impacts on patient experience (e.g. timely access to care) [35], at overall cost savings. Despite favorable initial assessments, it remains too early to evaluate the unique impact of the ACA and accountable care organizations specifically on improvements in care quality and reductions in medical expenditures. Additionally, the costs associated with establishing an efficient and well-coordinated ACO, such as a robust information technology infrastructure and timely collection of quality measure data, remain unknown [30, 36].

Concerns remain regarding the development of shared savings for ACOs under the ACA. Perhaps most importantly is whether the law will provide enough incentive to increase and engage primary care providers fully across the diversity of ACO models, especially those established by hospitals or specialty groups [30]. Some have suggested inclusion of primary care-oriented quality measures for ACOs as a means of ensuring their central role in a redesigned healthcare system [31]. Early data suggest that poorer performing ACOs and those in high-spending regions were more likely to achieve savings under MSSP [37]. While this should encourage participation and value creation for these ACOs, it has been suggested that adjusted (e.g. regional) benchmarks will incentivize lower-spending ACOs to participate in the MSSP. Quality is assessed across five domains: patient experience, care coordination, patient safety, preventive health, and health of at-risk and elderly populations. The costs associated with collecting 65 standardized measures may be significant with ACOs, especially those without a strong information technology infrastructure across their healthcare settings, and will need to be assessed when determining the overall value of ACOs [29, 37, 38]. Several diabetes quality measures have been incorporated into these measures. Finally, and not unexpectedly, there remains ongoing discussion regarding the balance of risks and rewards for providers considering participation in an ACO [29, 39].

Delivery system design

Although the best results are obtained when multiple facets of the CCM are implemented together, probably the single most effective quality improvement intervention in diabetes care involves delivery system design to incorporate a team-based approach [40]. Other key elements of delivery system design are case management and shared care.

Realistically, primary care providers have reached their limit in terms of additional tasks that they can undertake, and therefore it is inevitable that the care team needs to be expanded. In many ways, team management has been considered a central feature of superior diabetes care. Diabetes educators and dietitians have long been part of standard diabetes care and the expansion of their roles and the roles of other individuals within the healthcare system will likely continue.

Team-based care allows task distribution which includes identifying team members to:

1 track longitudinal information through flowsheets, registry data, or electronic health records;

2 deliver evidence-based process measures and conduct recommended clinical assessments;

3 ask patients about self-care goals and care barriers prior to the primary healthcare provider entering the room.

Standing orders can be used to empower office staff to order overdue laboratory screening and eye examination referral, and can even extend to algorithms for medication intensification. Appropriate communication between team members is the key, and the incorporation of clinic "huddles" at the beginning of the day can ensure that appropriately planned care is delivered to all individuals with diabetes. The goal is to ensure that every member of the team practices at "the top of their license" and utilizes their skills to improve care for people with diabetes.

Diabetes has been a fertile testing ground for care management approaches in which usually either a nurse or pharmacist meets regularly with high-risk individuals to provide intensified care [40, 41]. Care populations are segmented based on needs to ensure that appropriate care intensity is provided. Key elements of care management include:

1 Defining and identifying high-risk patients;

2 Case assessment;

3 Individualized care plans;

4 Development, implementation, and monitoring of outcomes.

Diabetes registries are an ideal source for identifying high-risk individuals either based on clinical measurements (e.g. HbA_{1c} levels), low self-management skills, or overdue visits. Intensification of therapy can be facilitated by empowering other healthcare providers through standing orders to implement changes, and by clearly assessing health management needs and support.

Care management is most effective when incorporated and embedded within the primary care clinic as opposed to "carve-out" models where an outside entity provides telephonic care management for patients and which subsequently leads to ineffective communication with the primary healthcare provider. Integration of care management with the primary care practice is needed to ensure appropriate information exchange, shared goals, and coordination of care.

Diabetes nurses are eager to increase their involvement and take on more responsibility for diabetes care, as surveyed internationally through the DAWN study [14]. Pharmacists have also been utilized to work in conjunction with primary care physicians in a case management role. Recent reimbursement changes within the US Medicare system have facilitated billing for these services based on non-randomized trials in which this care has been found to be cost-effective [42].

Care management approaches have been effective at improving glucose control, blood pressure and lipid control in many different settings in the USA and elsewhere [40, 41]. One controversy has been the extent to which case management permits medication titration. Two models have been used: one in which the case manager advises the primary care physician who then makes the medication change versus the second in which a standing order algorithm enables a case manager to intensify treatment without routinely checking with the primary care provider. Although studies suggest that standing order algorithms are more effective in lowering HbA_{1c} levels [40, 41], some physicians have concerns about nurses or pharmacists making these changes without routine provider input. As more studies and appropriate training programs are developed to allow other health professionals to assist in medication titration, this approach will continue to show promise in improving clinical outcomes while not overburdening the already overtaxed primary care system.

Shared care is defined as "the joint participation of primary care physicians and specialty care physicians in the planned delivery of care, informed by an enhanced information exchange over and above routine discharge and referral notices as the co-management of patients by primary care and subspecialty specialists" [43]. Currently, when most people with diabetes are referred to endocrinologists, care is subsumed by the specialists and true co-management is rare. In a Cochrane review which examined shared care across multiple chronic illnesses, limited data were available on effective models [44].

Decision support

The approach frequently used as decision support involves embedding evidence-based guidelines into daily practice to obtain clinical improvement. A number of organizations provide evidence-based clinical guidelines. Although there can be some discrepancies among them, most are generally disagreements on how low goals should be brought down. While these debates are important, overriding evidence suggests that the vast majority of people with diabetes are not at minimum clinical care goals. Establishing clinical goals is a first step; however, the best practices to achieve those goals are critically important to ensure positive clinical outcomes. The American Diabetes Association (ADA) and national bodies such as the National Institute for Health and Care Excellence (NICE) provide detailed guidelines [45]. This is a necessary first step, but decision support goes beyond the acceptance of consensus guidelines and focuses on the implementation of those guidelines in everyday practice. Although provider education regarding guidelines is important, these interventions typically have had limited impact beyond processes of care (i.e. ensuring that more patients are screened for complications). Effective multifaceted interventions most often include academic detailing, physician reminders, and audit and feedback to improve diabetes

outcomes. Patient tracking systems (patient registries) and nurse-led interventions are also effective [46].

Examples of guideline implementation can include incorporating decision support into electronic health records or reviewing the chart prior to a planned visit to identify gaps in care and strategies to intensify treatment plan. Although provider knowledge of guidelines is critical, these guidelines need to be shared with people with diabetes to encourage their participation. Empowering people with diabetes to "know their numbers" provides the basis for a negotiated treatment plan to achieve those goals. Ideally people with diabetes are involved in creating goals for care and incorporate "shared decision-making."

Given the evidence that blood pressure control can reduce both microvascular and macrovascular complications, future efforts will clearly focus on identifying better approaches for monitoring this outcome. Self or automated blood pressure monitoring offers many of the same advantages as glucose monitoring. An increased number of blood pressure recordings increase the accuracy of the measurement. It may also empower individuals to discuss their blood pressure with their physician [47]. Home monitoring, in conjunction with other interventions such as patient education, Internet communication, nurse or pharmacist follow-up, leads to improved blood pressure control [48, 49]. Telemonitoring may lead to reductions in both systolic and diastolic blood pressure [50].

One potential barrier to capitalizing on insights from self or automated blood glucose or blood pressure monitoring data is that clinicians may be overwhelmed by the sheer quantity of clinical information. The increasing availability of continuous glucose monitoring data, routine glucose self-monitoring results that can be shared through web portals, and ambulatory blood pressure monitoring are all at the expense of potentially overburdening the already busy clinician with much information, but inadequate—and often non-reimbursed—resources to manage this vital data. There will clearly be a need to develop more robust data filtering methodologies to analyze and package this information in clear concise summaries that can lead to appropriate clinician and patient action. Some evidence of this is already apparent in software for many of the blood glucose monitoring devices that provide ready access to glucose averages, standard deviations and other simple data analytical features. Merging this information with evidence-based decision support tools for providers is likely to increase their overall value to improve quality of care. Indeed, there has been a rapid evolution of mobile diet logbooks and "wearable devices," including pedometers, accelerometers, and other home monitoring devices that could provide objective measures of lifestyle behaviors [51].

Clinical information systems

Clinical information systems help to organize patient and population data to facilitate effective and efficient care delivery. Diabetes registries are being adopted in a variety of healthcare settings involving municipalities, academic health centers, third-party payers, the US Veterans Affairs Health System, and international registries in Europe, Canada, and elsewhere [52]. A registry is a searchable list of all people with a particular chronic disease. The well-designed registry lists all members of the patients' health team and provides key information for people with diabetes and providers. The critical impact of the registry is that it can allow timely identification of high-risk subpopulations, permitting the healthcare team to intensify treatment. A registry can also provide snapshots of care that can collate the many data elements needed for optimal care (e.g. last eye and foot examinations, nephropathy screening, HbA_{1c}, cholesterol, blood pressure) and can include prompts for care (decision support).

The primary challenges to further adoption of diabetes registries are cost and interoperability issues between different electronic health record systems. Information technology-related issues often receive the most attention by practices in the USA [22]; however, even non-technologic approaches such as incorporation of paper flowsheets can be an effective start. Furthermore, caution is needed to avoid wasting time and resources on implementing information technology solutions to diabetes care without attending to some of the more fundamental practice redesign issues. More robust results are often seen when team-based care and care management are in place.

A new challenge of information overload is entering into diabetes care. The widespread availability of the Internet makes it an attractive communication tool among people with diabetes and providers. It has been useful in multiple areas ranging from videoconferencing for diabetes education to tele-ophthalmology to patient support and education websites [53, 54]. People with diabetes desire an effective tool to communicate with their providers in order to receive responsive feedback and advice in a timely manner. Web-based management of diabetes through patient-initiated glucose meter uploads can facilitate provider treatment intensification and has demonstrated mixed results in different patient populations [55]. Glucose meter uploading is undoubtedly more accurate than patient recorded values. A potential advantage of between visit care offered by this type of telemedicine approach is an improvement in the "velocity to goal" (i.e. how fast the person reaches good diabetes control). This is particularly important because studies suggest that the average time between treatment intensification in some cases may be as long as 27–35 months [56]. Telemedicine provides a significant opportunity to give providers updated clinical data for more appropriate medication adjustments; however, enthusiasm is tempered by the data burden presented by the frequent communication between people with diabetes and providers related to blood glucose values. Reimbursement could facilitate greater adoption of this approach, and future advances could provide clinicians with treatment algorithms that can assist clinical decisions by interpreting data from glucose meter downloads.

The use of computerized glucose predicting engines shows promise in optimizing insulin management [57]. Albisser et al. [58] have demonstrated that utilizing a shared central database allowing for patient input of glucose self-monitoring values as

well as medication, diet, and exercise data, analyzed with a glucose predicting algorithm, enabled providers to reduce iatrogenic hypoglycemic events ninefold compared to that of baseline. The reduction in hypoglycemic events was accomplished without change in HbA_{1c}. Thus, the ability to predict future blood glucose levels improves glycemic stability and may also prove useful in patient self-management. Current research on closed-loop artificial pancreas systems are expected to provide more robust algorithms that will become available to guide patient self-titration of insulin and/or streamline provider titration decisions [59]. There are, however, potential regulatory issues with the widespread recommendations of these algorithms.

Self-management support

A distinction needs to be made between self-management support and self-management education. Self-management education is quite familiar in the diabetes community and encompasses the traditional role of the diabetes educator providing knowledge and skills to individuals with diabetes. Self-management support, however, need not be performed by a diabetes educator and, in fact, peer coaches have been utilized to foster self-management support. Self-management support involves the ongoing collaborative approach between coach and people with diabetes to define problems, set priorities, establish goals, and create treatment plans. Resources offered to problem-solve can include community-based organizations, peer support programs, and other groups. Individualized approaches that address the major concerns defined by the person with diabetes, typically involve a strong element of coaching with the goal of educating and empowering the individual. The challenge for the future is to make self-management support more widely available. Innovative approaches that leverage information technology to provide patient coaching are possible solutions [60].

Self-management has long been recognized as a key determinant of disease outcome. It has become increasingly clear, however, that knowledge is necessary but not sufficient to influence behavior. This has led to increased attention to determinants of patient behavior change. The overall importance of a behavior change is judged by the people with diabetes based on their values. Knowledge and education can clearly influence importance by providing the rationale for health improvement. Confidence, also referred to as self-efficacy, is the inherent confidence that a person with diabetes can be successful in making the behavior change. This can be augmented through problem-solving and discussion of alternative strategies. Adherence to diet, exercise, monitoring, and medication are required for optimal diabetes outcomes. Although many social and societal factors influence patient adherence, clinician counseling style has a profound impact on potential behavior change. Providers can either increase resistance to change, or help to facilitate readiness to change on the part of the patient. Patient empowerment and increased self-efficacy are key factors in enabling people with diabetes to feel confident in making necessary changes. Recent years have brought to the forefront behavior change approaches from the psychologic literature to be applied to diabetes. One of the most promising approaches is motivational interviewing [61, 62].

Motivational interviewing is a directive patient-centered counseling style for eliciting behavior change by helping patients to explore and resolve ambivalence. It is a collaborative patient–provider model that stresses that motivation must come from the patient, not the provider, and honors and respects the patient's autonomy. Initially utilized in the addiction field, it is now being applied to a number of chronic diseases including diabetes [63]. It is a teachable evidence-based approach that holds significant promise to improve patient adherence. Part of the attractiveness of motivational interviewing has been the well-defined set of skills that can be taught to different individuals. Certified trainers are available worldwide [64]. Brief motivational interviewing has adapted many of the skills of traditional motivational interviewing, as used by psychologists, for use in the busy time-pressured healthcare environment. Meta-analyses have shown this to be a powerful approach that can be learned by people with varying backgrounds and applied to multiple chronic illnesses [63] and the approach resonates with people with diabetes [65]. Studies in diabetes are promising [65–67] but others focused only on motivational interviewing have found mixed results. Fidelity to motivational interviewing technique and incorporating this approach with other changes in care delivery are likely to provide the most robust responses.

Several other behavior change models/theories, which can either explain or help practitioners conceptualize behavior change, have been identified. They include the health belief model, theory of reasoned action or theory of planned behavior, stages of change or transtheoretical model, social cognitive or social learning theory, community organization/building, and social marketing (See Chapter 56) [68].

Community

Community resources are often overlooked and not integrated into care for people with diabetes. Providers can become more familiar with these resources and work collaboratively to make individuals aware of opportunities. These can include safe exercise opportunities, healthy food availability, social programs, and support services that are available through non-governmental organizations. Communities can partner with healthcare organizations and governments to improve public awareness about diabetes. Overall, as prevention of diabetes and its complications becomes an increasing public focus, public awareness efforts to empower those with diabetes or at risk of diabetes to engage in appropriate diet and exercise will be needed. Social marketing provides a rationale for how this approach can be effective, and an excellent example of success is the change in tobacco use in the USA over the last three decades. Similar public health initiatives are needed to stem the epidemic of obesity that is fuelling the rise in diabetes.

Overwhelming evidence now suggests that the simultaneous incorporation of multiple components of the CCM is synergistic and more effective than traditional single intervention

approaches [22, 40]. Too much past research focused on only a single intervention and therefore missed the potential value of the concurrent implementation of multiple interventions for true "transformation of care."

Transformation of care, according to the CCM, has often been accomplished through "learning collaboratives" either through the Breakthrough Series Collaborative [69, 70] or through other similar experiences. Widespread implementation in the USA has generally occurred in large organizations, in part based on supportive reimbursement systems. Nevertheless, external support for practice transformation is being explored in several regional improvement programs [70, 71]. Position statements and guidelines from many professional societies have come out in strong support of the CCM [72, 73]. Another effective approach has been to use practice facilitators or coaches to guide clinical care teams to deliver timely, evidence-based care [74–76]. In the USA, the Primary Care Extension Program authorized by the Affordable Care Act aims to use Health extension agents to accelerate the transformation of primary care practices across the diverse practice and community settings. This service, modelled after the US Agricultural Cooperative Extension service, employs local change agents (practice facilitators) to guide practice transformation [77–79]. This concept clearly resonates with primary care providers [79], and could be utilized to spread diabetes innovations into primary care. As health systems move more towards the Institute of Medicine's model of a learning health system [80], diabetes has the opportunity to take center stage in many of the new models of care that are being proposed.

Another initiative to improve chronic disease management in the USA has focused on the patient-centered medical home. The patient-centered medical home is a concept being developed by the major primary care societies in the USA. It combines the principles of primary care (continuity of care, whole person orientation, quality/safety, prevention, timely access to care) with many of the elements of the CCM (coordinated/integrated care, teams, population health). One of the driving forces behind this concept is to revitalize primary care in the USA. Diabetes has been a common target condition of early pilots [81].

Although the concept of patient medical home has been attractive and a certification program has been established in the USA, there are concerns that this model may have limited application outside the country. In particular, many of the elements described for the National Center for Quality Assurance certification process require advanced information technology capabilities that generally necessitate an electronic health record. Despite the value of electronic health records, the mere availability of these tools is often insufficient to transform care. Often, practices and health systems can get side-tracked with the formidable information technology and interoperability challenges, losing sight of the overall goal of transforming healthcare. In comparison, the CCM elements are more easily translatable in low technology environments within the developing world.

In the USA, several states have explored integrated approaches to adopt the CCM. The foremost of these has been initial experience in Pennsylvania where insurers have agreed to provide significant reimbursement and incentives for primary care adoption of the CCM to improve diabetes care. Learning collaboratives are conducted across the state to teach clinicians and office staff the implementation aspects of the CCM. These efforts are supported by practice coaches who meet with practices individually to problem-solve implementation efforts. Clinics are required to report on clinical outcomes and care changes on a monthly basis, and payers have agreed to provide funding for needed practice changes such as case management in the hope of containing spiralling healthcare costs [82]. Evidence is accumulating that clinical outcomes improvements were associated with a concomitant reduction in healthcare utilization [83]. A national initiative is currently underway in Australia to implement the CCM through the Australian National Primary Care Collaboratives [84], and similar initiatives are being explored in Canada, Denmark, The Netherlands, New Zealand, and elsewhere.

Telemedicine

Technological advances over the last quarter century have created new opportunities for connecting people with diabetes to their healthcare providers. The established tradition of contacting on-call providers for urgent medical advice has evolved in the era of widespread internet- and phone-based connectivity. Increasingly, healthcare teams recognize the critical importance of staying connected to people with diabetes in-between routine, in-person clinical encounters in addition to improving access to people with diabetes for whom significant barriers may impede access to traditional face-to-face encounters. Telemedicine, broadly defined as the provision of medical care from a distance, may provide opportunities to serve the "triple aim" of better health and improved patient experience at reduced cost.

The promise of telemedicine relates directly to the challenges of effectively managing the epidemic of diabetes. Telemedicine may improve patient access for certain at-risk populations, such as those which are geographically (e.g. rural communities), functionally (e.g. elderly or disabled), and/ or socioeconomically isolated. Telemedicine may amplify the inadequate and concentrated supply of diabetes specialists, educators, and mental health personnel, to support primary care teams and their patients with diabetes. Telemedicine may even provide an alternative for engaging people with diabetes less motivated to visit their healthcare teams. Telemedicine has been used for a variety of chronic conditions, including diabetes and heart failure, with data suggesting increasing evaluations in both clinical and research settings [85].

Telemedicine encompasses numerous applications of established and emerging technologies. Not unexpectedly, there remains debate regarding the term "telemedicine" with ongoing efforts to standardize the definition by leading organizations such as the World Health Organization [86, 87]. Telemedicine interventions have used telephone, mobile phones, wireless devices, electronic mail, websites, or videoconferencing to deliver

care in real-time (synchronous) or using "store and forward" (asynchronous) approaches. The Food and Drug Administration has regulated the use of mobile health applications on "smart," internet-enabled mobile phones, a potential new option for telemedicine [88]. Telemedicine is often provided by medical staff, but trained, non-medical staff and automated messaging services have been used. There are many differences in published telemedicine interventions that may impact their relative cost-effectiveness for specific or more general populations living with diabetes. To date, most telemedicine evaluations occurred in addition to, not as a substitute for, traditional clinical encounters.

There have been a number of well-conducted meta-analyses and meta-regressions aimed at assessing the clinical effectiveness of dozens of telemedicine interventions for diabetes care [89–95]. The diversity of interventions has highlighted the wide range of opportunities, from diabetes education to medical care, including specialized services such as eye care and mental health support [96, 97]. These reviews have generally reported positive findings in terms of clinical outcomes (e.g. glycemic control and self-management) and patient experience (e.g. care coordination and access). However, many of the clinical improvements were modest and not consistent across studies. There were also some unintended negative findings, including challenges with technologies and diminished quality of interactions with healthcare teams. The generalizability and cost-effectiveness of telemedicine in diabetes care remains an important area for future investigation [91, 95].

In 1997, the US Government mandated the implementation and independent evaluation of the Informatics for Diabetes Education and Telemedicine (IDEATel) demonstration which would be the largest ever randomized controlled trial comparing telemedicine case management to usual care in the management of diabetes [98]. The IDEATel demonstration was delivered over two phases between 2000 and 2008 in New York State at a cost of $57 million. The trial targeted older, ethnically diverse, medically underserved Medicare beneficiaries with diabetes residing in medically underserved areas of New York State [99]. Videoconferencing by nurse case managers was enabled by a web- and camera-enabled computer, modem-based internet connectivity, and self monitoring equipment for blood glucose and blood pressure. Endocrinologists provided supervision as needed, and care recommendations were communicated to primary care physicians. Annual assessments of metabolic control were performed over the 5-year study period [100]. The trial demonstrated modest, but statistically significant, improvements in HbA_{1c}, blood pressure, and LDL cholesterol and no impact on mortality. There was significant attrition over the 5-year period much owing to challenges or frustrations with the computer. An independent evaluation demonstrated no reduction in Medicare use or costs for health services [101]. Despite sustained clinical improvements, the intervention costs were deemed "excessive" at over $8000/person annually given similar improvements noted in case management trials not using telemedicine, which occurred at a fraction of the cost. There were significant lessons learned and summarized in the final report to Congress which emphasized the need to target high-risk populations likely to benefit from telemedicine and the adoption of lower-cost, user-friendly technologies which have since entered the marketplace [102].

Telemedicine continues to evolve in the delivery of diabetes care. Short- and long-term studies have been generally favorable across a wide spectrum of measures including clinical outcomes, patient experience, and cost-effectiveness [89–94]. The IDEATel demonstration resulted in sustained clinical improvements which were likely to reduce the risk of long-term complications despite the high cost. It is conceivable that a similar trial in the current technological era could be implemented at significantly lower costs. It has been suggested that standardizing processes and outcomes (e.g. core dataset) may improve our understanding of the clinical and cost-effectiveness of telemedicine in the care of individuals with diabetes, perhaps most importantly, the absence of cost-effectiveness data may impede insurers' willingness to reimburse for telemedicine-based services [95]. State-level regulations and private insurance reimbursement are critical barriers to expanded use of telemedicine services [103]. There remains significant variation in reimbursement for telemedicine-based care in the commercial insurance market. Fortunately, there is evidence that reimbursement policies may be changing. The federal government is reimbursing telemedicine for certain at-risk populations as well as those receiving care in the Veterans Health Administration. In 2015, the Center for Medicare and Medicaid Services authorized reimbursement for telemedicince targeting rural communities faced with shortages of healthcare professionals [104].

However, standardization may also restrict the wide spectrum of telemedicine applications targeting the range of unmet needs for individuals living with diabetes. Most systematic reviews have recommended matching specific telemedicine approaches to targeted outcomes to optimize cost-effectiveness [89, 93]. That is, thoughtfully weighing the relative merits of specific patient populations, real-time versus asynchronous communication, use of medical staff versus trained non-medical professionals, individual versus group sessions, tailored versus generic feedback and education, and low versus high "dose" interventions. There is general consensus that effective telemedicine interventions, like most successful technological innovations, will benefit significantly from a participatory design approach in which people with diabetes are actively involved in identifying unmet needs and tailoring interventions to address them [89, 90, 93]. With the right design and careful implementation, telemedicine will continue to play an increasing role in supporting a healthcare system focused on delivering the right care in the right place at the right time.

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Index

Page numbers in *italics* denote figures, those in **bold** denote tables. Conditions prefixed by the word "diabetic," e.g. diabetic autonomic neuropathy, diabetic retinopathy, are indexed under the name of the condition, i.e. autonomic neuropathy, diabetic, retinopathy, diabetic.

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