Handbook of Diabetes

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4th edition

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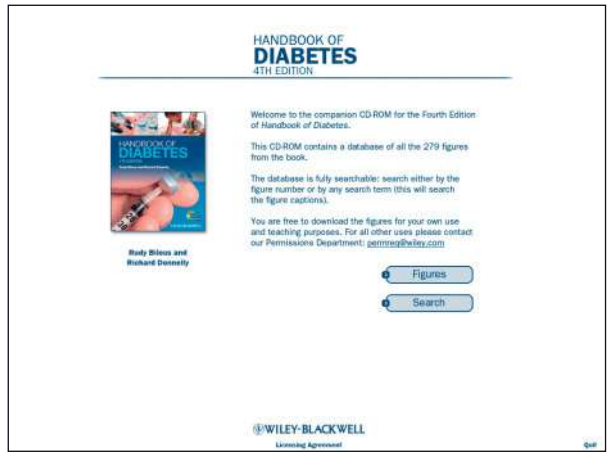

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Contents

Preface

The task of updating a much used and appreciated textbook is a daunting one. This is particularly so for the *Handbook of Diabetes*, which has been ubiquitous in its presence in most diabetes departments over the last decade, largely because of its clarity of text, its high quality illustrations and accessibility of information.

However, it is 6 years since the last edition and much has moved on. Moreover, previous editions have been a very recognisable offspring of the larger *Textbook of Diabetes*, which has been one of its strengths.

This edition, however, is a stand alone text that has been completely revised by the authors, independently of its larger relative but maintaining the ethos espoused in the preface to the third edition of an "easy-to-read, up-to-date and well-illustrated précis of the most important aspects of the science and clinical practice of diabetes". We have also endeavoured to make the information accessible to all professionals looking after people with diabetes. The organisation of the chapters is unchanged but their structure is broken down into sections. A list and occasional summary of landmark studies is included together with information on key websites. In addition we have included an illustrative case. Because we are increasingly working in an environment of evidence and eminence based guidelines, the text and tables include their recommendations and the source documents are listed at the end of each chapter.

References have been kept to a minimum and include as many recent reviews as possible but are inevitably a bit idiosyncratic. Apologies to those who feel we may have missed their magnum opus. Each of these features has been colour coded. A big plus is the provision of a CD of the illustrations for personal use.

The team at Wiley Blackwell have kept us to an almost impossible timetable and our thanks to Oliver Walter, Rob Blundell and Helen Harvey for their encouragement and positive feedback. Once again they have produced a beautifully laid out and illustrated text which we hope lives up to the high standards set by its predecessors.

Inevitably new information arrives while such a book is being written, so apologies if some sections seem out of date. We hope that you, the reader, will find this handbook as useful as the third edition and if so recommend it to all of your colleagues!

Rudy Bilous
Richard Donnelly

Key to the boxes

KEY POINTS

These points summarise important learning topics, things to remember and/or areas that are sometimes misunderstood by healthcare professionals.

CASE HISTORY

This is a typical case summary that illustrates a number of learning topics from the chapter.

LANDMARK CLINICAL TRIALS

These are often major trials underpinning the evidence base for clinical practice and decision-making in the area.

KEY WEBSITES

Websites that contain further information, practice guidelines and/or learning topics to supplement the information in the chapter.

FURTHER READING

Published reviews, original research or meta-analyses relevant to the chapter.

List of abbreviations

ABPI	Ankle Brachial Pressure Index
ACE	angiotensin-converting enzyme
ACEI	angiotensin-converting enzyme inhibitors
ADA	American Diabetes Association
AGE	advanced glycation endproduct
ALT	alanine aminotransferase
AMI	acute myocardial infarction
ARB	angiotensin type 1 receptor blocker
AST	aspartate aminotransferase
ATP	adenosine triphosphate
BB	BioBreeding
BMI	Body Mass Index
BP	blood pressure
CABG	coronary artery bypass grafting
CCB	calcium channel blockers
CETP	cholesterol ester transfer protein
CHD	coronary heart disease
CI	confidence interval
CIDP	chronic inflammatory demyelinating polyneuropathy
CKD	chronic kidney disease
CSF	cerebrospinal fluid
CSII	continuous subcutaneous insulin infusion
CT	computed tomography
CVD	cardiovascular disease
DAFNE	Dose Adjustment for Normal Eating
DAG	diacylglycerol
DCCT	Diabetes Control and Complications Trial
DESMOND	Diabetes Education and Self-Management for Ongoing and Newly Diagnosed
DKA	diabetic ketoacidosis
DME	diabetes-related macular oedema
DPP-4	dipeptidyl peptidase-4 (IV)
DSN	diabetes specialist nurse
eAG	estimated average glucose
ED	erectile dysfunction
EDIC	Epidemiology of Diabetes Complications
eGFR	estimated glomerular filtration rate
EPO	erythropoietin
ESRD	end-stage renal disease
ETDRS	Early Treatment Diabetic Retinopathy Study
FATP	fatty acid transporter protein
FDA	Food and Drug Administration
FFA	free fatty acids
FPG	fasting plasma glucose
FSD	female sexual dysfunction
GAD	glutamic acid decarboxylase
GBM	glomerular basement membrane
GDM	gestational diabetes mellitus
GFAT	glutamine:fructose-6-phosphate amidotransferase
GFR	glomerular filtration rate
GI	gastrointestinal
GIP	gastric inhibitory polypeptide
GIR	glucose infusion rate
GLP-1	glucagon-like peptide-1
GLUT	glucose transporter
HDL	high-density lipoprotein
HHS	hyperosmolar hyperglycaemic state
HL	hepatic lipase
HLA	human leukocyte antigen
HOMA	Homeostasis Model Assessment
HONK	hyperosmolar non-ketotic hyperglycaemic coma
HPLC	high-pressure liquid chromatography
HR	hazard ratio
hsCRP	high-sensitivity C-reactive protein
IAA	insulin autoantibody
IAPP	islet amyloid polypeptide
ICA	islet cell antibody
IDDM	insulin-dependent diabetes mellitus
IFG	impaired fasting glycaemia

IGT	impaired glucose tolerance
IM	intramuscular
IPPV	intermittent positive pressure ventilation
IQR	interquartile range
IRMA	intraretinal microvascular abnormality
IRS	insulin receptor substrate
ITU	intensive therapy unit
IV	intravenous
KATP	ATP-sensitive potassium channel
LADA	latent autoimmune diabetes of adults
LDL	low-density lipoprotein
LH	luteinizing hormone
MAP	mitogen-activated protein
MAPK	mitogen-activated protein kinase
MDI	multiple daily injection
MHC	major histocompatibility complex
MI	myocardial infarction
MODY	maturity-onset diabetes of the young
NADH	nicotinamide adenine dinucleotide plus hydrogen
NADPH	nicotinamide adenine dinucleotide phosphate hydrogen
NEFA	non-esterified fatty acid
NGT	normal glucose tolerance
NICE	National Institute of Health and Clinical Excellence
NIDDM	non-insulin dependent diabetes mellitus
NK	natural killer
NKCF	natural killer cell factor
NLD	necrobiosis lipoidica diabeticorum
NO	nitric oxide
NOD	non-obese diabetic
NPH	neutral protamine Hagedorn
NPY	neuropeptide Y
NSF	National Service Framework
NVD	new vessels on the disc
NVE	new vessels elsewhere
OCT	optical coherence tomography
OGTT	oral glucose tolerance test
OR	odds ratio
PAD	peripheral arterial disease
PAI-1	plasminogen activator inhibitor-1
PCI	percutaneous coronary intervention
PCOS	polycystic ovary syndrome
PG	plasma glucose
PI	phospatidylinositol
PKC	Protein kinase C
PNDM	permanent neonatal diabetes mellitus
PP	pancreatic polypeptide
PPARγ	peroxisome proliferator-activated receptor-γ
PRP	panretinal laser photocoagulation
QALY	quality-adjusted life-year
RAGE	receptor for AGE
RAS	renin-angiotensin system
RCT	randomised controlled trial
ROS	reactive oxygen species
RRR	relative risk reduction
RRT	renal replacement therapy
RXR	retinoid X receptor
SC	subcutaneous
SPK	simultaneous pancreas and kidney transplantation
SU	sulphonylurea
TCC	total contact casting
TCF7L2	transcription factor 7-like 2 gene
TG	triglyceride
TGF	transforming growth factor
TIA	transient ischaemic attack
TNF	tumour necrosis factor
TZD	thiazolidinedione
UKPDS	UK Prospective Diabetes Study
UTI	urinary tract infections
VCAM	vascular cell adhesion molecule
VDT	vibration detection threshold
VEGF	vascular endothelium-derived growth factor
VIP	vasoactive intestinal peptide
VLDL	very low-density lipoprotein
WHO	World Health Organization

Part 1

Introduction to diabetes

Chapter 1

Introduction to diabetes

KEY POINTS

- Diabetes is common and its incidence is rising.
- Type 2 diabetes is by far the most common accounting for 85–95% of cases.
- Complications in the microvasculature (eye, kidney and nerve) and the macrovasculature are responsible for considerable morbidity and excess mortality.

Diabetes mellitus is a condition of chronically elevated blood glucose concentrations which give rise to its main symptom of passing large quantities of sweet-tasting urine (*diabetes* from the Greek word meaning 'a siphon', as the body acts as a conduit for the excess fluid, and *mellitus* from the Greek and Latin for honey). The fundamental underlying abnormality is a net (relative or absent) deficiency of the hormone insulin. Insulin is essentially the only hormone that can lower blood glucose.

There are two categories of diabetes: type 1 is caused by an autoimmune destruction of the insulin-producing β cell of the islets of Langerhans in the pancreas (absolute deficiency); and type 2 is a result of both impaired insulin secretion and resistance to its action – often secondary to obesity (relative deficiency).

The precise level of blood glucose that defines diabetes has been revised several times and is covered in more detail in Chapter 3. Diabetes is common and is becoming more common. Age-adjusted prevalence is set to rise from 5.9% to 7.1% (246–380 million) worldwide in the 20–79 year age group, a 55% increase (Figure 1.1). The relative proportions of type 1 to type 2 vary from 15:85 for Western populations to 5:95 in developing countries.

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It is the short- and long-term complications of diabetes which make it a major public health problem. Absolute deficiency of insulin leads to ketoacidosis and coma with an appreciable mortality even in the UK and other Western countries. Hyperglycaemic hyperosmolar coma (now called hyperglycaemic hyperosmolar state) is less common and more insidious but remains an equally serious problem for people with type 2 diabetes (see Chapter 12).

Long-term hyperglycaemia affects the microvasculature of the eye, kidney and nerve as well as the larger arteries, leading to accelerated atherosclerosis. Diabetes is the most common cause of blindness in those of working age, the most common single cause of end-stage renal failure worldwide, and the consequences of neuropathy make it the most common cause of non-traumatic lower limb amputation. Mortality from ischaemic heart disease and stroke is 2–4-fold higher than in the age- and sex-matched non-diabetic population. All these important clinical problems will be covered in detail in subsequent chapters (Figure 1.2).

This handbook sets out to cover the essentials of diagnosis, epidemiology and management of diabetes and its distressingly many complications. By using case vignettes and summaries of key trials together with web links and suggestions for further reading, it will serve as a useful desktop reference for all healthcare professionals who provide diabetes care.

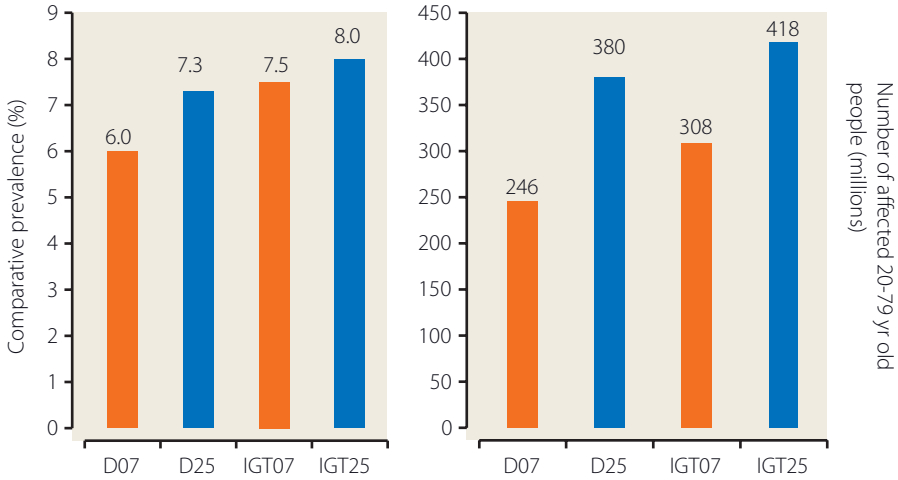

Figure 1.1 Estimated comparative prevalence (age adjusted) of diabetes and impaired glucose tolerance (IGT) together with numbers affected for the global population age 20–79 years for 2007 (red) and 2025 (blue). Data from *Diabetes Atlas*, 3rd edn, International Diabetes Federation.

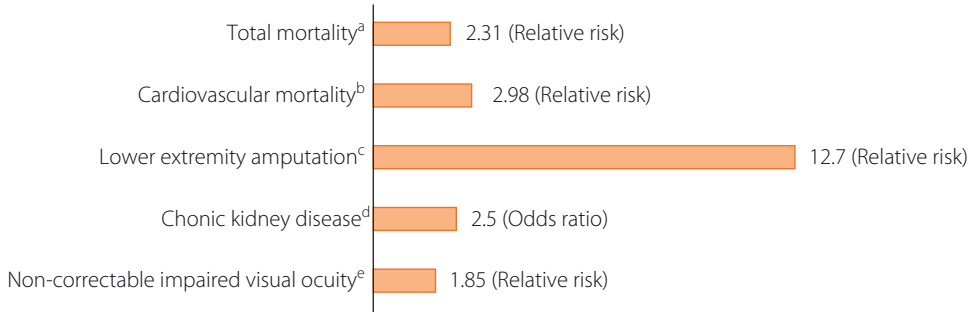

Figure 1.2 Rates of major complications of diabetes for the US population derived from NHANES or Medicare data. [a]NHANES data 1988–2000; [b]Medicare population Minnesota 1993–5; [c]NHANES data, 1999–2006 (chronic kidney disease defined as estimated GFR <60 mL/min/1.73 m^2.); [d]NHANES data, 1999–2002.

FURTHER READING

International Diabetes Federation. *Diabetes Atlas*, 4th edn. Brussels: International Diabetes Federation, 2009.

KEY WEBSITE

- Diabetes Atlas: www.eatlas.idf.org

Chapter 2

History of diabetes

KEY POINTS

- Diabetes has been known since ancient times.
- A link to the pancreas was established in 1889 culminating in the isolation of insulin in 1921.
- The structure of insulin was finally elucidated in the 1960s.
- Insulin was the first therapy to be manufactured using genetic engineering techniques.

Diseases with the clinical features of diabetes have been recognised since antiquity. The Ebers papyrus (Figure 2.1), dating from 1550 BC, describes a polyuric state that resembles diabetes.

The word 'diabetes' was first used by Aretaeus of Cappadocia in the second century AD. Aretaeus gave a clinical description of the disease (Box 2.1), noting the increased urine flow, thirst and weight loss, features that are instantly recognizable today.

The sweet, honey-like taste of urine in polyuric states, which attracted ants and other insects, was reported by Hindu physicians such as Sushrut (Susruta) during the fifth and sixth centuries AD. These descriptions even mention two forms of diabetes, the more common occurring in older, overweight and indolent people, and the other in lean people who did not survive for long. This empirical subdivision predicted the modern classification into type 1 and type 2 diabetes.

Diabetes was largely neglected in Europe until a 17th-century English physician, Thomas Willis (1621–75) (Figure 2.2), rediscovered the sweetness of diabetic urine. Willis, who was physician to King Charles II, thought that the disease had been rare in ancient times, but that its frequency was increasing in his age 'given to good fellowship'. Nearly a century later, the Liverpool physician Matthew Dobson (1735–84) showed that the sweetness of urine and serum was caused by sugar. John Rollo (d. 1809) was the first to apply the adjective 'mellitus' to the disease.

In the 19th century, the French physiologist Claude Bernard (1813–78) (Figure 2.3) made many discoveries relating to diabetes. Among these was the finding that the sugar that appears in the urine was stored in the liver as glycogen. Bernard also demonstrated links between the central nervous system and diabetes when he observed

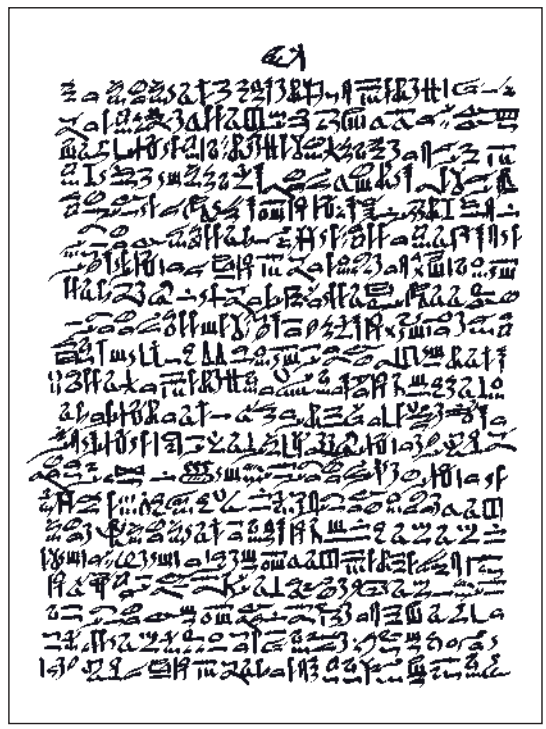

Figure 2.1 The Ebers papyrus. The Wellcome Institute Library, London, UK.

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Box 2.1 Description of diabetes by Aretaeus

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.

Adapted from Papaspyros S. *The History of Diabetes Mellitus*, 2nd edn. Stuttgart: Thieme, 1964.

Figure 2.2 Thomas Willis. The Wellcome Institue Library, London, UK.

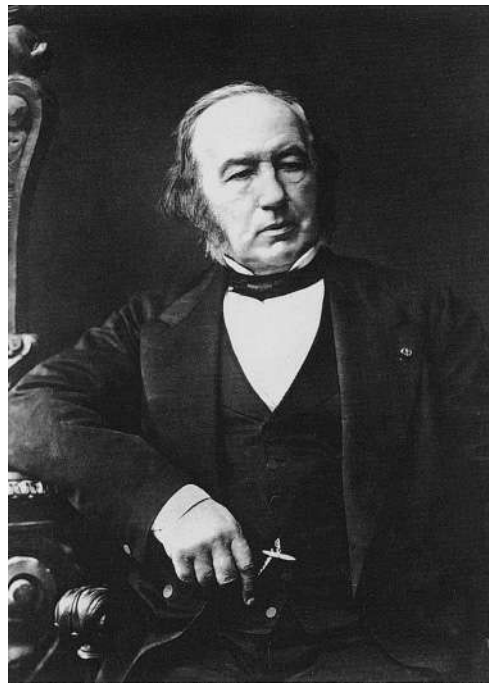

Figure 2.3 Claude Bernard. The Wellcome Institue Library, London, UK.

Figure 2.4 Paul Langerhans. The Wellcome Institue Library, London, UK.

temporary hyperglycaemia (piqûre diabetes) when the medulla of conscious rabbits was transfixed with a needle.

In 1889, Oskar Minkowski (1858–1931) and Joseph von Mering (1849–1908) from Strasbourg removed the pancreas from a dog to see if the organ was essential for life. The animal displayed typical signs of diabetes, with thirst, polyuria and wasting, which were associated with glycosuria and hyperglycaemia. This experiment showed that a pancreatic disorder causes diabetes, but they did not follow up on the observation.

Paul Langerhans (1847–88) (Figure 2.4) from Berlin, in his doctoral thesis of 1869, was the first to describe small clusters of cells in teased preparations of the pancreas. He did not speculate on the function of the cells, and it was Edouard Laguesse in France who later (1893) named the cells 'islets of Langerhans' and suggested that they were endocrine tissue of the pancreas that produced a glucose-lowering hormone.

In the early 20th century, several workers isolated impure hypoglycaemic extracts from the pancreas, including the Berlin physician Georg Zuelzer (1840–1949), the Romanian Nicolas Paulesco (1869–1931), and the Americans Ernest Scott (1877–1966) and Israel Kleiner (1885–1966).

Insulin was discovered in 1921 at the University of Toronto, Canada, through a collaboration between the

surgeon Frederick G Banting (1891–1941), his student assistant Charles H Best (1899–1978), the biochemist James B Collip (1892–1965) and the physiologist JJR Macleod (1876–1935). Banting and Best made chilled extracts of dog pancreas, injected them into pancreatectomised diabetic dogs, and showed a fall in blood gluocse concentrations (Figure 2.5).

Banting and Best's notes of the dog experiments refer to the administration of 'isletin', later called insulin by them at the suggestion of Macleod. They were unaware that the Belgian Jean de Meyer had already coined the term 'insuline' in 1909. (All these names ultimately derive from the Latin for 'island'.)

Collip improved the methods for the extraction and purification of insulin from the pancreas, and the first diabetic patient, a 14-year-old boy called Leonard Thompson, was treated on 11th January 1922. A commercially viable extraction procedure was then developed in collaboration with chemists from Eli Lilly and Co. in the USA, and insulin became widely available in North America and Europe from 1923. The 1923 Nobel Prize for Physiology or Medicine was awarded to Banting and Macleod, who decided to share their prizes with Best and Collip.

The American physician Elliot P Joslin (1869–1962) was one of the first doctors to gain experience with insulin. Working in Boston, he treated 293 patients in the first year after August 1922. Joslin also introduced systematic education for his diabetic patients.

In the UK, the discovery of insulin saved the life of the London physician Robin D Lawrence (1892–1968), who had recently developed type 1 diabetes. He subsequently played a leading part in the founding of the British Diabetic Association (now Diabetes UK).

Figure 2.5 Charles Best and Frederick Banting in Toronto in 1922 (the dog is thought to have been called Marjorie).

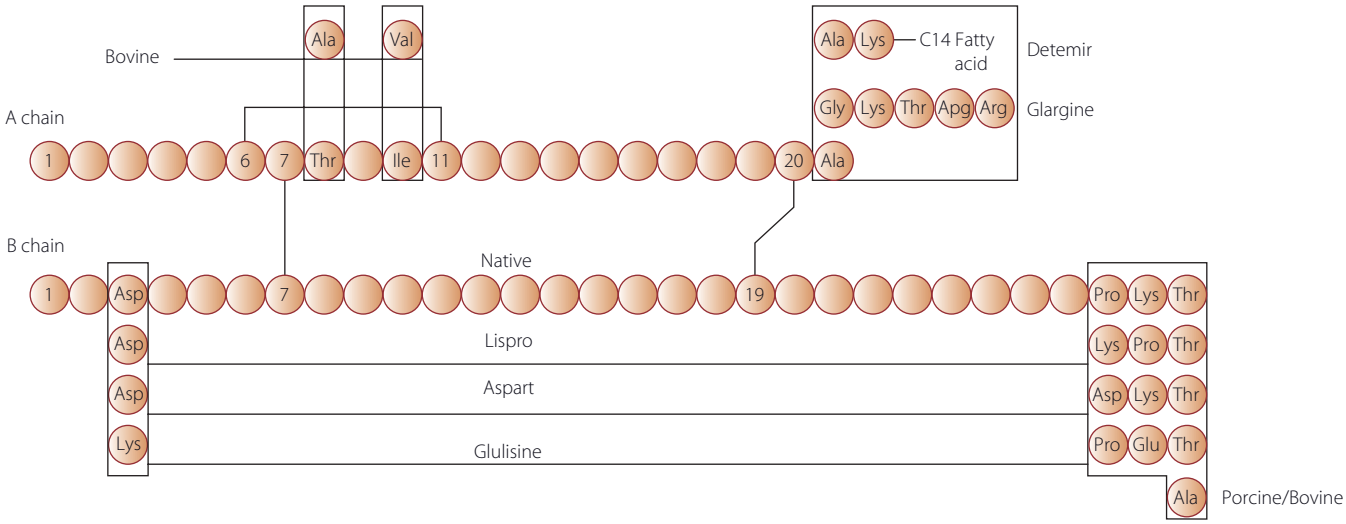

Figure 2.6 Schematic amino acid sequence of human insulin; porcine and bovine insulin; the short-acting insulin analogues aspart, lispro and glulisine; and the long-acting analogues glargine and detemir.

Among the many major advances since the introduction of insulin into clinical practice was the elucidation in 1955 of its primary structure (amino acid sequence) (Figure 2.6) by the Cambridge UK scientist Frederick Sanger (b. 1918), who received the Nobel Prize for this work in 1958.

Oxford-based Dorothy Hodgkin (1910–1994), another Nobel Prize winner, and her colleagues described the three-dimensional structure of insulin using X-ray crystallography (1969).

By the 1950s, it was accepted that tissue complications, such as those that occur in the eye and kidney, continued to develop in long-standing diabetes, in spite of insulin treatment. The definitive proof that normalization of glycaemia could prevent or delay the development of diabetic complications had to wait until 1993 for type 1 diabetes (the Diabetes Control and Complications Trial in North America) and 1998 for type 2 diabetes (the UK Prospective Diabetes Study – UKPDS).

Until the 1980s, insulin was derived only from animal pancreata, in increasingly more refined preparations. Using additives such as protamine or zinc, the subcutaneous absorption could be delayed, thus providing 24-hour availability using 2–4 injections a day of different preparations.

With the development of genetic engineering, it became possible to produce human insulin and subsequent further manipulations of the molecule have led to a wide range of preparations with different absorption profiles (Figure 2.6). Further developments along these lines are expected but a continuing dependence upon subcutaneous injection as the main route of administration is likely for the foreseeable future.

In type 2 diabetes oral agents have been available since the 1950s. It is now possible, however, to modify both insulin secretion and its action by using drugs that both increase insulin release from the β cell and improve insulin sensitivity peripherally. There is intensive research into therapies for diabetes and newer agents will undoubtedly become available as our understanding of the mechanism of glucose homeostasis increases.

These therapeutic areas will be covered in more detail in subsequent chapters.

FURTHER READING

Bliss M. *The Discovery of Insulin*. Toronto: McLelland and Stewart, 1982.

Chapter 3

Diagnosis and classification of diabetes

KEY POINTS

- WHO and ADA define a cut-off of 7 mmol/L in fasting plasma glucose concentration to define diabetes.
- Greater standardisation of HbA_{1c} assays has led to a recommendation that HbA_{1c} ≥6.5% (or 48 mmol/mol) be used as a diagnostic cut-off for diabetes.
- There are 23.6 million people in the USA with diabetes (nearly 8% of the population), >90% type 2 diabetes.
- Impaired glucose tolerance and impaired fasting glycaemia are intermediate states of prediabetes (type 2) associated with increased cardiovascular risk.
- HbA_{1c} is useful for surveillance of glycaemic control in established diabetes, but it will be increasingly used as a primary diagnostic and screening test (HbA_{1c} ≥6.5%).
- Type 2 diabetes is often undiagnosed in the community, and 20% of newly diagnosed patients already have evidence of diabetes-related CV complications.

Diabetes mellitus is diagnosed by identifying chronic hyperglycaemia. The World Health Organization (WHO) and the American Diabetes Association (ADA) have used a fasting plasma glucose (FPG) of 7 mmol/L or higher to define diabetes (Table 3.1). This originated from epidemiological studies in the 1990s which appeared to show that the risk of microvascular complications (e.g. retinopathy) increases sharply at a FPG threshold of 7 mmol/L (Figure 3.1). Lately, however, the notion of a clear glycaemic threshold separating people at high and low risk of diabetic microvascular complications has been called into question. Part of the rationale for switching to HbA_{1c} > 6.5% (48 mmol/mol) as a diagnostic test is that moderate retinopathy, in more recent trials, is rare below this HbA_{1c} threshold.

There are currently 23.6 million people in the USA with diabetes (7.8% of the population). The total number of people with diabetes worldwide is projected to increase from 171 million in 2000 to 366 million in 2030. A key demographic change to the rising prevalence of diabetes worldwide is an increasing proportion of people >65 years of age.

Table 3.1 Classification of diabetes and glucose intolerance according to ADA fasting and WHO 2-h glucose criteria. To convert glucose concentrations from mmol/L into mg/dL, multiply by 18

	Blood sample		
	Plasma	**Capillary**	**Whole**
Fasting blood glucose (mmol/L)			
Normal	<6.1	<5.6	<5.6
Impaired fasting glycaemia	6.1–6.9	5.6–6.0	5.6–6.0
Diabetes	≥7.0	≥6.1	≥6.1
2-hour blood glucose			
Normal	<7.8	<7.8	<6.7
Impaired glucose tolerance	7.8–11.0	7.8–11.0	6.7–9.9
Diabetes	≥11.1	≥11.1	≥10.0

Diabetes can be diagnosed in several ways.

- HbA_{1c} ≥6.5% (48 mmol/mol).
- A casual (random) plasma glucose level ≥11.1 mmol/L (200 mg/dL) in someone with typical symptoms of diabetes.
- A fasting plasma glucose level ≥7.0 mmol/L (126 mg/dL).
- A plasma glucose level ≥11.1 mmol/L (200 mg/dL) 2 hours after a 75 g load of glucose given by mouth (the oral glucose tolerance test – OGTT).

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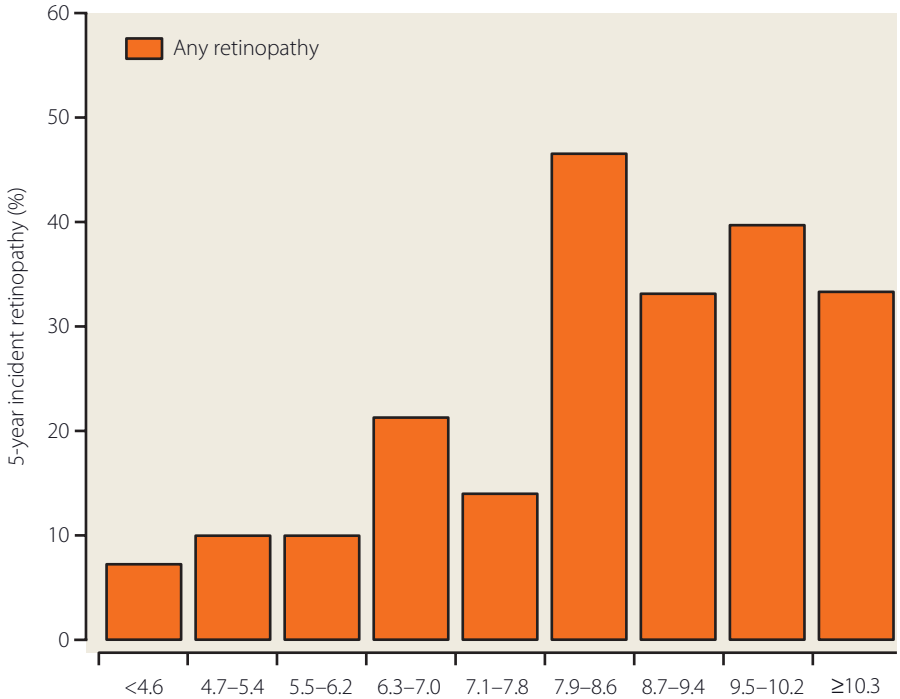

Figure 3.1 Relationship between FPG and incident retinopathy in the Blue Moutains Eye study. In more recent studies (using better methods for detecting retinopathy) there is no evidence of a threshold effect at 7 mmol/L. The risk of retinopathy is continuous. It is reassuring that significant retinopathy is extremely rare in individuals with HbA_{1c} below the diagnosis threshold of 6.5% (48 mmol/mol). Adapted from Wong et al. Lancet 2008; 371: 736–743.

Box 3.1 Some features of impaired glucose tolerance and/or impaired fasting glycaemia

- Intermediate stage of disordered glucose metabolism
- Increased risk of progression to diabetes
- Increased risk of cardiovascular disease
- Little or no risk of microvascular disease
- Some patients may revert to normoglycaemiaic
- IFG is predictive of future type 2 diabetes, whereas IGT is more predictive of CV risk

Intermediate categories of hyperglycaemia: prediabetes

During the natural history of all forms of diabetes, the disease passes through a stage of impaired glucose tolerance (IGT), defined as a plasma glucose of 7.8–11.0 mmol/L (140–200 mg/dL) 2 hours after an OGTT. Impaired fasting glycaemia (IFG) is an analogous category based on fasting glucose levels, and is defined as a FPG of 6.1–6.9 mmol/L (110–126 mg/dL) (Box 3.1).

LANDMARK CLINICAL TRIALS

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Impaired glucose tolerance and IFG are intermediate metabolic stages between normal glucose homeostasis and diabetes. They are both risk factors for future diabetes and cardiovascular disease, but the 2-hour plasma glucose concentration is a particularly strong predictor of cardiovascular risk and mortality (Figure 3.2).

A proportion of patients with IFG and/or IGT (5–10% per annum) will deteriorate metabolically into overt diabetes. Lifestyle modification (diet, exercise and weight loss) is the best approach to diabetes prevention for these patients. More recently, some genetic markers have been associated with an increased risk of progression from IGT to diabetes, e.g. common polymorphisms of the transcription factor 7-like 2 gene (TCF7L2).

For an OGTT, the subject is tested in the morning after an overnight fast, in the seated position. After taking a fasting blood sample, 75 g of glucose is given by mouth, often in the form of a glucose drink such as Lucozade (388 mL). For children, the glucose dose is calculated as 1.75 g/kg. A further blood sample is taken at 2 hours, and the fasting and 2-hour glucose values are interpreted as in Figure 3.3.

Screening for diabetes by the FPG level does not identify exactly the same population as that diagnosed by the plasma glucose 2 hours after an OGTT or by HbA_{1c} (Table 3.2). For example, in the US NHANES study, 1.6% of the population had HbA_{1c} ≥6.5% but 5% of these would be undiagnosed using FPG or 2h criteria. Only 55% of patients with FPG ≥ 7mmol/L and 2h glucose ≥11.1 mmol/L had an HbA_{1c} ≥6.5% (Cowie et al. 2010).

Glycosuria (the presence of glucose in the urine) cannot be used to diagnose diabetes because of the poor relationship between blood and urine glucose. This is for several reasons: the renal threshold for glucose reabsorption varies considerably within and between individuals, the urine glucose concentration is affected by the subject's state of

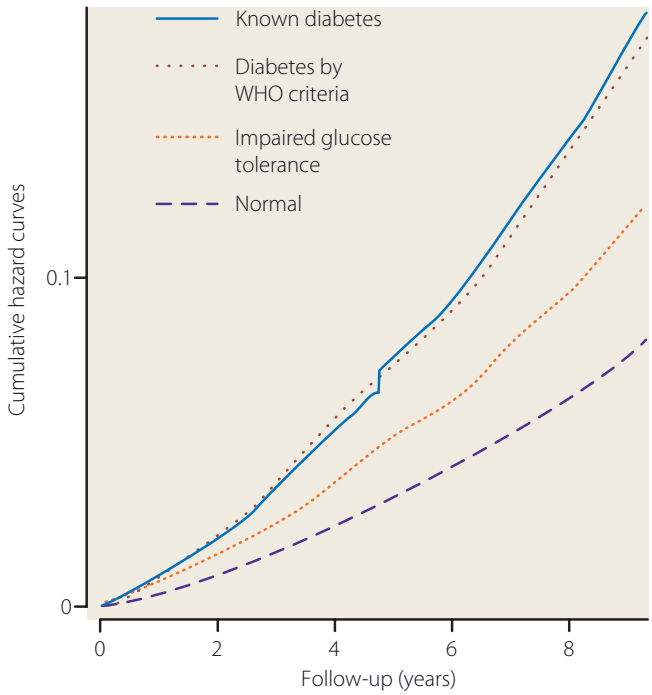

Figure 3.2 The relationship between 2-hour plasma glucose and survival in patients with normal glucose tolerance, patients with IGT, those with newly diagnosed diabetes by OGTT, and those with known diabetes, as shown by the DECODE study (combining data from 13 European cohort studies). Reproduced from DECODE Study Group. Lancet 1999; 354: 617–621.

Table 3.2 Use of HbA_{1C} ≥ 6.5% (48 mmol/mol) as a cut-off for making the diagnosis of diabetes offers some advantages but there are several potential disadvantages

Advantages	Disadvantages
• Avoids the need for a fasting blood sample, and the pre-analytical instability of glucose measurements • HbA_{1C} reflects glycaemia over several weeks • Lower biological variability of HbA_{1C} compared with FPG or 2 h glucose • Virtual absence of significant retinopathy among people with HbA_{1C} < 6.5%	• HbA_{1C} measurements can give spurious results in: ○ anaemia (Fe-deficiency) ○ haemoglobinopathies ○ renal failure ○ different ethnic groups • Diagnosis by HbA_{1C} will identify a different population to that diagnosed by FPG • Distribution of HbA_{1C} values varies in different ethnic groups • HbA_{1C} increases with age • Some patients and ethnic groups may be diagnosed with diabetes by some criteria but not others

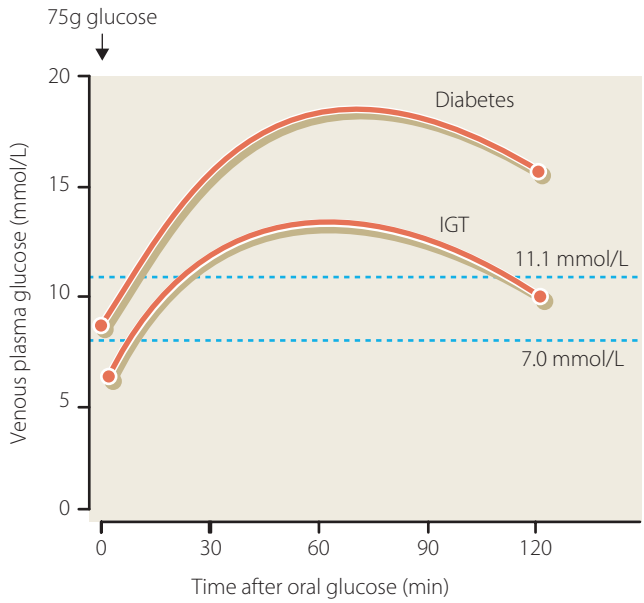

Figure 3.3 Diagnosis of diabetes and IGT by the oral glucose tolerance test.

Table 3.3 Historically, HbA_{1c} has been reported in percentage values describing the proportion of haemoglobin that is glycated. The assay was aligned to that used in the Diabetes Control and Complications (DCCT) trial. The International Federation of Clinical Chemistry (IFCC) has now established a new reference system, and values will be reported in mmol HbA_{1c} per mol haemoglobin without glucose attached. Conversion for HbA_{1c} is shown below

DCCT (%)	IFCC (mmol/mol)	DCCT (%)	IFCC (mmol/mol)
6.0	42	9.0	75
6.2	44	9.2	77
6.4	46	9.4	79
6.5	48	9.5	80
6.6	49	9.6	81
6.8	51	9.8	84
7.0	53	10.0	86
7.2	55	10.2	88
7.4	57	10.4	90
7.5	58	10.5	91
7.6	60	10.6	92
7.8	62	10.8	95
8.0	64	11.0	97
8.2	66	11.2	99
8.4	68	11.4	101
8.5	69	11.5	102
8.6	70	11.6	103
8.8	73	11.8	105

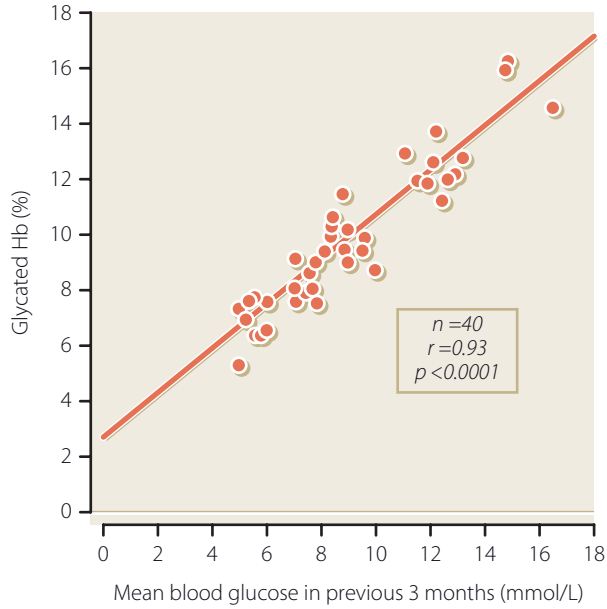

Figure 3.4 HbA_{1c} correlates well with previous mean blood glucose levels over several weeks. From Paisey. Diabetologia 1980; 19: 31–34.

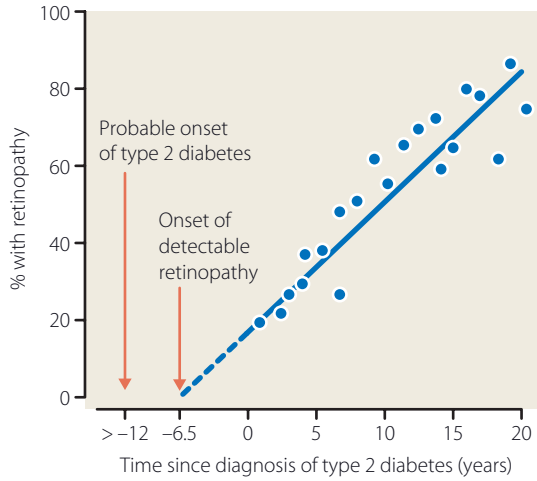

Figure 3.5 The prevalence of retinopathy in type 2 diabetes relative to the time of clinical diagnosis. Note the presence of retinopathy at diagnosis and the likely onset of retinopathy and diabetes some years before diagnosis. From Harris et al. Diabetes Care 1992; 15: 815–819.

hydration and the result reflects the average blood glucose during the period that urine has accumulated in the bladder. The average renal threshold is 10 mmol/L (i.e. blood glucose concentration above this level will 'spill over' into the urine), but a negative urine test can be associated with marked hyperglycaemia.

Longer term indices of hyperglycaemia include the glycated haemoglobin percentage (HbA_{1c}), a measure of integrated blood glucose control over the preceding few weeks. HbA_{1c} is used primarily to assess glycaemic control among people with diabetes on treatment (aiming for HbA_{1c} 6–7%). HbA_{1c} analyses are now being calibrated to the IFCC assay(rather than the NGSP DCCT HPLC assay). Thus, the units of HbA_{1c} are changing from percent to mmol/mol (Table 3.3).

The potential value of screening for diabetes is to facilitate early diagnosis and treatment. About 20% of newly diagnosed subjects with types 2 diabetes already have evidence of vascular complications. This suggests that complications begin about 5–6 years before a diagnosis is made, and that the actual onset of (type 2) diabetes may occur several years before the clinical diagnosis.

In most countries, there is no systematic screening policy for diabetes, yet there are estimates that up to 50% of patients with diabetes are undiagnosed. *Ad hoc* screening of high-risk groups is becoming more common. The FPG is quick and cheap, but can miss those with isolated postchallenge hyperglycaemia. In future, HbA_{1c} will be increasingly used for screening and diagnosis. Screening policies should target high-risk groups (Box 3.2).

Classification of diabetes

The current classification of diabetes is based on the aetiology of the disease (Box 3.3). There are four categories.

Box 3.2 High-risk patients who should be screened annually for type 2 diabetes

- Metabolic syndrome
- Patients >45 years of age, especially the obese
- Those with parents or siblings with type 2 diabetes
- Ethnic minorities, e.g. South Indians, even if non-obese
- Patients with cardiovascular risk factors, e.g. hypertension or dyslipidaemia, and those with established atherosclerotic disease
- Women with previous gestational diabetes
- Women with polycystic ovary syndrome
- Patients with IFG/IGT

Box 3.3 Classification of diabetes

- Type 1 (β cell destruction, usually leading to absolute insulin deficiency)
  - Autoimmune
  - Idiopathic
- Type 2
  - Ranges from predominantly insulin resistant, with relative insulin deficiency, to a predominantly insulin-secretory defect, with or without insulin resistance
- Other specific types
  - Genetic defects of β cell function
  - Genetic defects of insulin action
  - Diseases of exocrine pancreas
  - Endocrinopathies
  - Drug induced or chemical induced, e.g. steroids
  - Infections
  - Uncommon forms of immune-mediated diabetes
  - Other genetic syndromes sometimes associated with diabetes
- Gestational diabetes

CASE HISTORY

A 66-year-old retired policeman attends his family doctor for a routine blood pressure (BP) check. He has had hypertension for 4 years. He reports incidentally that he has been feeling generally tired and lethargic. On further questioning, he admits to nocturia ×3 and volunteers that in recent months he has been taking a glass of water to bed since he often wakes feeling thirsty. The GP notices that he had a cutaneous boil lanced 6 weeks ago. Apart from hypertension, there is no other significant past medical history but his bodyweight has gradually risen (95 kg, Body Mass Index (BMI) 32). He takes an angiotensin-converting enzyme (ACE) inhibitor, lisinopril 10 mg, for hypertension. His mother had type 2 diabetes, he is a non-smoker and drinks 15 units of alcohol per week. His only exercise is golf, twice per week. The doctor takes a random venous blood sample, which shows a plasma glucose level of 13 mmol/L. Further blood tests show a normal haematology profile, normal electrolytes and renal function, HbA_{1c} 8.3%, and fasting lipids show total cholesterol 6.6 mmol/L, low-density lipoprotein (LDL)-cholesterol 4.3 mmol/L, triglycerides 3.9 mmol/L and high-density lipoprotein (HDL)-cholesterol 0.6 mmol/L. Minor abnormalities of liver function are also noted (aspartate aminotransferase (AST) and alanine aminotransferase (ALT) 2–3× upper limit).

Comment: This man presents with typical symptoms of type 2 diabetes and several risk factors (age, obesity, hypertension, family history). The random plasma glucose, in the context of symptoms, is diagnostic. He has features of the metabolic syndrome, including hypertension, dyslipidaemia (high triglycerides and low HDL-cholesterol) and central obesity, and fatty infiltration of the liver is common in this scenario. The HbA_{1c} is quite high, reflecting chronic hyperglycaemia over at least 8 weeks. Susceptibility to infections is typical.

- Type 1 diabetes (caused by pancreatic islet cell destruction).
- Type 2 diabetes (caused by a combination of insulin resistance and β cell insulin secretory dysfunction).
- Other specific types of diabetes (caused by conditions such as endocrinopathies, diseases of the exocrine pancreas, genetic syndromes, etc.; see below).
- Gestational diabetes (defined as diabetes that occurs for the first time in pregnancy).

Type 1 diabetes is subdivided into two main types: 1a or autoimmune (about 90% of type 1 patients in Europe and North America, in which immune markers, such as circulating islet cell antibodies, suggest autoimmune destruction of the β cells) and 1b or idiopathic (where there is no evidence of autoimmunity).

A steady increase (2.5–3% per annum) in the incidence of type 1 diabetes has been reported worldwide, especially among young children <4 years old. There are large differences between countries in the incidence of type 1 diabetes, e.g. up to 10-fold difference among European countries.

This classification has now replaced the earlier, clinical classification into 'insulin-dependent diabetes mellitus' (IDDM) and 'non-insulin dependent diabetes mellitus' (NIDDM), which was based on the need for insulin treatment at diagnosis. IDDM is broadly equivalent to type 1 diabetes and NIDDM to type 2 diabetes (Table 3.4). One of the disadvantages of the old classification according to treatment was that subjects could change their type of diabetes – for example, some type 1a patients diagnosed after the age of 40 years masquerade as NIDDM, before eventually becoming truly insulin dependent (this is now classified as latent autoimmune diabetes in adults; LADA).

Table 3.4 Type 1 and 2 diabetes correspond to IDDM and NIDDM in the old classification system

IDDM	NIDDM
Type 1 LADA (late stage)	Type 2 LADA (early stage)

Various clinical and biochemical features can be used to decide whether the patient has type 1 or type 2 diabetes (Box 3.4). The distinction may be difficult in individual cases.

The category of 'other specific types of diabetes' is a large group of conditions (Box 3.5), which includes genetic defects in insulin secretion (such as in maturity-onset diabetes of the young (MODY) and insulinopathies), genetic defects in insulin action (e.g. syndromes of severe insulin resistance), pancreatitis and other exocrine disorders, hormone-secreting tumours such as acromegaly (growth hormone)

Box 3.4 Clinical features of type 1 and type 2 diabetes

Type 1 diabetes
- Sudden onset with severe symptoms of thirst and ketoacidosis (vomiting, hyperventilation, dehydration)
- Recent, marked weight loss. Usually lean
- Spontaneous ketosis
- Life-threatening; needs urgent insulin replacement
- Absent C-peptide
- Markers of autoimmunity present (e.g. islet cell antibodies)

Type 2 diabetes
- Usually insidious onset of tiredness, thirst, polyuria, nocturia
- No ketoacidosis
- Usually overweight or obese; often no recent weight loss
- Frequent infections, e.g. urine, skin, chest
- Symptoms may be minimal and/or ignored by patient
- Often other features of 'metabolic syndrome', e.g. hypertension
- C-peptide detectable

Box 3.5 Other specific types of diabetes

Genetic defects of β cell function
- Chromosome 12, HNF-1a (formerly MODY-3)
- Chromosome 7, glucokinase (formerly MODY-2)
- Chromosome 20, HNF-4a (formerly MODY-1)
- Mitochondrial DNA
- Insulinopathies

Genetic defects in insulin action
- Type A insulin resistance
- Leprechaunism
- Rabson–Mendenhall syndrome
- Lipoatrophic diabetes

Diseases of the exocrine pancreas
- Pancreatitis
- Trauma/pancreatectomy
- Neoplasia
- Cystic fibrosis
- Haemochromatosis
- Fibrocalculous pancreatopathy

Endocrinopathies
- Acromegaly
- Cushing's syndrome
- Glucagonoma
- Phaeochromocytoma
- Hyperthyroidism
- Somatostatinoma
- Aldosteronoma

Drug induced or chemical induced
- Glucocorticoids
- Thiazides
- Pentamidine
- Nicotinic acid
- Thyroid hormone
- β-adrenergic agonists
- Interferon-α

Infections
- Congenital rubella
- Cytomegalovirus
- Others

- Uncommon forms of immune-mediated diabetes
- 'Stiff man' syndrome
- Anti-insulin receptor antibodies

Other genetic syndromes sometimes associated with diabetes
- Down's syndrome
- Klinefelter's syndrome
- Turner's syndrome
- Wolfram's syndrome
- Friedreich's ataxia
- Huntington's chorea
- Lawrence–Moon–Biedl syndrome
- Myotonic dystrophy
- Porphyria
- Prader–Willi syndrome

KEY WEBSITES

- www.who.int/diabetes/publications/en/
- www.diabetes.org/about-diabetes.jsp
- www.idf.org/home/index.cfm?node=4

and Cushing's syndrome (cortisol). Some cases are caused by the administration of drugs such as glucocorticoids. Some genetic syndromes are sometimes associated with diabetes (e.g. Down's syndrome, Klinefelter's syndrome and many more).

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Chapter 4

Public health aspects of diabetes

KEY POINTS

- The annual economic burden of diabetes in the USA was estimated at $132 billion in 2002 (>10% of total US healthcare expenditure). Drug expenditure alone was $12.5 billion in 2007.
- There is an increasing focus on the cost-effectiveness of healthcare interventions in diabetes.
- Overall, life expectancy of patients with diabetes is reduced by 25% and cardiovascular disease accounts for most of the premature mortality.
- Each 1% increment in HbA_{1c} is associated with an 18% increase in risk of a major fatal or non-fatal CV event and a 12–14% increase in the risk of death.
- The global prevalence of diabetes will rise from 171 million in 2000 to 366 million by 2030. The incidence of type 1 and type 2 diabetes is increasing.
- Providing structured education for all patients with diabetes, targeted screening for high-risk individuals and appropriate lifestyle/dietary advice for diabetes prevention are major public health challenges.

Impact on healthcare expenditure

Diabetes is an expensive disease. About 75% of the direct costs are absorbed by the long-term complications, rather than the management of diabetes itself. In the USA in 2002, the annual economic burden of diabetes was estimated at $132 billion (accounting for >10% of total US healthcare expenditure). About 75% of the direct costs are attributable to managing the longterm vascular complications of diabetes, and 90% of resources are spent on type 2 diabetes. In terms of the costs of managing hyperglycaemia, self-monitoring of blood glucose concentrations is the single biggest item.

The management of diabetes is becoming more complex and more intensive, and therefore more expensive (Figure 4.1). The mean number of diabetes medications per treated patient increased from 1.14 in 1994 to 1.63 in 2007. Recent trends in the use of newer insulins and oral antidiabetic drugs have resulted in extra costs (mean cost per prescription in the USA increased from $56 in 2001 to $76 in 2007). Overall, drug expenditure in the US rose from $6.7 billion in 2001 to $12.5 billion in 2007.

There is an increasing awareness of the clinical and cost-effectiveness of diabetes interventions on the longer term outcomes. Based on the UK Prospective Diabetes Study (UKPDS), each quality-adjusted life-year (QALY) gained by intensive blood glucose control cost approximately £6028 (in 2004 values). In contrast, the equivalent cost for implementing an intensive blood pressure (BP) control policy was only £369. Both of these estimates are well below the threshold, or affordability index, of £20,000 per QALY set by the UK National Institute of Health and Clinical Excellence (NICE) when advising on the use of a new technology in the National Health Service (NHS). In particular, the total annual cost of providing UKPDS treatment to reduce diabetes complications amounted to <1% of the UK NHS budget for 2001–5.

Health economic analyses in the US have shown that a 50-year-old patient recently diagnosed with diabetes has an annual medical expenditure that is $4174 greater than an identical person without diabetes. Furthermore, each additional year with diabetes increases the annual medical expenditure by $158 over and above the increases in medical costs attributable to ageing (Figure 4.2).

Patterns of survival and cardiovascular outcomes

The overall life expectancy of patients with diabetes is reduced by about 25%, and cardiovascular disease accounts for three-quarters of all deaths among patients with diabetes.

Handbook of Diabetes, 4th edition. By © Rudy Bilous & Richard Donnelly. Published 2010 by Blackwell Publishing Ltd.

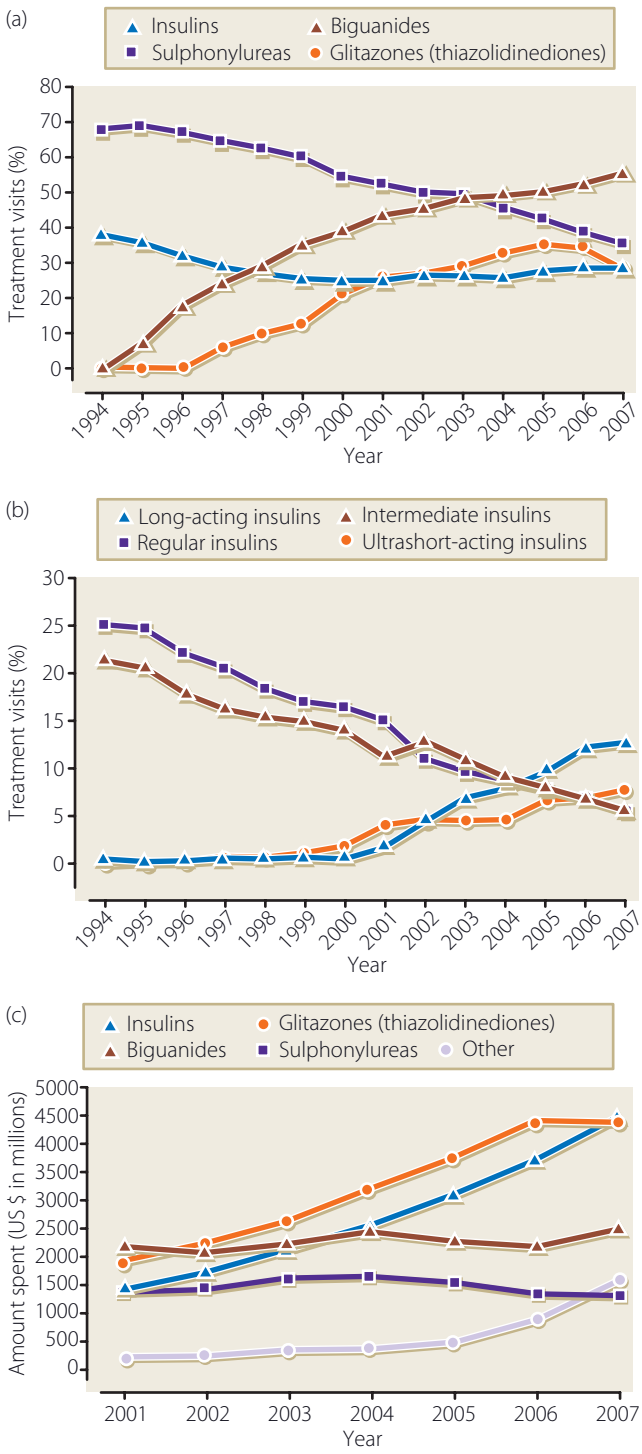

Figure 4.1 Data from the IMS Health National Disease and Therapeutic Index (USA) showing national trends in America over recent years: (a) trends in the use of insulins, sulphonylureas, biguanides and glitazones from 1994 to 2007; (b) the use of different types of insulin (1994–2007); and (c) the amount spent per year on diabetes drugs (2001–2007); 'other' includes insulin secretagogues (e.g. nateglinide), α-glucosidase inhibitors (e.g. acarbose), DPP-4 inhibitors (e.g. sitagliptin) and GLP-1 agonists (e.g. exenatide). Adapted from Alexander et al. Arch Intern Med 2008; 168: 2088–2094.

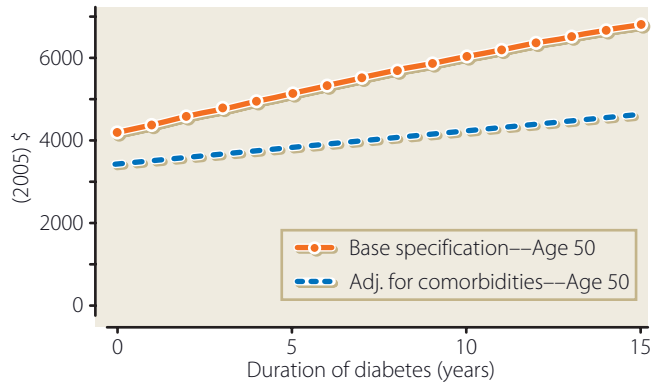

Figure 4.2 This graph shows the average incremental cost of diabetes as a function of the number of years with diabetes. Under the base specification, a 50-year-old person just diagnosed with diabetes has medical expenditures that are $4174 higher than an identical person without diabetes. A 50-year-old patient who has had diabetes for 10 years has medical expenditures that are $6054 greater than an identical person without diabetes (2005 values). Adapted from Trogdon & Hylands. Diabetes Care 2008; 31: 2307–2311.

Table 4.1 Causes of death in patients with type 1 and type 2 diabetes. From Marks HH, Krall LP. In: Marble A et al. (eds) *Joslin's Diabetes Mellitus*, 12th edn. Philadelphia: Lea and Febiger, 1988: 209–254

	Type 1 (%)	Type 2 (%)
Cardiovascular disease	15	58
Cerebrovascular disease	3	12
Nephropathy	55	3
Diabetic coma	4	1
Malignancy	0	11
Infections	10	4
Others	13	11

Diabetes confers an equivalent risk to ageing 15 years. The causes of death are proportionately different in type 1 and type 2 diabetes (Table 4.1). In long-duration type 1 diabetes, for example, nephropathy and heart disease are common, whereas in type 2 diabetes most deaths are due to premature cardiovascular disease (coronary heart disease and stroke). After adjustment for other risk factors, an increase in HbA_{1c} of 1% is associated with an 18% increase in the risk of a cardiovascular event and a 12–14% increase in the risk of death.

Type 1 diabetes is associated with at least a 10-fold increase in cardiovascular disease compared with an age-matched population without diabetes, and in recent years mortality rates from type 1 diabetes have been falling in many countries as a result of more intensive glycaemic and BP control (Figure 4.3).

The relative risk for fatal coronary heart disease (CHD) in patients with type 2 diabetes compared with no diabetes is

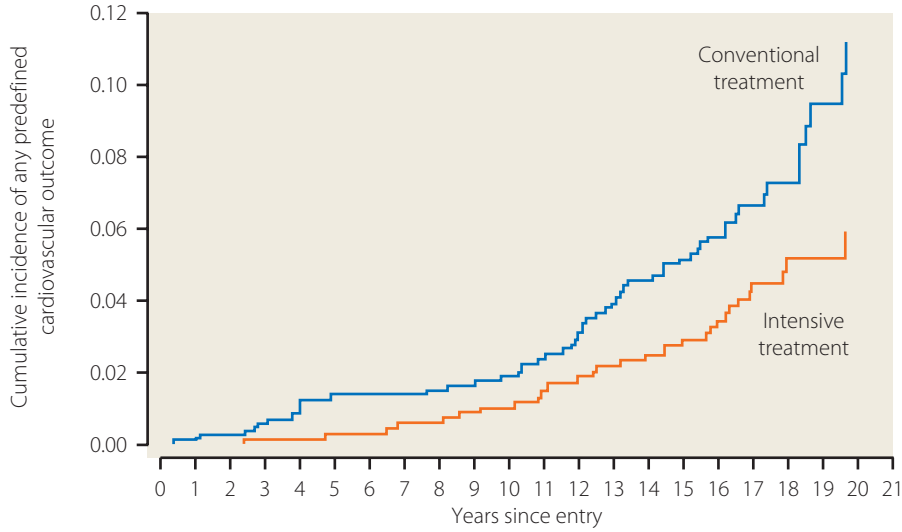

Figure 4.3 The long-term cardiovascular outcomes for patients with type 1 diabetes are improved by early intensive glycaemic control. Intensive control reduces the risk of any cardiovascular disease event by 42%. Adapted from the DCCT/EDIC Research Group. N Engl J Med 2005; 353: 2643–2653.

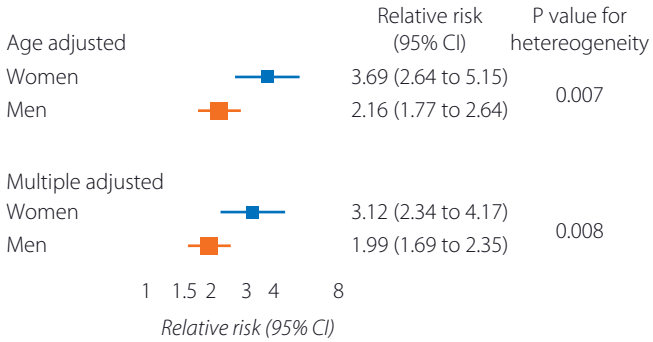

Figure 4.4 Based on a meta-analysis of 22 studies, this graph shows the relative risks of fatal CHD in men and women with type 2 diabetes. Adapted from Huxley et al. BMJ 2006; 332: 73–76.

Table 4.2 The relative risk of ischaemic heart disease and stroke for every 1 mmol/L increase in fasting plasma glucose (FPG) concentration, even in the non-diabetic range, according to different age groups (after adjustment for confounding and regression dilution bias). FPG is a continuous variable in the global risk of mortality attributable to heart disease and stroke. From Danaei et al. Lancet 2006; 368: 1651–1659

	<60 years	60–69 years	≥70 years
Ischaemic heart disease	1.424	1.196	1.196
Stroke	1.360	1.284	1.081

significantly higher for women (3.5-fold increased risk) than for men (2.5-fold) (Figure 4.4). Patients with diabetes also have a worse prognosis following a cardiovascular event. For example, the relative risk of death after myocardial infarction is 2–3-fold higher in patients with diabetes compared with non-diabetics.

Cardiovascular mortality risk increases continuously with blood glucose concentrations starting at levels well below the current thresholds for defining diabetes or impaired fasting glycaemia. Based on population health surveys in 52 countries and a meta-analysis involving >200,000 subjects in the Asia-Pacific region, public health analysts have concluded that 21% of all deaths from ischaemic heart disease and 13% of deaths from stroke were attributable to higher than optimum blood glucose levels (Table 4.2).

Diabetes is a serious global health problem, and one that is going to become much worse. It already affects at least 5–7% of the world's population, and its prevalence is expected to increase from 171 million in 2000 to 366 million people by 2030; 90% of these people will have type 2 diabetes. Currently, there are 57 million people in the USA with prediabetes; most have the 'metabolic syndrome'.

Incidence of type 1 and type 2 diabetes and regional variations

An epidemic of obesity is driving the increased prevalence of type 2 diabetes (Figure 4.5), but the incidence of type 1 diabetes is also steadily increasing. If the present trends continue, there will be a doubling in the number of children in Europe with type 1 diabetes below the age of 5 years before 2020. An emerging dietary risk factor for type 1 diabetes is consumption of root vegetables (potatoes, carrots, etc.). In addition, placental transmission of viruses leading to type 1 diabetes (e.g. rubella) has been recognised. The genetic risk for type 1 diabetes is conferred mainly by HLA-DR and HLA-DQ haplotypes, but environmental

CASE HISTORY

A 66-year-old man of South Asian origin is admitted to hospital as an emergency with chest pain and acute (non-ST elevation) myocardial infarction. His only past medical history is of hypertension and obesity (BMI 33.8). He is a non-smoker and runs a newsagent shop. He takes lisinopril 10 mg daily. On talking to his wife, there is no known history of diabetes and he has not been previously tested. He takes little exercise. Admission blood tests show a random blood glucose of 21.6 mmol/L and HbA_{1c} 9.5%. He is treated with low molecular weight heparin and combination antiplatelet therapy, and blood glucose levels are controlled using a sliding scale IV insulin infusion. Subsequent investigations show that he has triple vessel disease, and he is referred for coronary artery bypass grafting. Blood sugar levels settle with metformin 850 mg bid, and he is seen by a dietitian.

Comment: This case illustrates a number of public health issues. Firstly, the elevated HbA_{1c} indicates that his diabetes has probably been present for some time; given that he has at least three risk factors for type 2 diabetes (hypertension, obesity and ethnicity), why was this not detected earlier? There is still some uncertainty about the benefits, costs and practicalities of screening. Secondly, late presentation and diagnosis usually means that more severe and more costly complications occur which could have been prevented. And thirdly, the South Asian population represents a particularly high-risk group in whom health inequalities often compound the clinical complications of diabetes.

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Figure 4.5 The relationship between Body Mass Index and the hazard ratio for death from any cause. Data for men according to smoking status, relative to females who never smoked, in a large Asian cohort study. Obesity carries an increased risk of several unwanted health outcomes, including diabetes, cardiovascular disease and certain forms of cancer. Adapted from Jee et al. N Engl J Med 2006; 355: 779–787.

triggers are needed to induce islet autoimmunity in genetically predisposed individuals.

The frequency of diabetes is rising, especially in developing countries, where the lifestyle has changed from one based on traditional, agricultural subsistence to a westernised, urban culture. Readily available high-energy foods and physical inactivity lead to obesity, and to diabetes in these susceptible populations. Many diabetic patients in developing countries present late with serious infections or tissue complications. Diabetic emergencies have a high mortality. Practical difficulties in developing countries include lack of doctors, nurses and dietitians and shortages of drugs, including insulin (Figure 4.6). India and China are particularly affected by the type 2 diabetes epidemic. There are an estimated 40 million patients with diabetes in India alone, and available data suggest that the mean HbA_{1c} is high, at 9%.

In the UK and other Western countries, type 2 diabetes is increasing most rapidly among south Asian people living in urban communities (Figure 4.7). Their risk of developing type 2 diabetes is 4–6-fold higher, the disease occurs at an earlier age and the risk of renal and cardiovascular complications is much higher than for other ethnic groups. Overcoming health inequalities, and providing intensive multiple risk factor interventions, is a priority for this group of patients who require specialist medical and dietetic input.

Figure 4.6 A morning education session, led by a nursing sister, at a hospital in Soweto, South Africa. All these patients had been admitted with diabetic emergencies in the previous 24 hours.

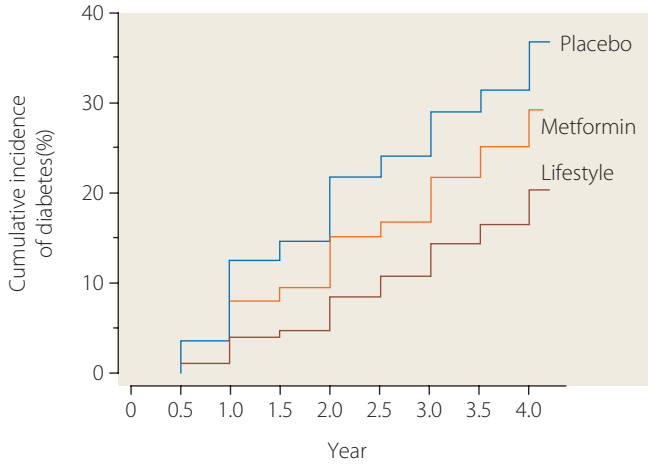

Figure 4.8 A structured lifestyle modification program (aimed at delivering >7% weight loss and 150 minutes of physical activity per week) is superior to drug treatment with metformin and placebo in diabetes prevention. Lifestyle intervention reduced the risk of type 2 diabetes by 58%. Adapted from Diabetes Prevention Study. N Engl J Med 2002; 346: 393–403.

Figure 4.7 A structured diabetes education class for South Asians with type 2 diabetes.

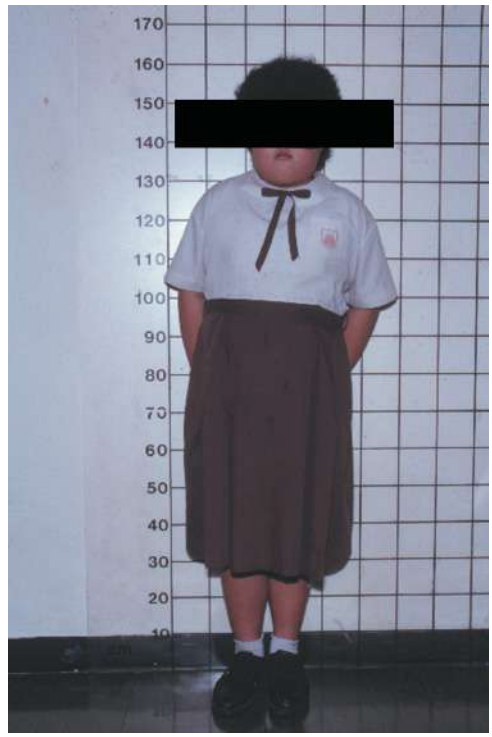

Figure 4.9 An 11-year-old girl from Hong Kong with type 2 diabetes. Note the marked truncal obesity.

Despite the rising incidence, costs and morbidity associated with diabetes, there is no clear policy in many countries for routine screening. A new primary care initiative in the UK recommends systematic assessment of cardiovascular risk among people aged 40–75 years, which includes testing for diabetes and impaired glucose tolerance (IGT) in high-risk groups. Adoption of HbA_{1c} for screening and diagnosis overcomes many of the practical limitations of fasting glucose and OGTT. Lifestyle modification is the most clinically effective and cost-effective intervention to prevent type 2 diabetes (Figure 4.8).

Traditionally, type 2 diabetes has been a disease of the middle aged and elderly, but the disease is now becoming a problem among adolescents and even children (Figure 4.9). A sedentary lifestyle and obesity are the main contributory factors, though many have a positive family history of type 2 diabetes. In some parts of the USA, type 2 diabetes now accounts for one-third of new cases of diabetes in adolescence.

KEY WEBSITES

- NHS Diabetes website: www.diabetes.nhs.uk/work-areas/information/national-diabetes-public-health-info-group
- Diabetes National Service Framework: www.dh.gov.uk/en/Healthcare/NationalServiceFrameworks/Diabetes/index.htm
- Diabetes information homepage of the US Centers for Disease Control and Prevention: www.cdc.gov/Diabetes/

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Chapter 5

Normal physiology of insulin secretion and action

KEY POINTS

- Islets of Langerhans in the endocrine pancreas contain β (insulin-producing) and α (glucagon-producing) cells that regulate glucose homeostasis.
- Pancreatic β cells may change in size, number and function during normal ageing and development. Insulin biosynthesis and secretion involves a number of steps; insulin exists in the circulation as a monomer of 6000 Da molecular weight.
- Insulin secretion is biphasic: an acute first phase that lasts a few minutes followed by a sustained second phase. Glucose is the main stimulator of insulin secretion, entering β cells via the GLUT-2 transporter.
- Sulphonylureas stimulate insulin secretion by binding to a component of the potassium-ATP (KATP) channel, resulting in KATP channel closure.
- The incretin effect (meal-stimulated augmentation of insulin secretion) is diminished in type 2 diabetes, mainly because of reduced GLP-1 secretion.
- Insulin receptor signalling in key tissues (skeletal muscle, fat and liver) is highly complex and activates a number of second messenger steps which result in the various biological effects of insulin on glucose, lipid and protein metabolism.
- Incretinmimetics (GLP-1 agonists and DPP-4 inhibitors) reverse the abnormalities in insulin and glucagon secretion, and may have longer term trophic effects on β cell number, structure and function.

Islet structure and function

Insulin is synthesised in and secreted from the β cells within the islets of Langerhans in the pancreas. The normal pancreas has about 1 million islets, which constitute about 2–3% of the gland's mass. All of the islet cell types are derived embryologically from endodermal outgrowths of the fetal gut. The islets can be identified easily with various histological stains, such as haematoxylin and eosin (Figure 5.1), with which the cells react less intensely than does the surrounding exocrine tissue. The islets vary in size from a few dozen to several thousands of cells and are scattered irregularly throughout the exocrine pancreas.

The main cell types of the pancreatic islets are β cells that produce insulin, α cells that secrete glucagon, δ cells that produce somatostatin and PP cells that produce pancreatic polypeptide. The different cell types can be identified by immunostaining techniques, *in situ* hybridization for their hormone products (using nucleotide probes complementary to the target mRNA) and the electron microscope appearance of their secretory granules. The β cells are the most numerous cell type and are located mainly in the core of the islet, while α and δ cells are located in the periphery (Figure 5.2).

Islet cells interact with each other through direct contact and through their products (e.g. glucagon stimulates insulin secretion and somatostatin inhibits insulin and glucagon

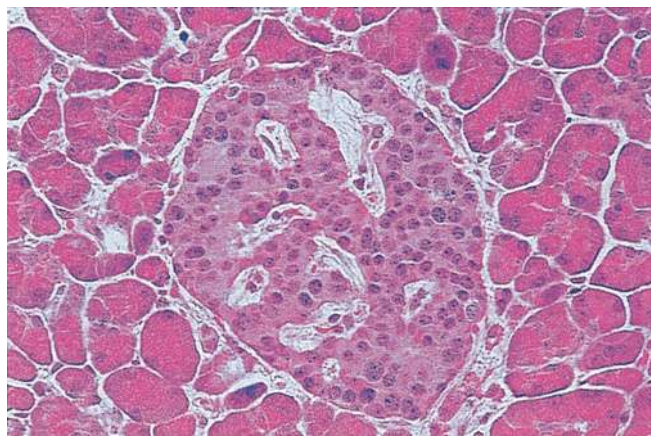

Figure 5.1 A section of normal pancreas stained with haematoxylin and eosin. As observed by Paul Langerhans, the islet in the centre is identified easily by its distinct morphology and lighter staining than that of the surrounding exocrine tissue (original magnification ×350).

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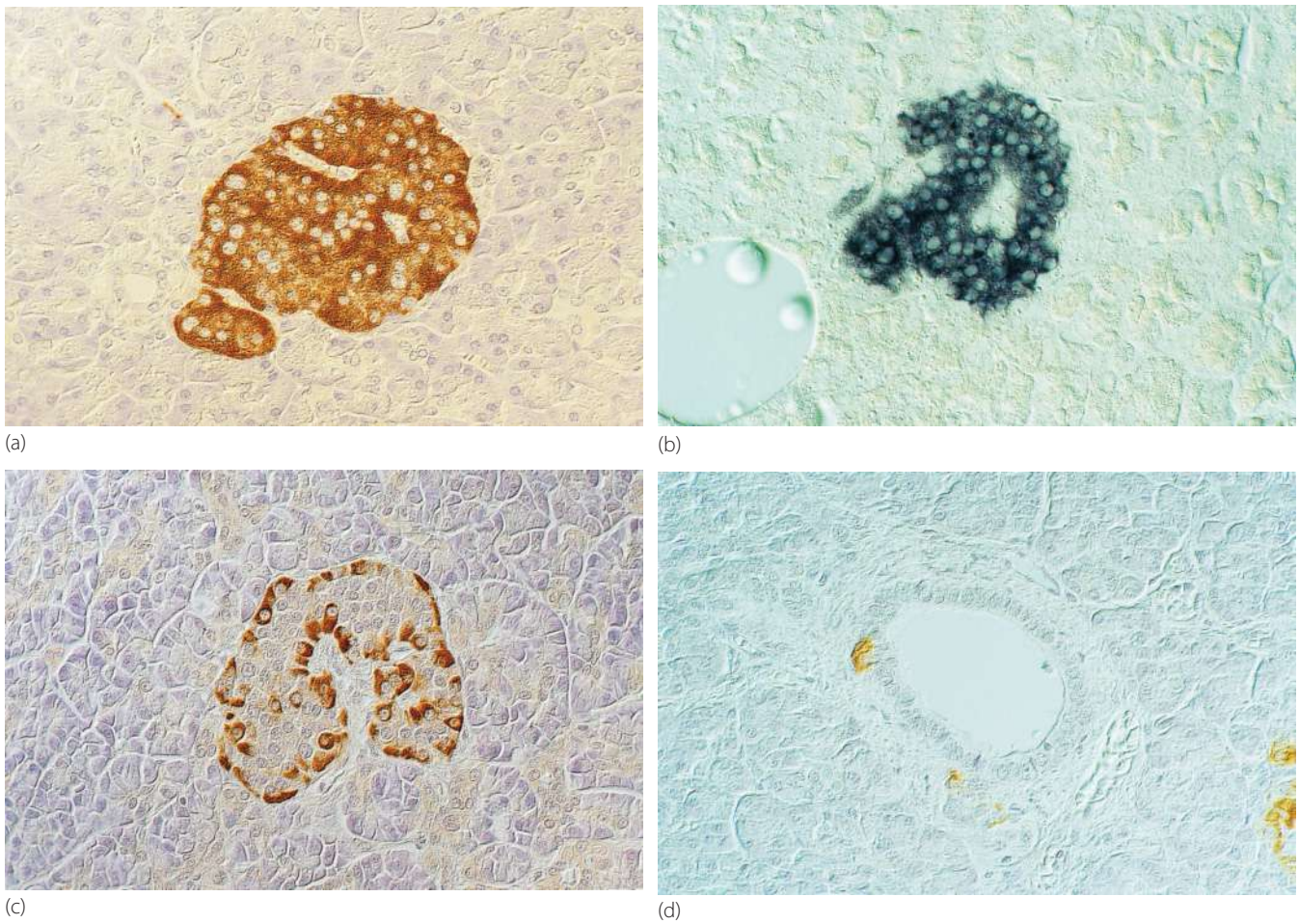


Figure 5.2 The localization of pancreatic hormones in human islets. (a) Insulin immunostained in the majority of cells that form the core of the islet (peroxidase–antiperoxidase immunostain with haematoxylin counterstain). (b) Insulin mRNA localized by *in situ* hybridization with a digoxigenin-labelled sequence of rat insulin cRNA (which cross-reacts fully with human insulin mRNA). (c) Peripherally located α cells immunostained with antibodies to pancreatic glucagon using the same method as for (a). (d) Weakly immunoreactive PP cells in the epithelium of a duct in the ventral portion of the pancreatic head. Magnifications approximately ×150.

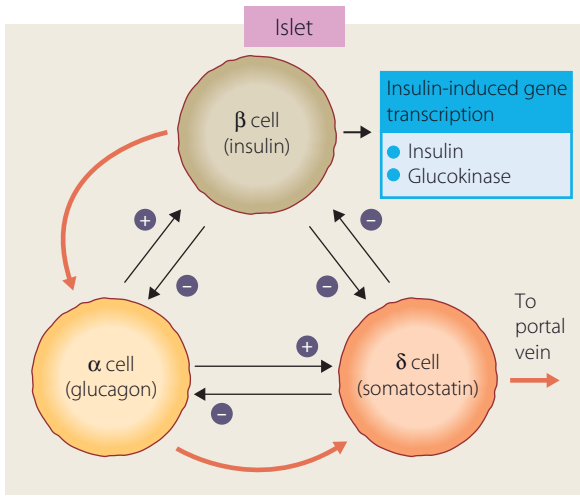


Figure 5.3 Potential interactions between the secretory products of the major islet cell types. Black arrows indicate paracrine stimulation or inhibition. The direction of blood flow within the islet is indicated by the red arrows.

secretion) (Figure 5.3). The blood flow within the islets is organised centrifugally so that the different cell types are supplied in the sequence β → α → δ. Insulin also has an 'autocrine' (self-regulating) effect that alters the transcription of insulin and glucokinase genes in the β cell.

The pancreatic islets are densely innervated with autonomic and peptidergic nerve fibres (Figure 5.4). Parasympathetic innervation from the vagus stimulates insulin release, while adrenergic sympathetic nerves inhibit insulin and stimulate glucagon secretion. Other nerves that originate within the pancreas contain peptides such as vasoactive intestinal peptide (VIP), which stimulates the release of all islet hormones, and neuropeptide Y (NPY) which inhibits insulin secretion. The overall importance of these neuropetides in controlling islet cell secretion remains unclear.

Pancreatic β cells may change in size, number and function during normal ageing and development (Figure 5.5). β cell mass is determined by the net effect of four independent

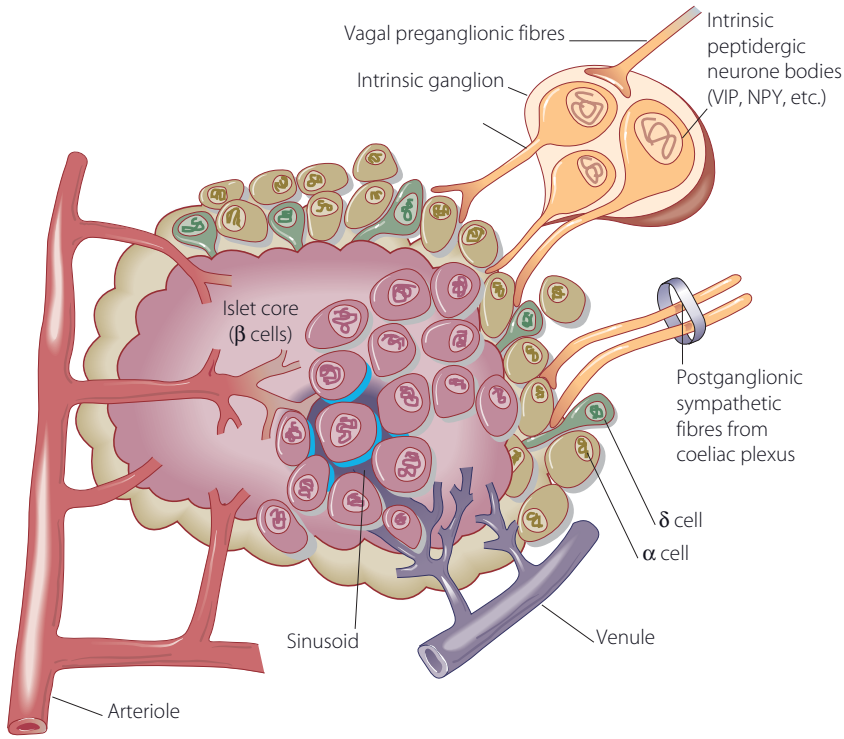


Figure 5.4 Structure of a pancreatic islet, showing the anatomical relationships between the four major endocrine cell types. NPY, neuropeptide Y; VIP, vasoactive intestinal polypeptide.

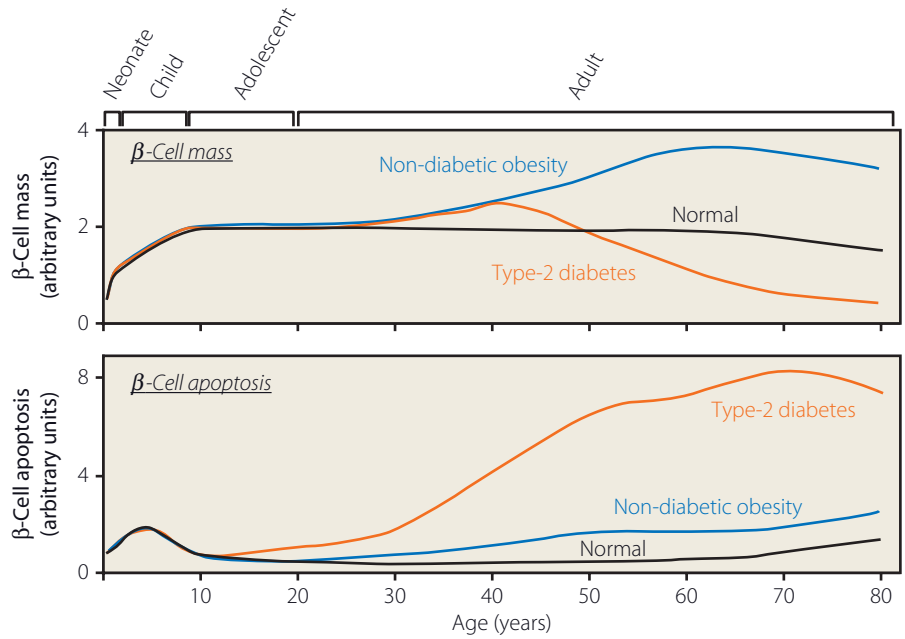
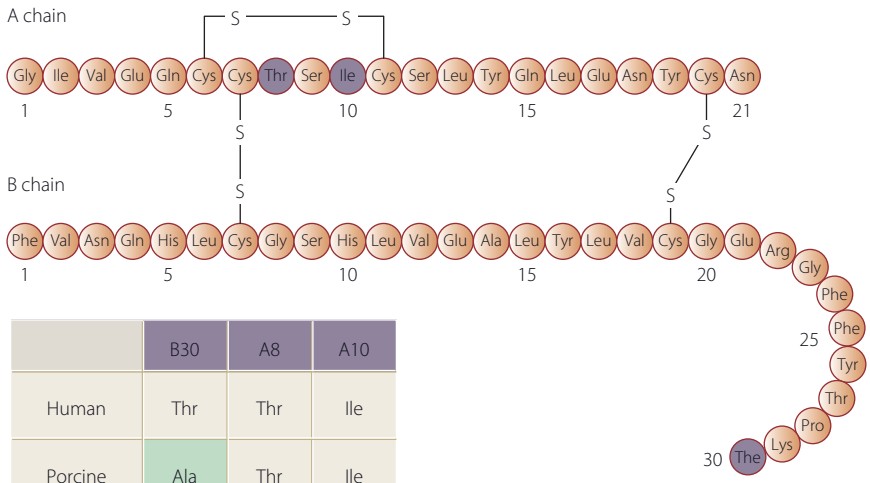


Figure 5.5 A hypothetical model for postnatal pancreatic β cell growth in humans. Adapted from Rhodes et al. Science 2005; 307: 380–384.



	B30	A8	A10
Human	Thr	Thr	Ile
Porcine	Ala	Thr	Ile
Bovine	Ala	Ala	Val

Figure 5.6 The primary structure (amino acid sequence) of human insulin. The highlighted residues are those that differ in porcine and bovine insulins, as shown in the inset.

CASE HISTORY

A 32-year-old woman develops impaired glucose tolerance at 34 weeks into her second pregnancy. She is managed with dietary modification, and the baby is delivered at 37 weeks. Her glucose tolerance returns to normal 6 weeks later. Her BMI is 31 kg/m^2, and her mother developed type 2 diabetes at the age of 55 years.

Comment: This woman had normal glucose tolerance prior to pregnancy, but the metabolic and endocrine changes associated with pregnancy resulted in transient impairment of glucose tolerance. This occurred because pancreatic insulin secretion was insufficient to compensate for increased insulin resistance as a result of pregnancy (on a background of obesity and a genetic predisposition). Genetic, dietary and endocrine factors affect β cell function. A history of gestational diabetes is a major risk factor for later development of type 2 diabetes in women.

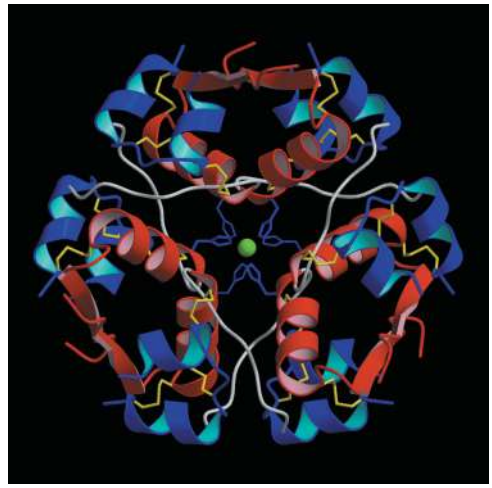


Figure 5.7 The double zinc insulin hexamer composed of three insulin dimers in a threefold symmetrical pattern.

mechanisms: (i) β cell replication (i.e. division of existing β cells), (ii) β cell size, (iii) β cell neogenesis (i.e. emergence of new β cells from pancreatic ductal epithelial cells) and (iv) β cell apoptosis. The contribution made by each of these processes is variable and may change at different stages of life.

Insulin synthesis and polypeptide structure

The insulin molecule consists of two polypeptide chains, linked by disulphide bridges; the A-chain contains 21 amino acids and the B-chain 30 amino acids. Human insulin differs from pig insulin (an animal insulin which was used extensively for diabetes treatment prior to the 1990s) at only one amino acid position (B30) (Figure 5.6).

In dilute solution and in the circulation, insulin exists as a monomer of 6000 Da molecular weight. The tertiary (three-dimensional) structure of monomeric insulin consists of a hydrophobic core buried beneath a surface that is hydrophilic, except for two non-polar regions involved in the aggregation of the monomers into dimers and hexamers. In concentrated solution (such as in the insulin vial supplied by the pharmaceutical company for injection) and in crystals (such as in the insulin secretory granule), six monomers self-associate with two zinc ions to form a hexamer (Figure 5.7). This is of therapeutic importance because the slow absorption of native insulin from the subcutaneous tissue partly results

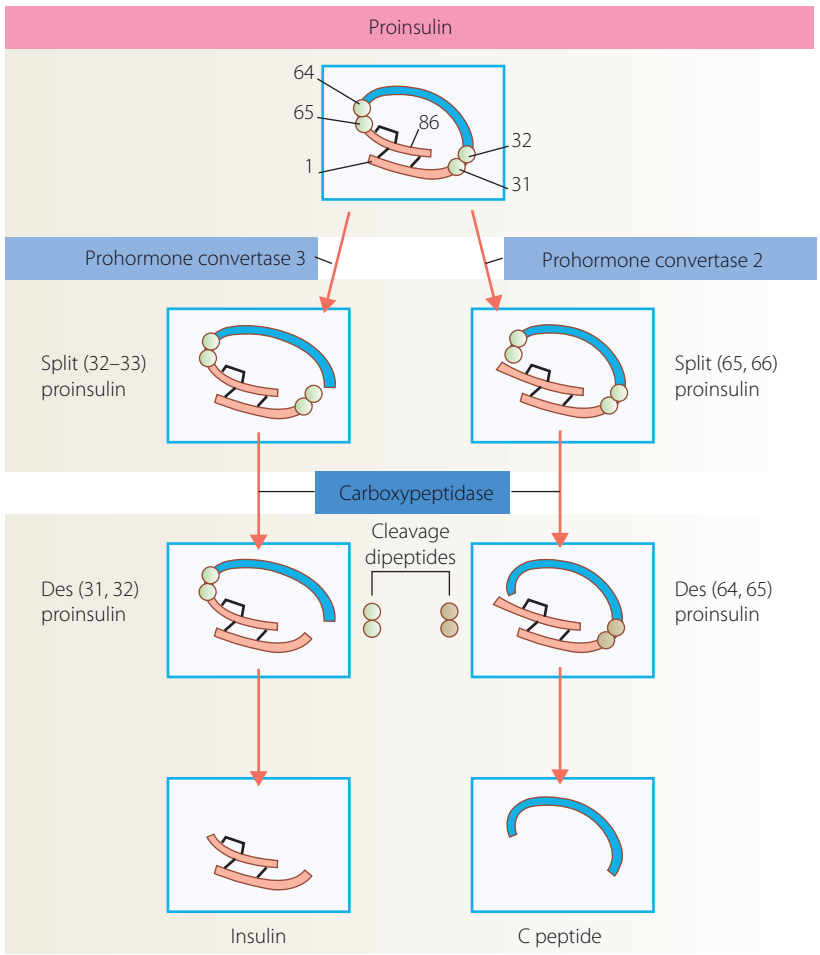


Figure 5.8 Insulin biosynthesis and processing. Proinsulin is cleaved on the C-terminal side of two dipeptides. The cleavage dipeptides are liberated, so yielding the 'split' proinsulin products and ultimately insulin and C-peptide.

LANDMARK CLINICAL TRIALS

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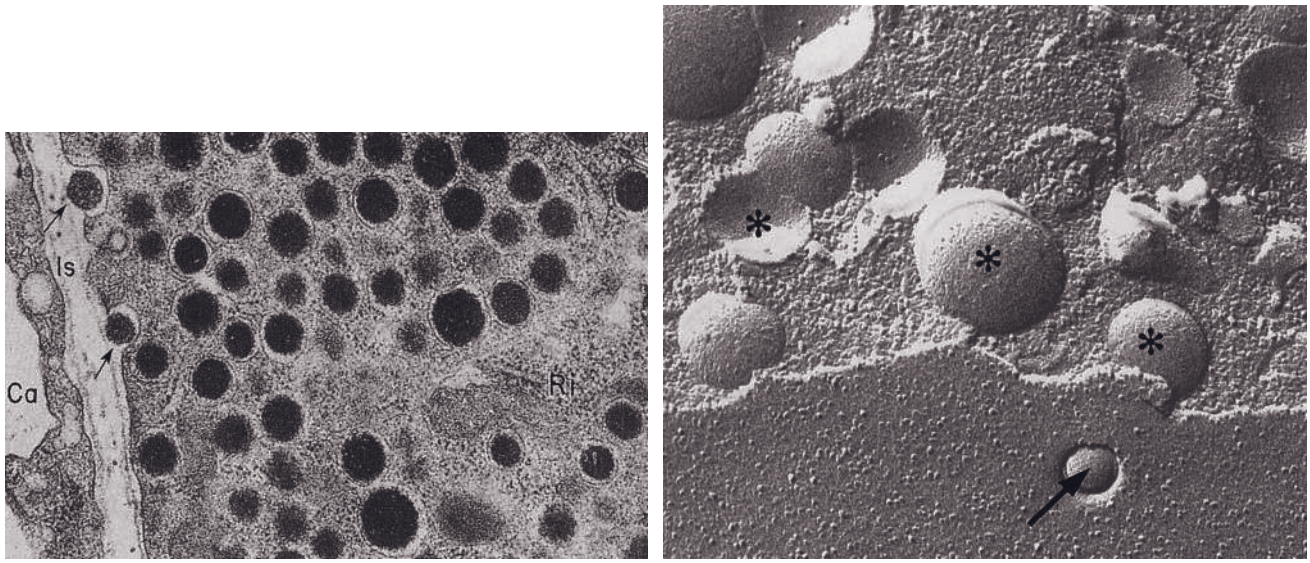
from the time taken for the hexameric insulin to dissociate into the smaller, more easily absorbed monomeric form.

Insulin is synthesised in the β cells from a single amino acid chain precursor molecule called proinsulin (Figure 5.8). Synthesis begins with the formation of an even larger precursor, preproinsulin, which is cleaved by protease activity to proinsulin. The gene for preproinsulin (and therefore the 'gene for insulin') is located on chromosome 11. Proinsulin



(a) (b)

Figure 5.9 (a) Electron micrograph of insulin secretory granules in a pancreatic β cell and their secretion by exocytosis. Arrows show exocytosis occurring. Ca, capillary lumen; Is, interstitial space. (b) Freeze-fracture views of β cells that reveal the secretory granules in the cytoplasm (*asterisks*) and the granule content released by exocytosis at the cell membrane (*arrows*). Magnification: ×52,000. From Orci. Diabetologia 1974; 10: 163–187.

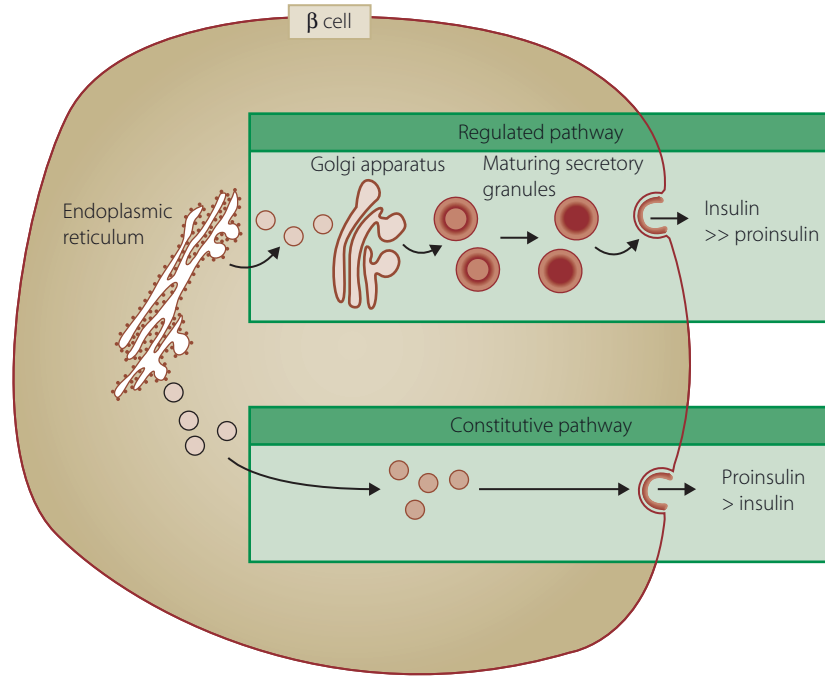


Figure 5.10 The regulated (normal) and constitutive (active in type 2 diabetes) pathways of insulin processing.

is packaged into vesicles in the Golgi apparatus of the β cell; in the maturing secretory granules that bud off it, proinsulin is converted by enzymes into insulin and connecting peptide (C-peptide).

Insulin and C-peptide are released from the β cell when the granules are transported ('translocated') to the cell surface and fuse with the plasma membrane (exocytosis) (Figure 5.9). Microtubules, formed of polymerised tubulin, probably provide the mechanical framework for granule transport, and microfilaments of actin, interacting with myosin and other motor proteins such as kinesin, may provide the motive force that propels the granules along the tubules. Although the actin cytoskeleton is a key mediator of biphasic insulin release, cyclic GTPases are involved in

F-actin reorganization in the islet β cell and play a crucial role in stimulus-secretion coupling.

This 'regulated pathway', with almost complete cleavage of proinsulin to insulin, normally carries about 95% of the β cell insulin production (Figure 5.10). In certain conditions, such as insulinoma and type 2 diabetes, an alternative 'constitutive' pathway operates, in which large amounts of unprocessed proinsulin and intermediate insulin precursors ('split proinsulins') are released directly from vesicles that originate in the endoplasmic reticulum.

Insulin secretion

Glucose is the main stimulator of insulin release from the β cell, which occurs in a characteristic biphasic pattern – an acute 'first phase' that lasts only a few minutes, followed by a sustained 'second phase' (Figure 5.11). The first phase of release involves the plasma membrane fusion of a small, readily releasable pool of granules; these granules discharge their contents in response to both nutrient and non-nutrient secretagogues. In contrast, second-phase insulin secretion is evoked exclusively by nutrients. The shape of the glucose–insulin dose–response curve is determined primarily by the activity of glucokinase, which governs the rate-limiting step for glucose metabolism in the β cell. Glucose levels below 5 mmol/L (90 mg/dL) do not affect insulin release; half-maximal stimulation occurs at about 8 mmol/L (144 mg/dL).

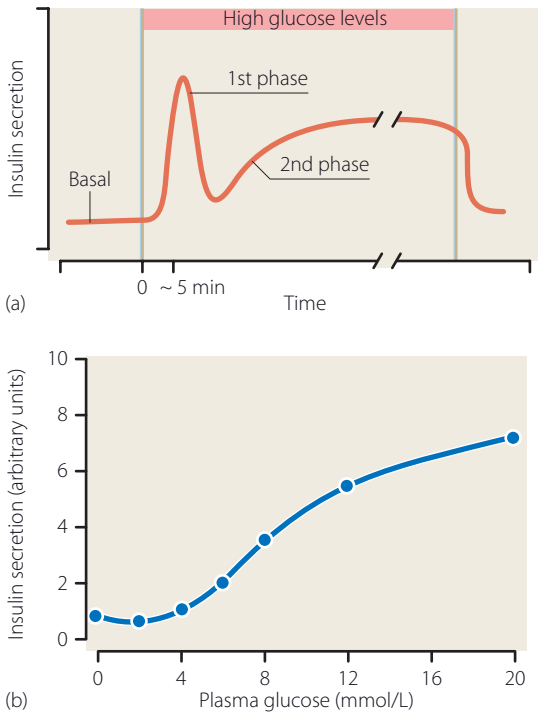


Figure 5.11 (a) The biphasic glucose-stimulated release of insulin from pancreatic islets. (b) The glucose–insulin dose–response curve for islets of Langerhans.

Glucose must be metabolised within the β cell to stimulate insulin secretion (Figure 5.12). It enters the β cell via the GLUT-2 transporter and is then phosphorylated by glucokinase, which acts as the 'glucose sensor' that couples insulin secretion to the prevailing glucose level. Glycolysis and mitochondrial metabolism produce adenosine triphosphate (ATP), which closes ATP-sensitive potassium (KATP) channels. This in turn causes depolarization of the β cell plasma membrane, which leads to an influx of extracellular calcium through voltage-gated channels in the membrane. The increase in cytosolic calcium triggers granule translocation and exocytosis. Sulphonylureas stimulate insulin secretion by binding to a component of the KATP channel (the sulphonylurea receptor, SUR-1) and closing it. The KATP channel is an octamer that consists of four K+-channel subunits (called Kir6.2) and four SUR-1 subunits.

The incretin effect

There is a significant difference between the insulin secretory response to oral glucose compared with the response to IV glucose – a phenomenon known as the 'incretin effect' (Figure 5.13). The incretin effect is mediated by gut-derived hormones, released in response to the ingestion of food, which augment glucose-stimulated insulin release. In particular, there are two incretin hormones: glucagon-like peptide-1 (GLP-1) and gastric inhibitory polypeptide (GIP). Both augment insulin secretion in a dose-dependent fashion. GLP-1 is secreted by L cells and GIP is secreted by K cells in the wall of the upper jejunum.

In patients with type 2 diabetes, GLP-1 secretion is diminished (Figure 5.14). However, in contrast to GIP, GLP-1 retains most of its insulinotropic activity. GIP secretion is maintained in type 2 diabetes, but its effect on the β cell is greatly reduced. GLP-1 also suppresses glucagon secretion from pancreatic α cells, and has effects on satiety and gastric emptying. There is also considerable interest in the trophic effects of GLP-1 on β cells.

Insulin receptor signalling

Insulin exerts its main biological effects by binding to a cell surface receptor, a glycoprotein that consists of two extracellular α subunits and two β subunits that span the cell membrane. The receptor has tyrosine kinase enzyme activity (residing in the β subunit), which is stimulated when insulin binds to the receptor. This enzyme phosphorylates tyrosine amino acid residues on various intracellular proteins, such as insulin receptor substrate (IRS)-1 and IRS-2, and the β subunit itself (Figure 5.15) (autophosphorylation). Tyrosine kinase activity is essential for insulin action.

Postreceptor signalling involves phosphorylation of a number of intracellular proteins that associate with the β subunit of the insulin receptor, including IRS-1 and IRS-2

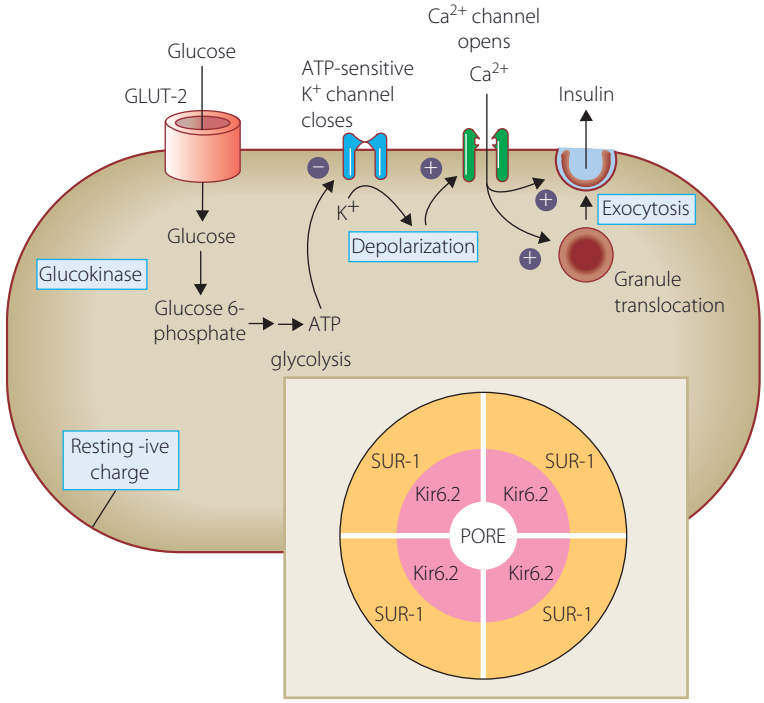


Figure 5.12 The mechanism of glucose-stimulated insulin secretion from the β cell. The structure of the KATP channel is shown in the inset.

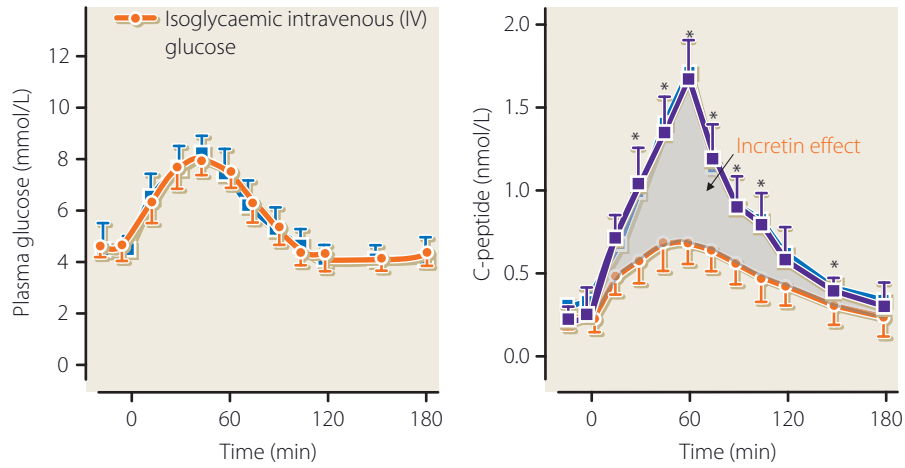


Figure 5.13 The classic experiment illustrating the incretin effect in normal subjects who were studied on two separate occasions. On one occasion, they were given an oral glucose load and on the second occasion an IV glucose bolus was administered in order to achieve identical venous plasma glucose concentration-time profiles on the two study days (left panel). The insulin secretory response (shown by C-peptide) was significantly greater after oral compared with IV glucose (right panel). Adapted from Nauck et al. J Clin Endocrinol Metab 1986; 63: 492–498.

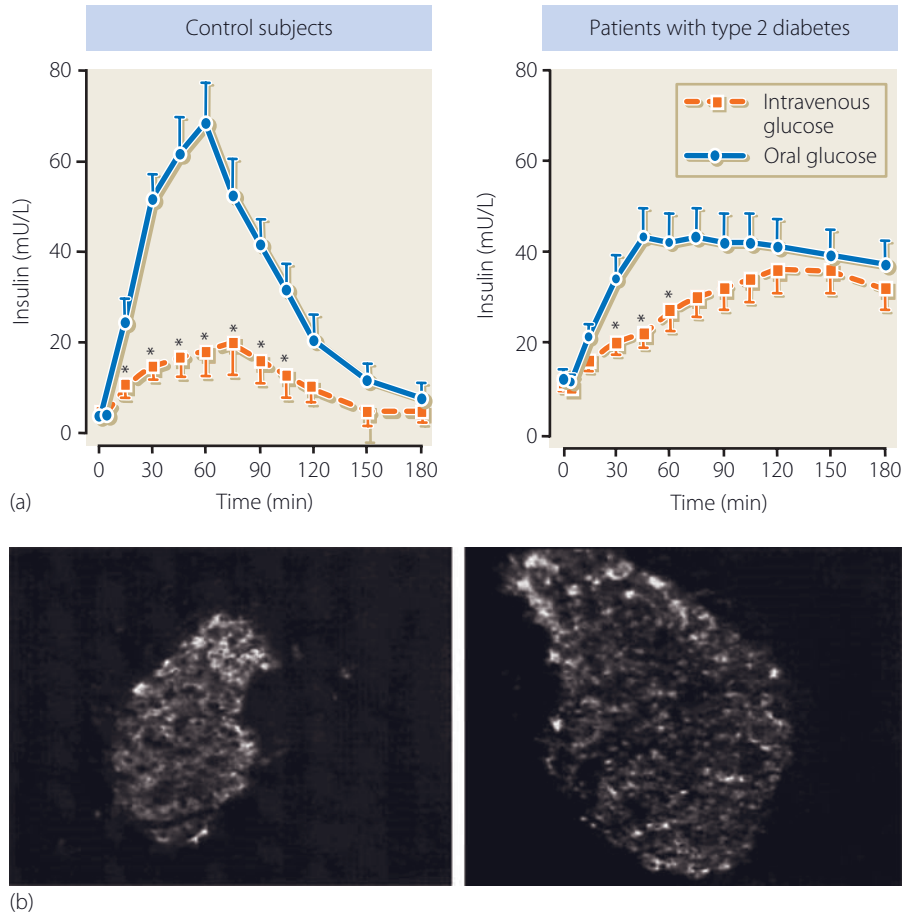


Figure 5.14 (a) The incretin effect is greatly diminished in patients with type 2 diabetes compared with normal subjects. This contributes to the impaired insulin secretory response observed in type 2 diabetes. (b) GLP-1 has a trophic effect on pancreatic islets . Shown here is an islet from a db/db mouse before (*left*) and after (*right*) 2 weeks treatment with synthetic GLP-1. Adapted from Stoffers et al. Diabetes 2000; 49: 741–748.

(Figure 5.16). Phosphorylated tyrosine residues on these proteins act as docking sites for the non-covalent binding of proteins with specific 'SH2' domains, such as phospatidylinositol 3-kinase (PI 3-kinase), Grb2 and phosphotyrosine phosphatase (SHP2). Binding of Grb2 to IRS-1 initiates a cascade that eventually activates nuclear transcription factors via activation of the protein Ras and mitogen-activated protein (MAP) kinase. IRS–PI 3-kinase binding generates phospholipids that modulate other specific kinases and regulate responses such as glucose transport, and protein and glycogen synthesis.

GLUT transporters

Glucose is transported into cells by a family of specialised transporter proteins called glucose transporters (GLUTs) (Figure 5.17). The process of glucose uptake is energy independent. The best characterised GLUTs are:

- GLUT-1: ubiquitously expressed and probably mediates basal, non-insulin mediated glucose uptake
- GLUT-2: present in the islet β cell, and also in the liver, intestine and kidney. Together with glucokinase, it forms the β cell's glucose sensor and, because it has a high Km, allows glucose to enter the β cell at a rate proportional to the extracellular glucose level
- GLUT-3: together with GLUT-1, involved in non-insulin mediated uptake of glucose into the brain
- GLUT-4: responsible for insulin-stimulated glucose uptake in muscle and adipose tissue, and thus the classic hypoglycaemic action of insulin
- GLUT-8: important in blastocyst development
- GLUT-9 and 10: unclear functional significance.

Most of the other GLUTs are present at the cell surface, but in the basal state GLUT-4 is sequestered within vesicles in the cytoplasm. Insulin causes the vesicles to be translocated to the cell surface, where they fuse with the membrane and the inserted GLUT-4 unit functions as a pore that allows glucose entry into the cell. The process is reversible: when insulin levels fall, the plasma membrane GLUT-4 is removed by endocytosis and recycled back to intracellular vesicles for storage (Figure 5.18).

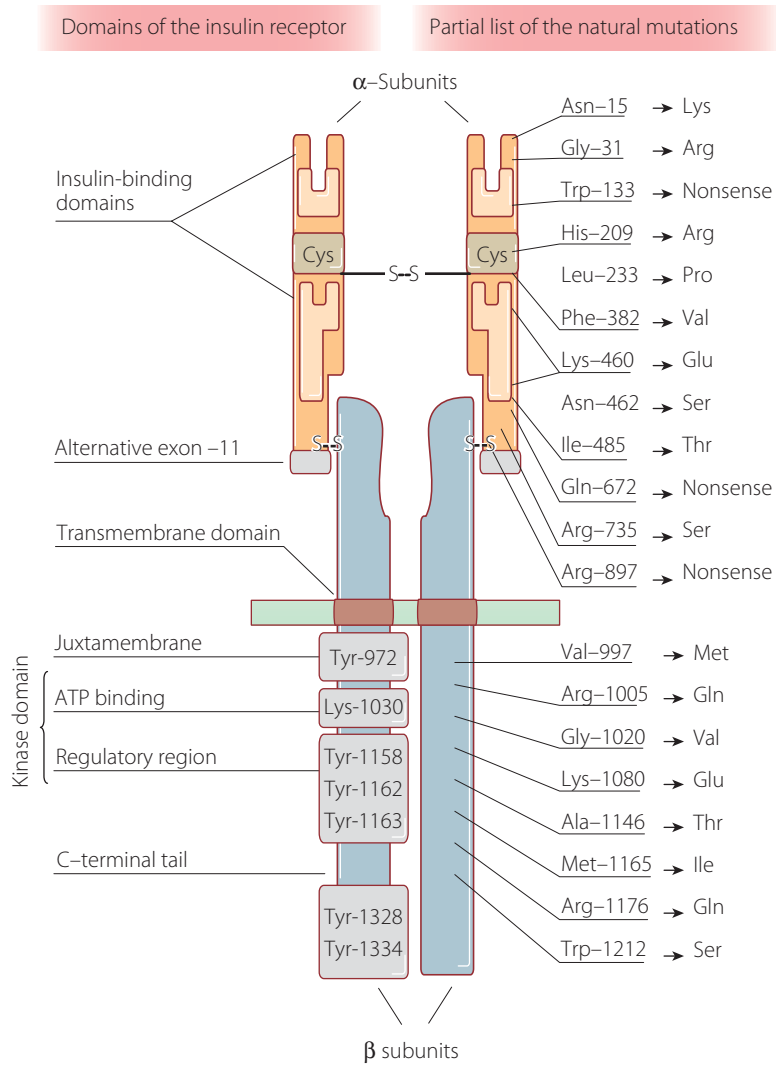


Figure 5.15 The insulin receptor and its structural domains. Many mutations have been discovered in the insulin receptor, some of which interfere with insulin's action and can cause insulin resistance; examples are shown in the right column.

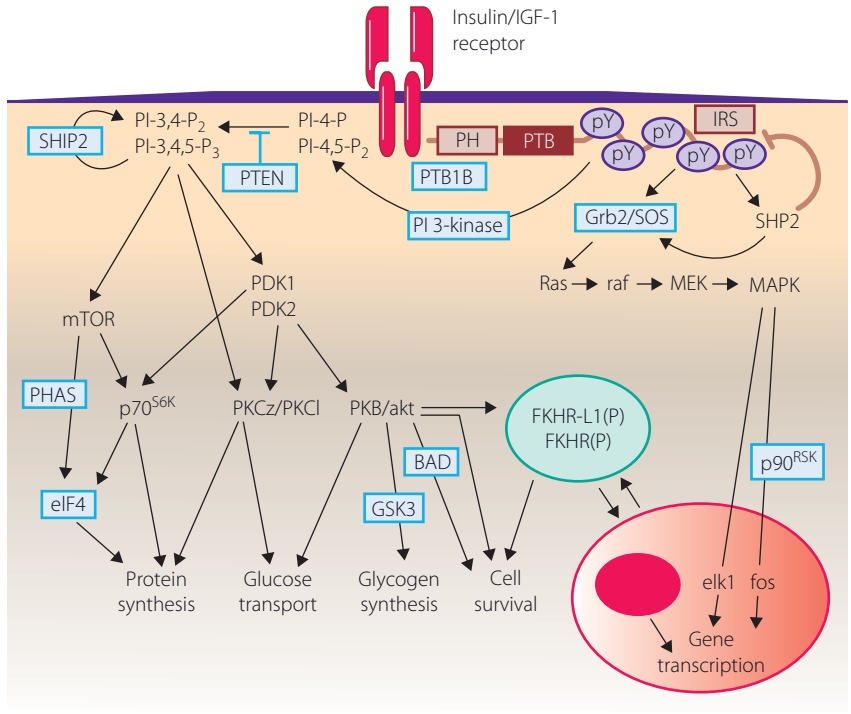
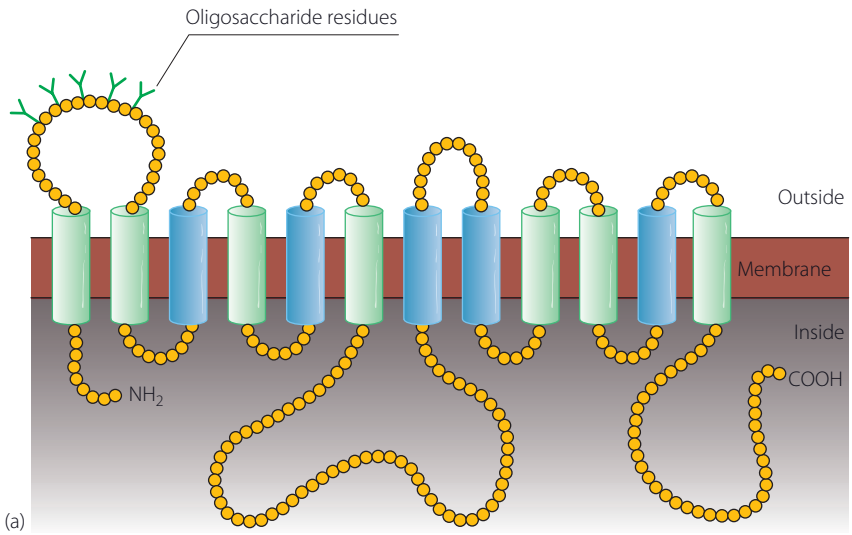


Figure 5.16 The insulin signalling cascade. Insulin binding and autophosphorylation of the insulin (and IGF-1) receptor results in binding of the IRS-1 protein to the β subunit of the insulin receptor via the IRS phosphotyrosine-binding domain (PTB). There is then phosphorylation of a number of tyrosine residues (pY) at the C-terminus of the IRS proteins. This leads to recruitment and binding of downstream signalling proteins, such as PI-3 kinase, Grb2 and SHP2.



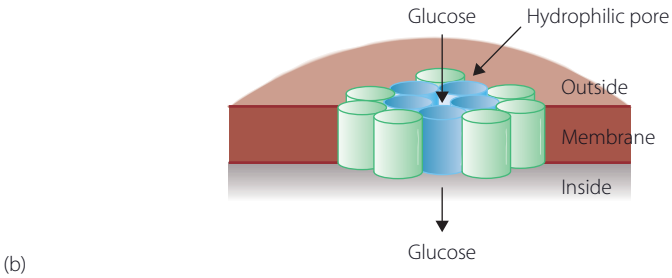


Figure 5.17 (a) The structure of a typical glucose transporter (GLUT). (b) The intramembrane domains pack together to form a central hydrophilic channel through which glucose passes.

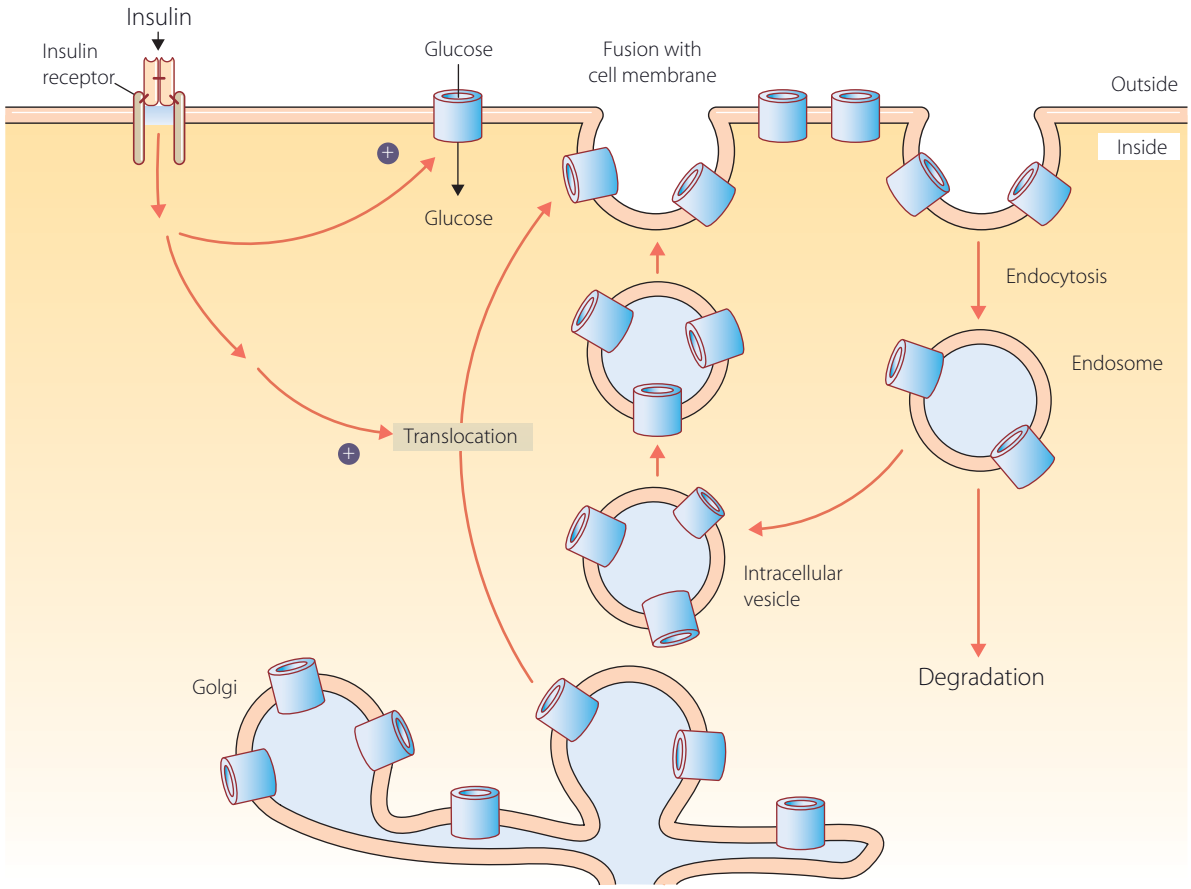


Figure 5.18 Insulin regulation of glucose transport into cells.

In normal subjects, blood glucose concentrations are maintained within relatively narrow limits at around 5 mmol/L (90 mg/dL) (Figure 5.19). This is achieved by a balance between glucose entry into the circulation from the liver and from intestinal absorption, and glucose uptake into the peripheral tissues such as muscle and adipose tissue. Insulin is secreted at a low, basal level in the non-fed state, with increased, stimulated levels at mealtimes.

At rest in the fasting state, the brain consumes about 80% of the glucose utilised by the whole body, but brain glucose uptake is not regulated by insulin. Glucose is the main fuel for the brain, so that brain function critically depends on the maintenance of normal blood glucose levels.

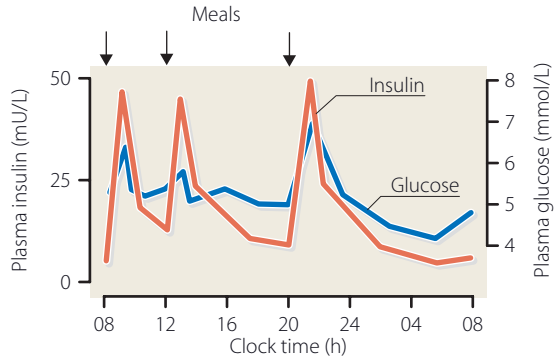


Figure 5.19 Profiles of plasma glucose and insulin concentrations in individuals without diabetes.

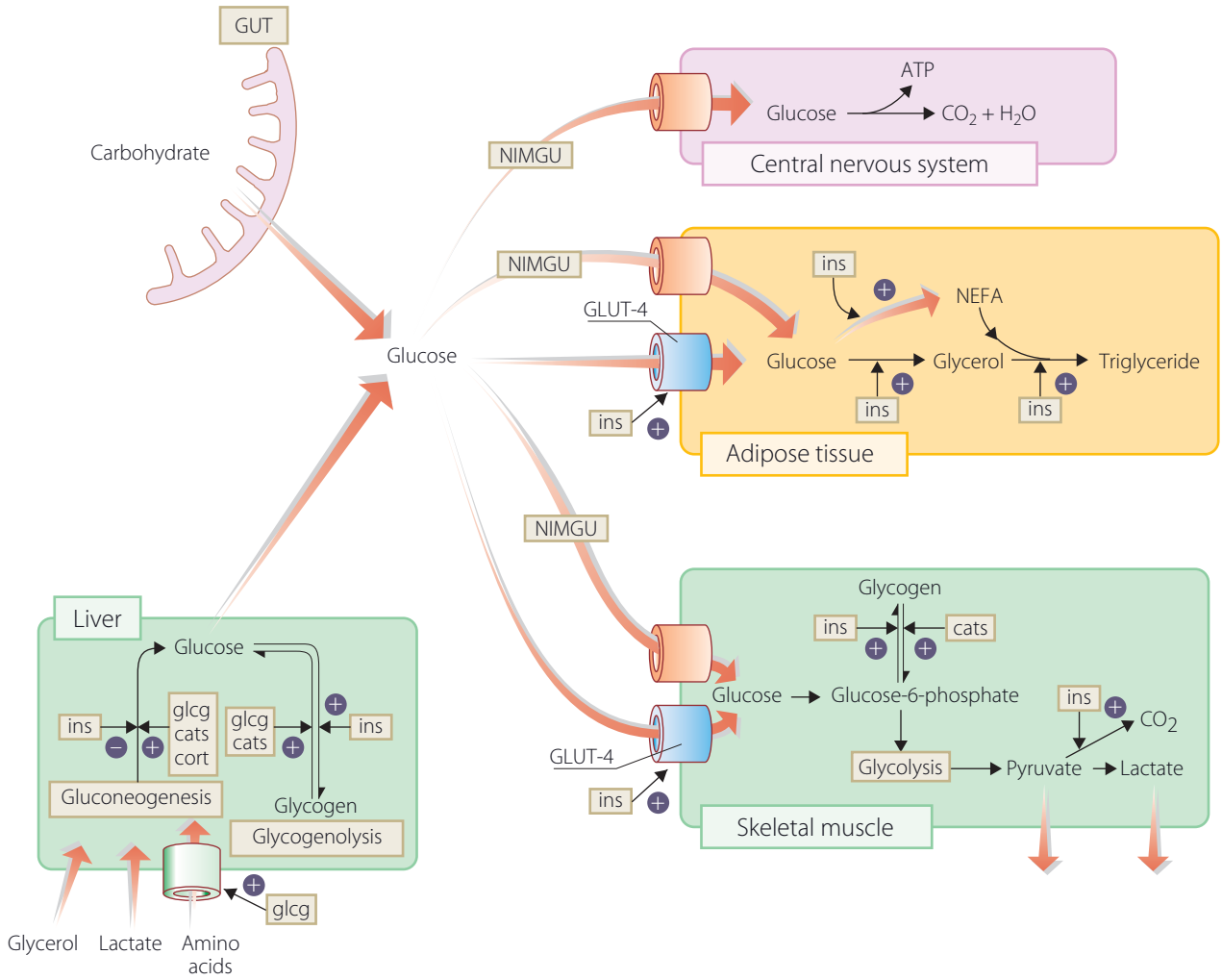


Figure 5.20 Overview of carbohydrate metabolism. cats, catecholamines; cort, cortisol; glcg, glucagon; ins, insulin; NIMGU, non-insulin mediated glucose uptake.

Insulin lowers glucose levels partly by suppressing glucose output from the liver, both by inhibiting glycogen breakdown (glycogenolysis) and by inhibiting gluconeogenesis (i.e. the formation of 'new' glucose from sources such as glycerol, lactate and amino acids, like alanine). Relatively low concentrations of insulin are needed to suppress hepatic glucose output in this way, such as occur with basal insulin secretion between meals and at night. With much higher insulin levels after meals, GLUT-4 mediated glucose uptake into the periphery is stimulated.

KEY WEBSITES

- www.vivo.colostate.edu/hbooks/pathphys/endocrine/pancreas/index.html
- www.accessmedicine.com/content.aspx?aid=2090245

FURTHER READING

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Chapter 6

Epidemiology and aetiology of type 1 diabetes

KEY POINTS

- Type 1 diabetes is one of a number of autoimmune endocrine diseases with a genetic and familial basis, although the majority of cases occur sporadically.
- Incidence rates vary from <5 to >40 per 100,000, generally being highest in northern latitudes.
- These rates are increasing more rapidly than can be explained by genetic factors alone.
- Environmental factors such as viruses and diet are responsible for some of the increase.

The most common cause of type 1 diabetes (over 90% of cases) is T cell-mediated autoimmune destruction of the islet β cells leading to a failure of insulin production. The exact aetiology is complex and still imperfectly understood. However, it is probable that environmental factors trigger the onset of diabetes in individuals with an inherited predisposition. Unless insulin replacement is given, absolute insulin deficiency will result in hyperglycaemia and ketoacidosis, which is the biochemical hallmark of type 1 diabetes.

There is a striking variation in the incidence of type 1 diabetes between and within populations, with high frequencies in Finland (49 cases/100,000/year) and Sweden (32/100,000/year), and low frequencies in areas of China and Venezuela (both 0.1/100,000/year) and the Ukraine (1/100,000/year). Marked differences also occur within the same country: the incidence in Sardinia (37/100,000/year) is 3–5 times that of mainland Italy. These differences in frequency suggest that environmental and/or ethnic–genetic factors may influence the onset of the disease.

The geographical variation within Europe has been highlighted by the EURODIAB epidemiology study. This survey found a 10-fold difference in the incidence of type 1 diabetes between Finland and Macedonia. The incidence generally falls along a north–south gradient, but Sardinia is a notable 'hot spot' with a much higher frequency than the surrounding Mediterranean areas. Interestingly, there are also different incidences in genetically similar countries such as Finland and Estonia, or Norway and Iceland. Moreover, the most recent report suggests an overall annual rate of increase

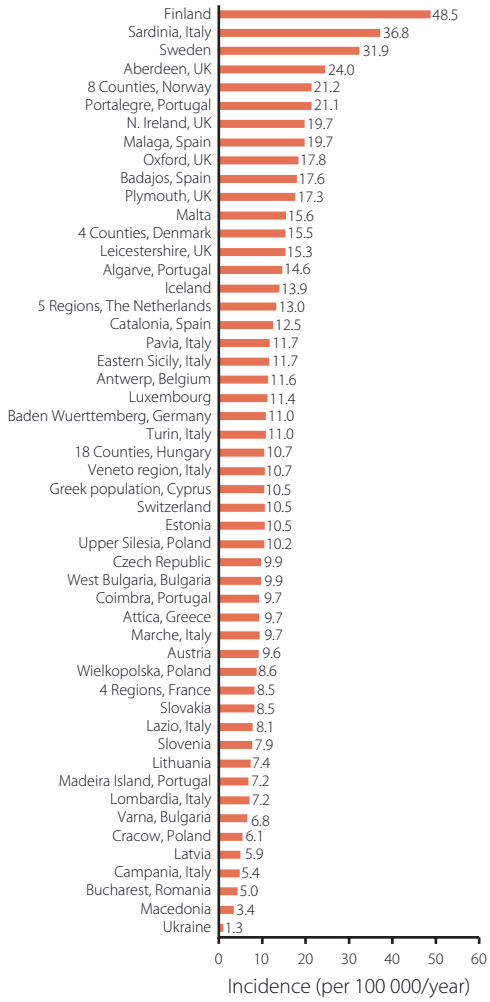

Figure 6.1 Age-standardised incidence of type 1 diabetes in children 14 years of age (per 100,000 per year). From Pickup & Williams. *Textbook of Diabetes*, 3rd edition. Blackwell Publishing Ltd, 2003.

Handbook of Diabetes, 4th edition. By © Rudy Bilous & Richard Donnelly. Published 2010 by Blackwell Publishing Ltd.

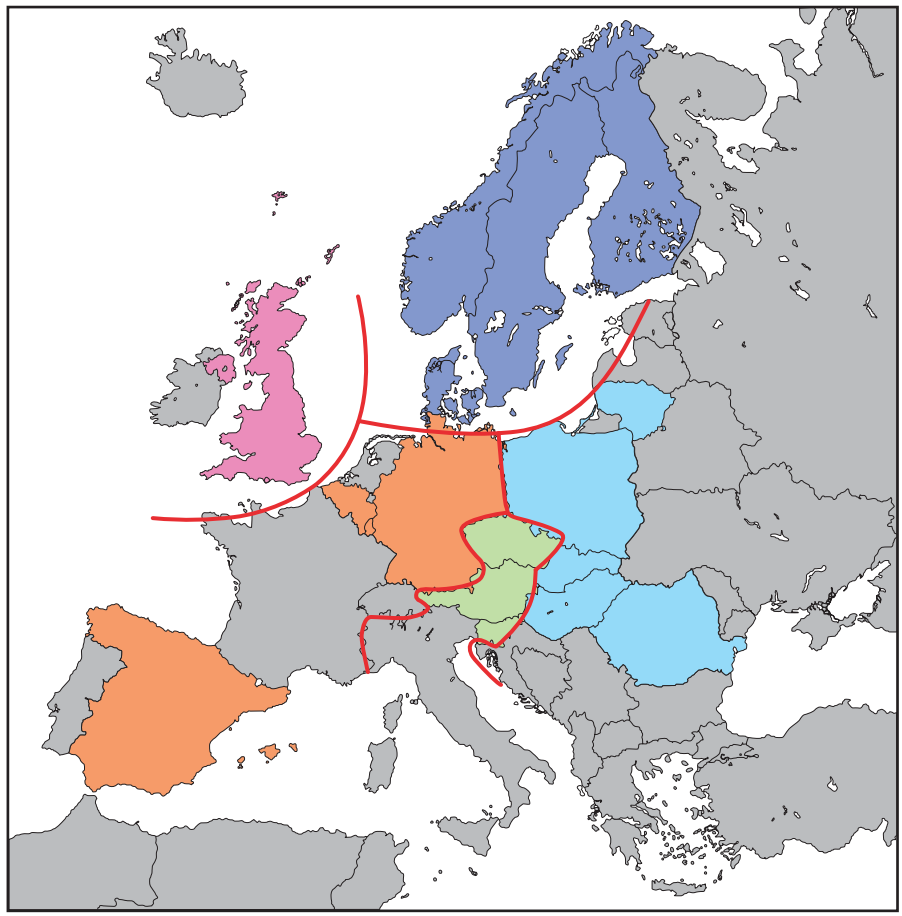

Figure 6.2 Incidence rates (1999–2003) of type 1 diabetes in 0–14 year olds in 17 European countries grouped into regions with roughly homogeneous rates. Purple 22.9–52.6/100,000; pink 22.4–29.8/100,000; orange 13–18.3/100,000; green 11.1–17.2/100,000; and blue 11.3–13.6/100,000. Reproduced from Patterson et al. Lancet 2009; 373: 2027–2033).

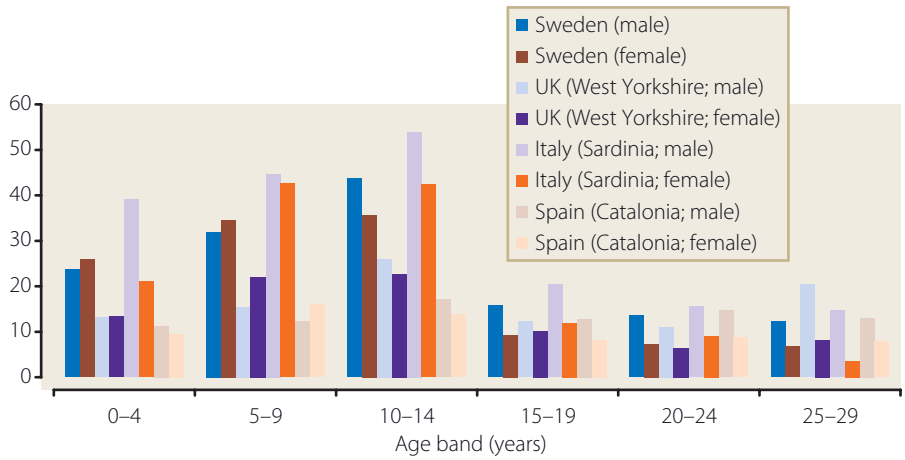

Figure 6.3 Incidence rates for type 1 diabetes in quintile age ranges 0–29 years in four countries in Europe in 1996–7. Note different rates in Catalonia and Sardinia despite a similar geographical latitude; and persistent male preponderance in all groups, especially aged 10–14 years. Data from *Diabetes Atlas*, 3rd edn.

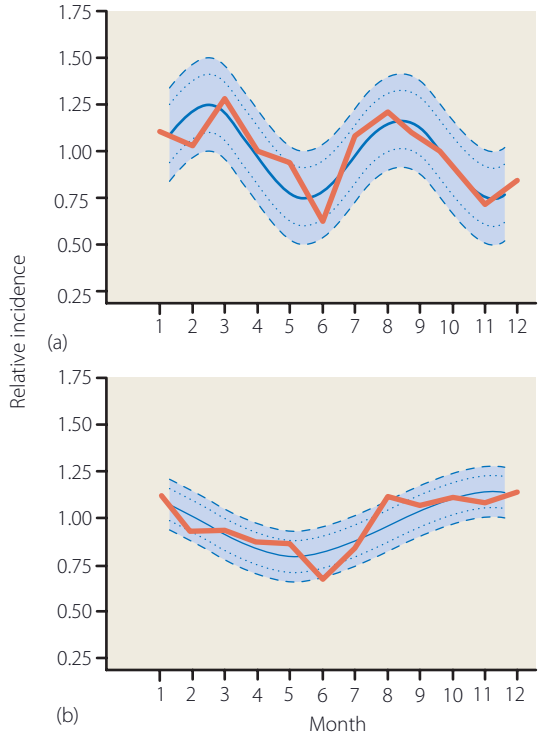

Figure 6.4 Seasonal variation of type 1 diabetes among Finnish children (a) 0–9 years of age, (b) 10–14 years of age during 1983–92. (The observed monthly variation in incidence is the solid line with dots.) The inner interval is the 95% confidence interval (CI) for the observed seasonal variation and the outer interval is the 95% CI for the estimated seasonal variation. Data from Padaiga et al. Diabetic Med 1999; 16: 1–8.

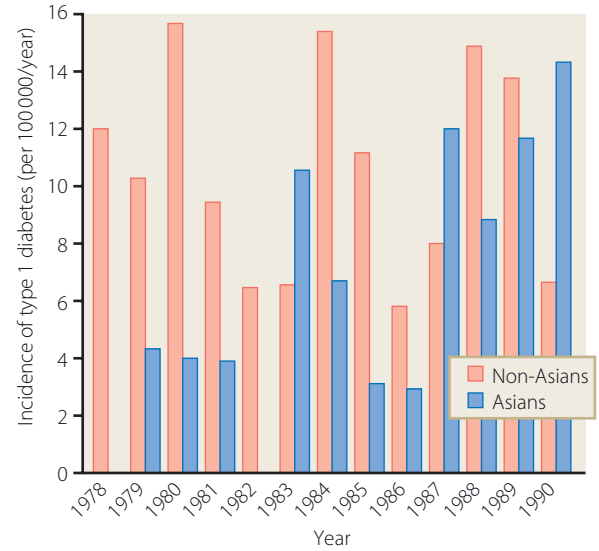

Figure 6.5 Evidence of environmental factors: incidence of type 1 diabetes in children from Asian families who moved to Bradford, UK, compared to non-Asian local UK children. Data from Bodansky et al. BMJ 1992; 304: 1020–1022.

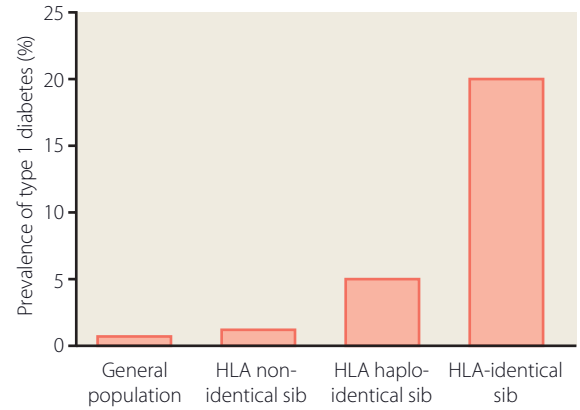

Figure 6.6 Familial clustering of type 1 diabetes: evidence for genetic factors in the aetiology. From Pickup & Williams. *Textbook of Diabetes*, 3rd edition. Blackwell Publishing Ltd, 2003.

in incidence in children aged below 15 years of 3.9% (range 0.6–9.3%). Prevalence is predicted to rise from 94,000 (2005) to 160,000 in 2020 in Europe. This suggests that environmental influences may predominate over genetic susceptibility in causing or triggering the disease.

Further evidence for environmental influences comes from studies that show a seasonal variation in the onset of type 1 diabetes in some populations, with the highest frequency in the colder autumn and winter months (Figure 6.4). This is often thought to reflect seasonal exposure to viruses, but food or chemicals might also be involved.

People who have migrated from an area of low to an area of high incidence for type 1 diabetes seem to adopt the same level of risk as the population to which they move. For example, children of Asian families (from the Indian subcontinent and Tanzania) who moved to the UK traditionally have a low frequency of type 1 diabetes but now have a rising incidence of the disease, which is approaching that of the indigenous population (Figure 6.5).

Familial clustering of type 1 diabetes provides evidence for complex genetic factors in its aetiology (Figure 6.6). In (European) siblings of children with type 1 diabetes, 5–6% have developed type 1 diabetes by the age of 15 years and

CASE HISTORY

A 4-year-old boy whose mother has had type 1 diabetes since age 13 years developed thirst, polyuria, hyperphagia and weight loss shortly after recovering from a head cold. His mother tested his capillary blood glucose with her own meter and found it to be 25.3 mmol/L. His birth weight was 4.1 kg and he was bottle fed with cow's milk from birth.

Comment: This case illustrates several cardinal features of type 1 diabetes. A positive family history, age of onset <5 years, symptoms beginning after a minor infection, and early exposure to cow's milk. Birth weight >4 kg is linked to type 2 diabetes in some populations.

LANDMARK STUDY

The Barts–Windsor study was the first prospective family study in type 1 diabetes and was created by the fortuitous collaboration between Andrew Cudworth (then at St Bartholmew's Hospital) and John Lister who was the diabetologist in Windsor who kept a file index of all new cases of type 1 diabetes that he had seen in the district. Around 200 families with a proband with type 1 diabetes and an unaffected sibling were identified and serum collected from as many family members as possible. The findings contributed to what Edwin Gale termed a paradigm shift in the thinking around the aetiology of type diabetes (see 2001 reference below for masterful description). The original objective was to detect the viral culprit for type 1 diabetes. Instead, they confirmed the autoimmune basis of the disease; the clinically silent but immunologically active stage in individuals who had islet cell and GAD autoantibodies years before developing diabetes; and the causative links with some HLA antigens and the protective nature of others. Sadly Andrew died just as the study was producing its most impressive results but it remains a fine example of how happenchance and clinical diligence can combine to change our thinking about disease in fundamental ways.

20% have diabetes if they are human leukocyte antigen (HLA) identical, compared with the population frequency of about 0.4%. However, only 10–15% of type 1 diabetes occurs in families with the disease ('multiplex') and most cases are said to be 'sporadic'. The chance of a child developing type 1 diabetes is around 5% if one parent is affected or 15% if both have the condition. The risk is greater if the father is affected and there is also a small male preponderance in overall prevalence. The reasons for these sex differences remain unknown.

The incidence of type 1 diabetes is increasing in many countries. In Europe, the overall increase is 3.4% per year, but the increase is particularly notable in those diagnosed under the age of 5 years, where it is 6.3% per year and total numbers are likely to double by 2020 (Figure 6.7). Based on these figures, the prevalence of type 1 diabetes may be 70% higher in 2020 than in 1989. This sharp rise in frequency over a short period of time suggests changing environmental factors that operate in early life, as genetic factors would take much longer over several generations to make an impact.

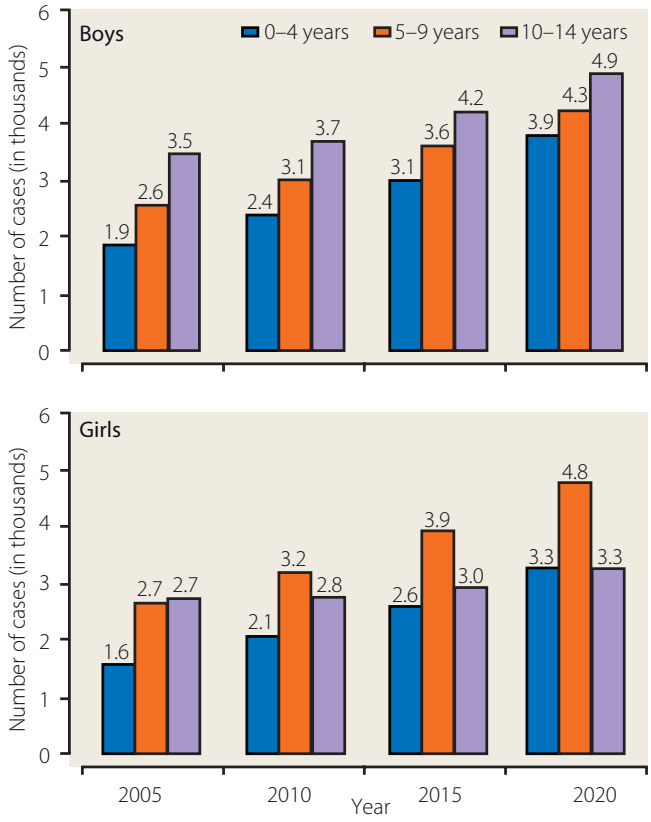

Figure 6.7 Estimated (2005) and predicted 2020 cases of newly diagnosed type 1 diabetes by age and sex for Europe excluding Belarus, the Russian Federation, Ukraine, Moldova and Albania using Poisson regression modelling. Reproduced from Patterson et al. Lancet 2009; 373: 2027–2033.

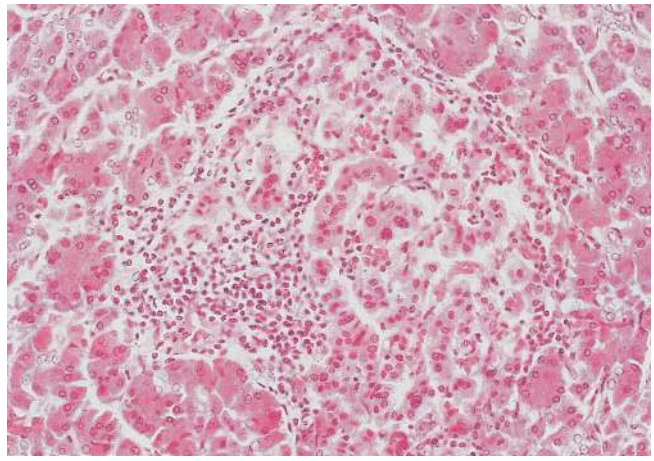

Figure 6.8 Insulitis. There is a chronic inflammatory cell infiltrate centred on this islet. Haematoxylin–eosin stain, original magnification ×300.

Aetiology

Autoimmunity

Evidence for autoimmunity in the pathogenesis of type 1 diabetes comes from postmortem studies in patients who have died shortly after presentation and pancreatic biopsies from living patients. They have revealed a chronic inflammatory mononuclear cell infiltrate ('insulitis') (Figure 6.8) associated with the residual β cells in the islets of recently diagnosed type 1 diabetic patients. The infiltrate consists of T cell lymphocytes and macrophages. Later in the disease, there is complete loss of β cells, while the other islet cell types (α, δ and PP cells) all survive.

A major marker of insulitis is the presence of four circulating islet-related autoantibodies in patients with newly

diagnosed type 1 diabetes; islet cells (ICAs), insulin molecule (IAAs), tyrosine phosphatase (IA-2) and glutamic acid decarboxylase (GAD) antibodies. However, not all those with islet autoantibodies go on to develop diabetes, which suggests that insulitis does not necessarily progress to critical β cell damage. Type 1 diabetes is manifest clinically after a prodromal period of months or years, during which immunological abnormalities, such as circulating islet autoantibodies, can be detected, even though normoglycaemia is maintained.

In family studies, positivity to three or more autoantibodies confers a risk of developing type 1 diabetes of 60–100% over 5–10 years. Single positivity carries a much lower positive predictive value.

The autoimmune basis for type 1diabetes is also suggested by its association with other diseases such as hypothyroidism, Graves' disease, pernicious anaemia and Addison's disease which are all associated with organ-specific autoantibodies (Box 6.1). Up to 30% of people with type 1 diabetes have autoimmune thyroid disease.

The detection of ICAs and GAD antibodies in older persons with type 2 diabetes in Finland and the UKPDS, who were shown subsequently to be more likely to require insulin therapy, has led to the concept of latent autoimmune diabetes of adults (LADA). However, this concept has been challenged. Although GAD positivity had a specificity of 94.6% for early insulin use in the UKPDS, its sensitivity was only 37.9%. Moreover, the positive predictive value for GAD-positive antibodies was only 50.8% (i.e. only half of those positive went on to need insulin). Furthermore, people with LADA had a similar pattern of HLA haplotype (see below) as those developing type 1 diabetes in childhood. It is likely therefore that as LADA patients have some but not all of the immunological markers of type 1 diabetes of childhood, they represent part of a spectrum of autoimmune disease rather than a separate entity in their own right.

Genetics

Genetic susceptibility to type 1 diabetes is most closely associated with HLA genes that lie within the major histocompatibility complex (MHC) region on the short arm of chromosome 6 (now called the IDDM1 locus). HLAs are cell surface glycoproteins that show extreme variability through polymorphisms in the genes that code for them. Both high- and low-risk HLA haplotypes have been identified. HLA DR/4, DQA1* 0301–DQB1* 0302 and DQA1* 0501–DQB1* 0201 account for over 50% of genetic susceptibility; whereas DQA1* 0102–DQB1* 0602 and DRB1* 1401 are protective.

Class II HLAs (HLA-D) play a key role in presenting foreign and self-antigens to T-helper lymphocytes and therefore in initiating the autoimmune process (Figure 6.11). Polymorphisms in the DQB1 gene that result in amino acid substitutions in the class II antigens may affect the ability to accept and present autoantigens derived from the β cell. This is a critical step in 'arming' T lymphocytes, which initiate the immune attack against the β cells.

Over 20 regions of the human genome are associated with type 1 diabetes, but most make only a minor contribution. IDDM2 corresponds to the insulin VNTR gene locus on

Box 6.1 Autoimmune disorders associated with type 1 diabetes

- Addison's disease
- Graves' disease
- Hypothyroidism
- Hypogonadism
- Pernicious anaemia
- Vitiligo
- Autoimmune polyglandular syndromes, types 1 and 2
- Coeliac disease

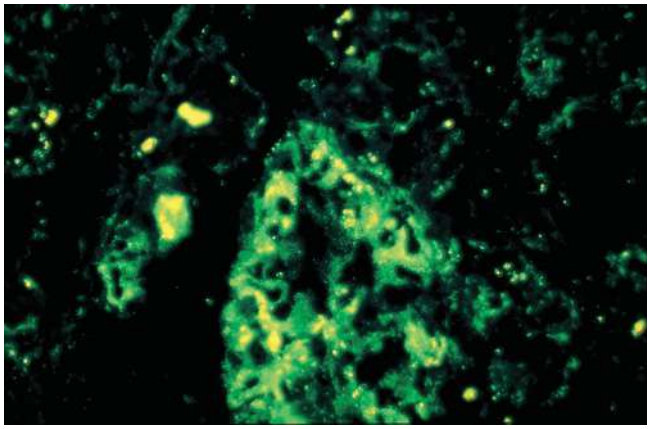

Figure 6.9 ICA demonstrated by indirect immunofluorescence in a frozen section of human pancreas.

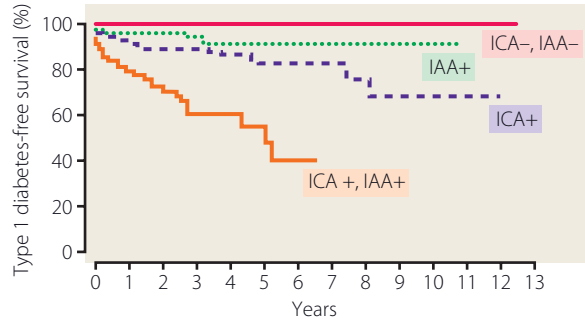

Figure 6.10 The probability of remaining free of type 1 diabetes in 4694 non-diabetic relatives of patients with type 1 diabetes. Disease-free survival was dependent on the presence of islet-related antibodies, the greatest risk being when both islet cell antibodies (ICAs) and insulin autoantibodies (IAAs) were present together. Data from Krischer et al. J Clin Endocrinol Metab 1993: 77:743–749.

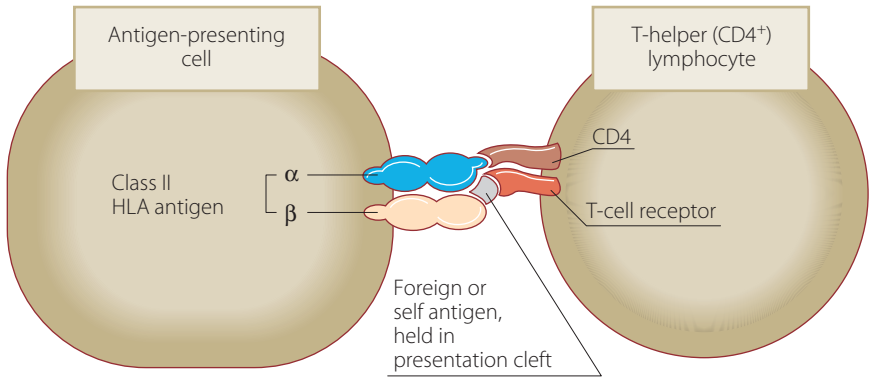

Figure 6.11 Antigen associated with class II HLA is presented to T cells.

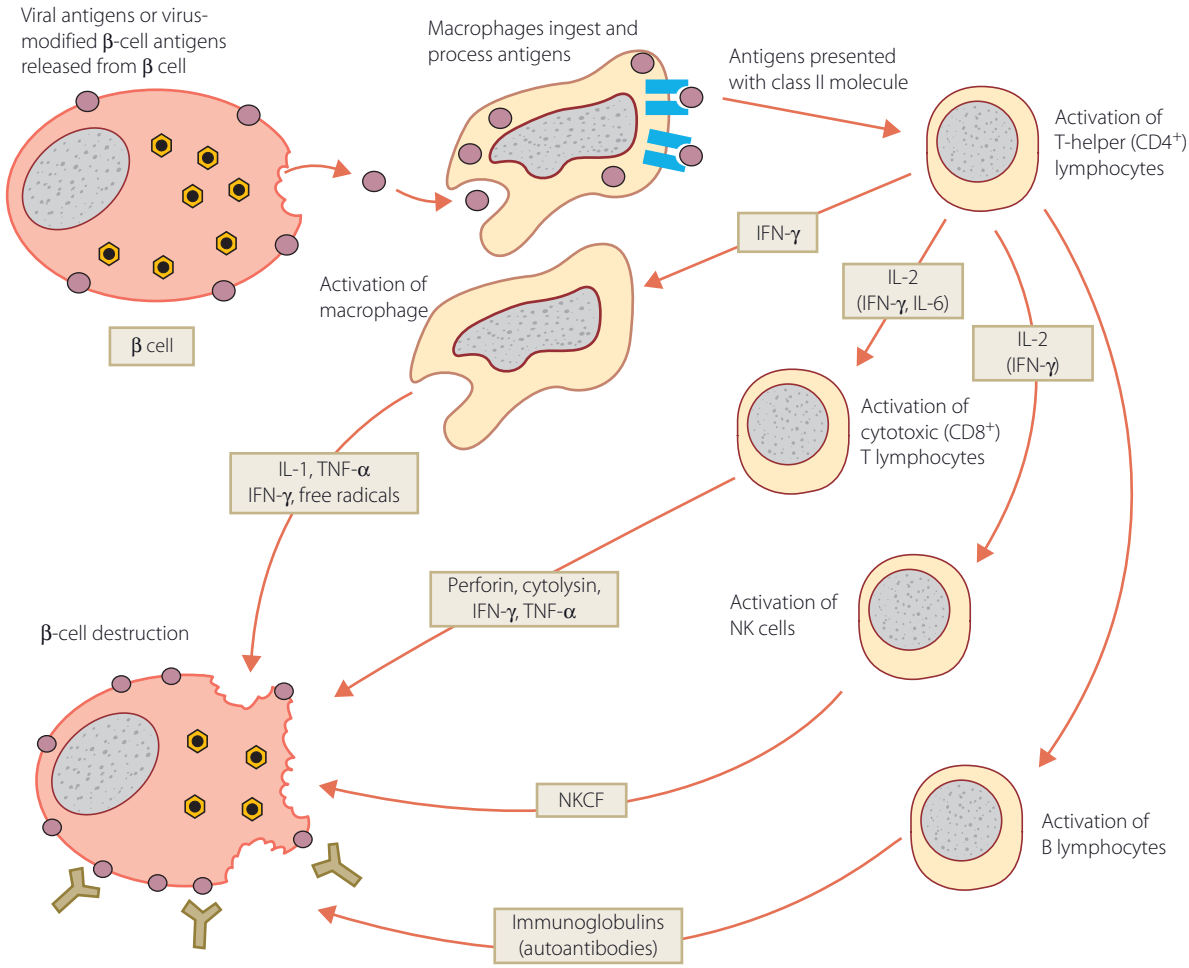

Figure 6.12 Hypothetical scheme that shows ways in which viruses could initiate an autoimmune attack on β cells. Some viruses (e.g. retroviruses and rubella virus) may induce β cells to express viral (foreign) antigens or render an endogenous β cell antigen immunogenic. Viral antigens released from β cells during normal β cell turnover might be processed by macrophages and presented to T-helper lymphocytes (CD4+) associated with HLA class II antigens. Activated T lymphocytes then secrete interleukin (IL)-2 and other cytokines that activate other immune cells. B lymphocytes produce immunoglobulins against the viral antigens, while activated natural killer (NK) cells and cytotoxic (CD8+) lymphocytes cause destruction of β cells that carry the viral antigens. Macrophages, activated by interferon-γ (IFN-γ), also participate in the destruction of the target cells. NKCF, natural killer cell factor; TNF, tumour necrosis factor.

chromosome 11, has a smaller effect than IDDM1 and acts independently. Together with IDDM 12 (CTLA-4), it contributes around 15% of the genetic risk. The other 17 genes individually contribute little. The predisposing polymorphism in the IDDM 2 gene and how it influences the disease has yet to be determined.

Environmental and maternal factors

Although genetic factors are undoubtedly important, the relatively low concordance of <50% in monozygotic twins together with the rapidly increasing incidence rates for type 1 diabetes at a younger age strongly suggest that external or environmental factors are playing a part. Much of the evidence that links environmental factors with the aetiology of type 1 diabetes is circumstantial, based upon epidemiology and animal research. The factors most often implicated are viruses, and diet and toxins, but a number of other influences, such as early feeding with cow's milk and psychological stress, are being investigated.

Recent meta-analyses and pooled cohort studies have shown a link to birth weight (a 7% increase in risk for every 1 kg in weight); Caesarean section (a 20% increase); and maternal age (5% increase for each 5 years). These associations remain unexplained.

Viruses

The viruses that have been implicated in the development of human diabetes have been deduced from temporal and geographical associations with a known infection. For example, mumps can cause pancreatitis and occasionally precedes the development of type 1 diabetes in children. Intrauterine rubella infection induces diabetes in up to 20% of affected children. Many people with recent-onset type 1 diabetes have serological or clinical evidence of coxsackie B virus infection, particularly the B4 serotype. Marked islet β cell damage has been detected in children who died from coxsackie B virus infection.

In a few cases, coxsackie viral antigens have been isolated in islets postmortem, and viruses isolated from the pancreas have been shown to induce diabetes in susceptible mouse strains. Electron microscopy of the pancreas in some subjects who died shortly after the onset of type 1 diabetes identified retrovirus-like particles within the β cells, associated with insulitis.

Viruses may target the β cells and destroy them directly through a cytolytic effect or by triggering an autoimmune attack (Figure 6.12). Autoimmune mechanisms may include 'molecular mimicry'; that is, immune responses against a viral antigen that cross-react with a β cell antigen (e.g. a coxsackie B4 protein (P2-C) has sequence homology with GAD, an established autoantigen in the β cell). Also, anti-insulin antibodies from type 1 diabetic patients cross-react with the retroviral p73 antigen in about 75% of cases. Alternatively, viral damage may release sequestered islet antigens and thus restimulate resting autoreactive T cells, previously sensitised against β cell antigens ('bystander activation'). Persistent viral infection could also stimulate interferon-α synthesis and hyperexpression of HLA class I antigens, and the secretion of chemokines that recruit activated macrophages and cytotoxic T cells.

Apoptosis

One model of β cell destruction is via the process of apoptosis or programmed cell death (Figure 6.13). This is effected by the activation of cellular caspases triggered by several means, including the interaction of cell surface Fas (the death-signalling molecule) with its ligand FasL on the surface of infiltrating cells. Other factors that induce apoptosis include macrophage derived nitric oxide (NO) and toxic free radicals, and disruption of the cell membrane by perforin and granzyme B produced by cytotoxic T cells. T cell cytokines (e.g. interleukin-1, tumour necrosis factor-α, interferon-γ) upregulate Fas and FasL and induce NO and toxic free radicals.

Dietary factors

Wheat gluten is a potent diabetogen in animal models of type 1 diabetes (BB rats and NOD mice; see below), and 5–10% of patients with type 1 diabetes have gluten-sensitive enteropathy (coeliac disease). Recent studies have demonstrated that patients with type 1 diabetes and coeliac disease share disease-specific alleles. Wheat may induce subclinical gut inflammation and enhanced gut permeability to lumen antigens in some patients with type 1 diabetes, which may lead to a breakdown in tolerance for dietary proteins. Other possible diabetogenic factors in diet include N-nitroso compounds, speculatively implicated in Icelandic smoked meat, which was a common dietary constituent in winter months.

It has been suggested that early weaning and introduction of cow's milk may trigger type 1 diabetes, but this remains controversial. Surveys have shown associations between both the consumption of milk protein and a low prevalence of breastfeeding with the incidence of type 1 diabetes in different countries (Figure 6.14). It is hypothesised that antibodies against bovine serum albumin may cross-react with an islet antigen (ICA69). The studies are inconsistent, perhaps because of variations in milk composition or the existence of a subset of milk-sensitive, diabetes-prone people. Immune tolerance to insulin might also be compromised by cow's milk, which contains much less insulin than human milk.

Toxins

The notion that there may be environmental β cell toxins is supported by the existence of chemicals that cause an insulin-dependent type of diabetes in animals. Examples are

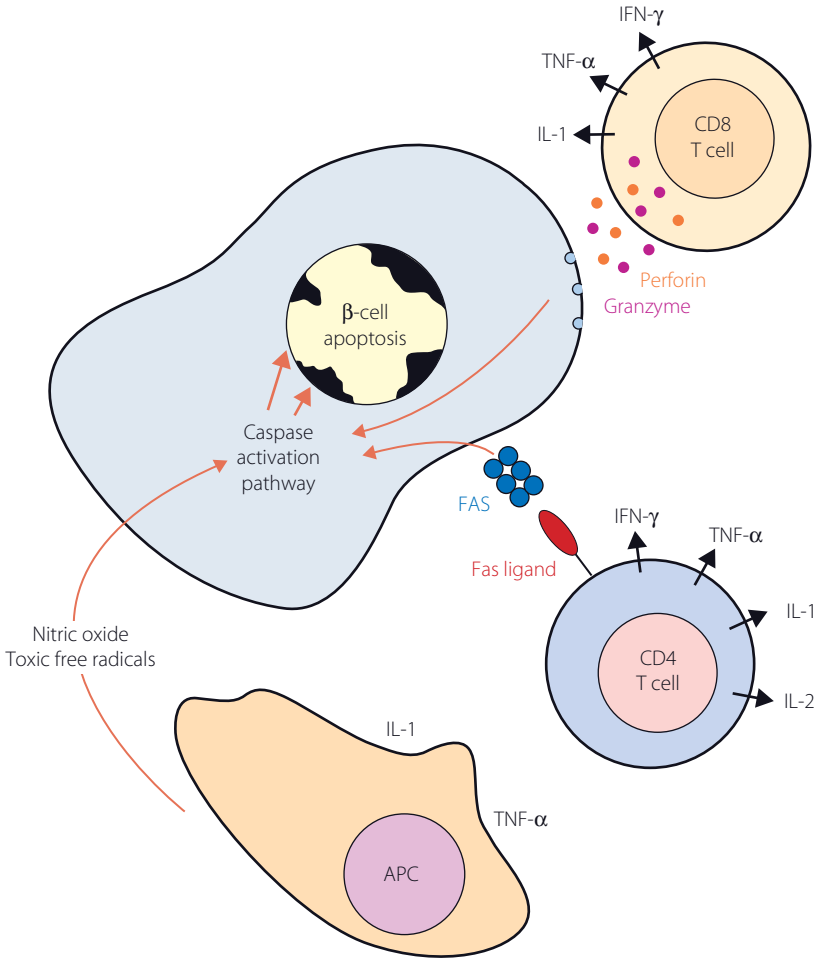

Figure 6.13 Proposed mechanisms of β cell death. B cells die through a process known as apoptosis, characterised by condensation and fragmentation of nuclear chromatin, loss of cytoplasm and expression of surface receptors that signal macrophages to ingest the apoptotic cell. Apoptosis is effected by activation of the caspase pathway.

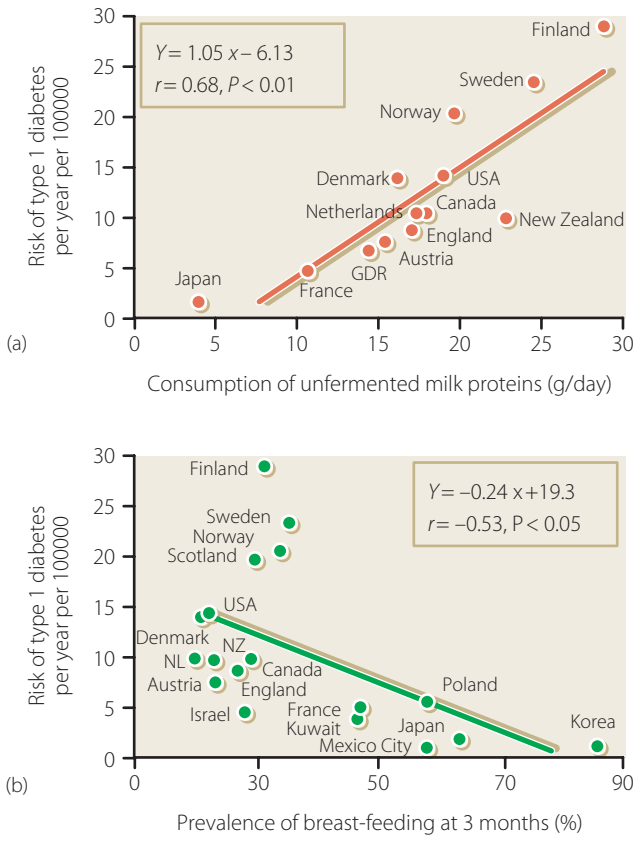

Figure 6.14 The relationship between risk of type 1 diabetes and (a) the consumption of milk protein and (b) the prevalence of breastfeeding in different countries. Data from Sandler. Abstracts of Uppsala Dissertations from the Faculty of Medicine, University of Uppsala, Sweden, 1983.

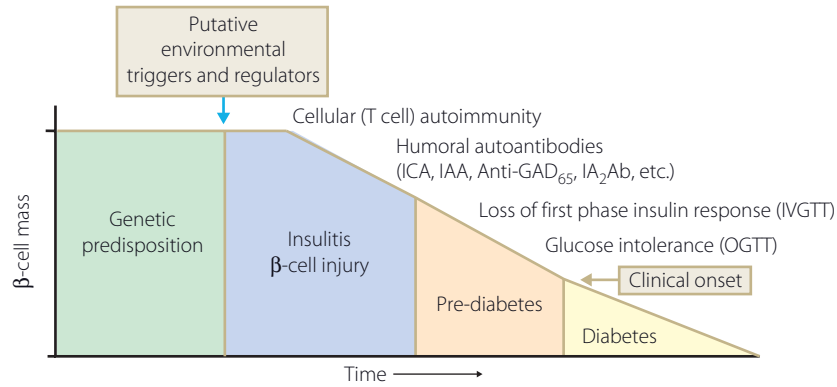

Figure 6.15 Depiction of the evolution of type 1 diabetes.

alloxan and streptozocin, both of which damage the β cell at several sites, including membrane disruption, enzyme interaction (e.g. with glucokinase) and DNA fragmentation. The rat poison vacor causes type 1 diabetes in humans, possibly because it has a similar action to streptozocin.

Animal models

Spontaneous diabetes that resembles type 1 diabetes in humans occurs in some animals, notably the BioBreeding (BB) rat and the non-obese diabetic (NOD) mouse. These 'animal models' have many of the same characteristics as human autoimmune diabetes, including a genetic predisposition, MHC association, insulitis, circulating islet cell surface and GAD autoantibodies, a long prediabetic period that precedes overt hyperglycaemia and environmental factors that trigger or accelerate the appearance of diabetes, such as wheat and cow's milk proteins.

Hygiene hypothesis

The increasing incidence of atopy as well as early-onset type 1 diabetes in Western societies may be a consequence of a lack of exposure to common pathogens such as mycobacteria, lactobacilli and helminth worms. Chronic exposure might include a more tolerant T cell response to antigens, while a cleaner, more sterile early environment would result in an exaggerated response. This hypothesis has increasing supportive associative data but remains unproven.

KEY WEBSITE

- Diabetes Atlas: www.eatlas.idf.org

Combined model

One model of the evolution of type 1 diabetes is that individuals destined to develop the disease are born with genes that confer predisposition and they outweigh any genes with protective effects (Figure 6.15). Environmental factors then act as triggers of the T cell-mediated autoimmune destructive process, which results in insulitis, β cell injury and loss of β cell mass. As β cell function declines, there is loss of the first-phase insulin response to intravenous glucose, subsequent glucose intolerance (pre-diabetes) and eventually the clinical onset of overt diabetes. An alternative view is that there is a chronic interaction between genetic susceptibility, cumulative exposure to environmental factors and immune regulatory processes over the entire period until a critical loss of β cell mass results in insulin deficiency and hyperglycaemia. These events are assumed to proceed more rapidly in children.

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Chapter 7

Epidemiology and aetiology of type 2 diabetes

KEY POINTS

- Type 2 diabetes prevalence is set to increase to around 380 million persons worldwide by 2025, with the highest rates in the Eastern Mediterranean and Middle East, North and South America.
- Rates are also higher in urban compared to rural populations and are increasing dramatically in younger age groups, particularly adolescents.
- Obesity is closely linked to development of type 2 diabetes through its association with insulin resistance, partly mediated by hormones and cytokines such as adiponectin, tumour necrosis factor-α and possibly resistin.
- A genetic basis has been confirmed by the identification of variants in the transcription factor-7-like 2 allele and subsequent development of type 2 diabetes.
- The usefulness of the metabolic syndrome as a predictor of diabetes is still debated. β cell dysfunction is present at the diagnosis of type 2 diabetes and gradually declines with time.

Epidemiological studies of diabetes prevalence are often based upon age and self-reported diagnosis. Consequently differentiating type 1 and type 2 patients in population studies is difficult. The most recent authoritative review of global prevalence published by the International Diabetes Federation (IDF) acknowledges these drawbacks. However, as 85–95% globally of all adult diabetes is type 2 then total prevalence rates will overwhelmingly relate to it.

The IDF has also published adult prevalence rates for impaired glucose tolerance (IGT) which closely reflect those for type 2 diabetes. Conversion rates from IGT to diabetes have been reported at 5–11% per annum.

Prevalence

Overall prevalence corrected for age for both type 2 diabetes and IGT is set to increase from 6.0% to 7.3% and 7.5% to 8.0% respectively over the 18 years from 2007 to 2025 – an absolute increase from 246 to 380 and 308 to 418 million persons aged 20–79 years, respectively (Figure 7.1).

The highest rates are currently in the Eastern Mediterranean and Middle East with North and South America close behind. These reflect the increased life expectancy and overall ageing of the North American population (diabetes is more common in older years). In terms of absolute numbers, the Western Pacific region (particularly China) will have the largest increase of nearly 50%, to 100 million people with diabetes by 2025.

The highest number of people with diabetes is currently in the 40–59-year-old age group, but there will be almost parity with 60–79 year olds by 2025, at 166 and 164 million worldwide respectively.

There is considerable variation within each region, however. For example, in the Western Pacific, the tiny island of Nauru has a comparative prevalence in 2007 of 30.7%, whilst nearby Tonga has less than half that rate at 12.9%, the Philippines 7.6% and China 4.1%.

In the European region, comparative rates range from 1.6% in Iceland to 7.9% in Germany, Austria and Switzerland. The UK rate is 2.9% age adjusted and 4.0% absolute, increasing to 3.5% and 4.6% respectively in 2025 (representing an increase from 1.7 to 2.16 million in absolute numbers).

Urban versus rural

There is a global trend for rates of diabetes to increase in populations as they move from a rural to an urban existence. The reasons are unclear but probably relate to both

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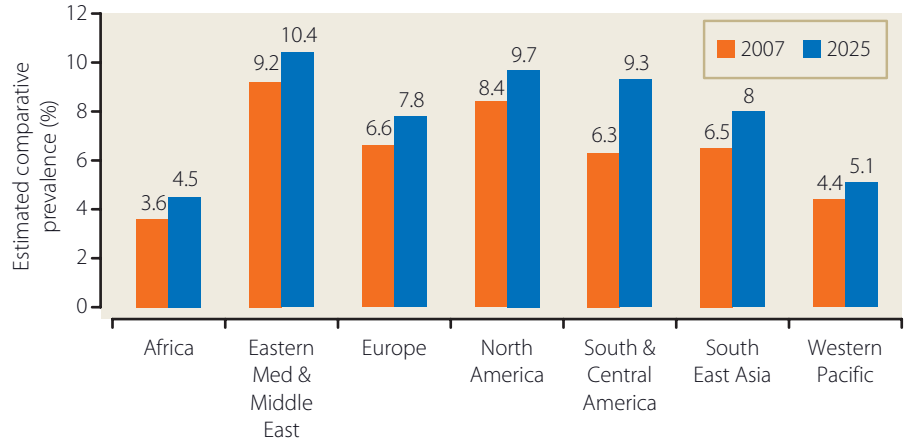


Figure 7.1 Comparative prevalence (corrected for age) of diabetes by region estimated for the years 2007 (red) and 2025 (blue). Data from *Diabetes Atlas*, 3rd edn.

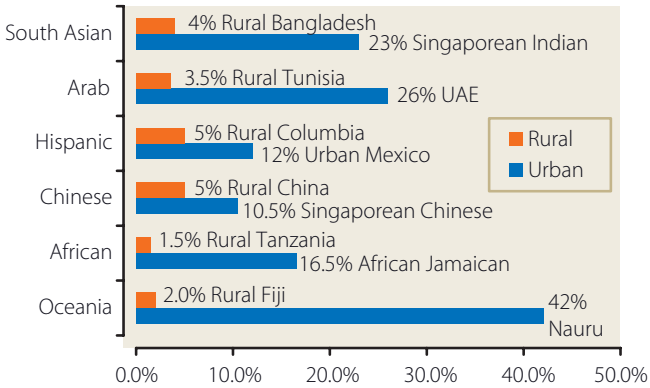


Figure 7.2 Varying prevalence rates of type 2 diabetes by ethnicity/region and location (red, rural; blue, urban) for 2007. UAE, United Arab Emirates. Data from *Diabetes Atlas*, 3rd edn.

decreasing physical activity as well as dietary changes. For example, rural Chinese have a prevalence of type 2 diabetes of 5%, less than half the rate of Singaporean Chinese (10.5%). Much larger differences are seen in South Asian, Hispanic, African and Polynesian peoples (Figure 7.2).

Impaired glucose tolerance

Comparative prevalence for IGT vary by region with rates almost double those for type 2 diabetes in Africa, but slightly lower elsewhere. These differences are almost certainly a reflection of socio-economic factors as well as a paucity of studies in many African countries where extrapolation is necessary between very different populations. In Europe, the comparative prevalence will increase slightly from 9.1% in 2007 to 9.6% in 2025, representing an absolute change from 65.3 to 71.2 million (UK figures 4.7% to 4.9%, 2.17 to 2.4 million respectively).

Incidence

Reported incidence rates vary according to population under study and year of observation. For white Europid populations, rates of 0.1–1% per annum have been reported. For Hispanic populations in the USA, rates of 2.8% were recorded in the San Antonio Study, similar to those of the Pima Indians in Arizona (approximately 2.5%), and Australian aborigines (2.03%).

Over 20 years, incidence in the Pima has not changed although the age of onset has been declining. The occurrence of type 2 diabetes in adolescence is now a great cause for concern worldwide. In US Asian and Pacific Islanders, for example, rates of 12.1/100,000 patient-years have been reported in 10–19 year olds, similar to rates reported for type 1 diabetes. In the UK, the overall incidence for <16 year olds is much lower, at 0.53 per/100,000 patient-years, but 10 times more common in South Asian or black African compared to white children.

The rural:urban ratio remains for incidence even in the presence of other risk factors such as central obesity. In Japanese, there is an approximately threefold increase in incidence for obese urban compared to rural populations (15.8 versus 5.8% over 10 years). Similarly, there is a twofold increase in incidence for USA versus Mexican Hispanic people corrected for age and economic circumstance, probably a reflection of changes in diet and lifestyle. For the Pima, the contrast is more striking, with a >5-fold increase in those living in the US compared to northern Mexico.

The magnitude of these figures has opened a debate on population screening for diabetes, but a Health Technology Assessment report in the UK from 2007 and a report from the US Preventive Services Task Force in 2008 both concluded that there is not enough evidence at present to support such a policy.

Risk factors for development of type 2 diabetes

Obesity

About 80% of people with type 2 diabetes are obese, and the risk of developing diabetes increases progressively as the BMI (weight (kg)/height (m)^2) increases. A BMI >35 kg/m^2 increases the risk of type 2 diabetes developing over a 10-year period by 80-fold, as compared to those with a BMI <22 kg/m^2. Latest data from the NHANES survey in the USA confirm a 6–10-fold increased lifetime risk of type 2 diabetes for 18 year olds with a BMI >35 kg/m^2 compared to those <18.5 kg/m^2 with an associated average 6–7 year reduction in overall life expectancy. Obesity is still widely defined as a BMI >30 kg/m^2 although BMI is not an accurate reflection of fat mass or its distribution, particularly in Asian people. A simple waist circumference may be better (see metabolic syndrome below).

The pattern of obesity is also important in that central fat deposition has a much higher risk for development of diabetes compared to gluteofemoral deposition. In clinical practice such central obesity can be assessed by measuring the weight:hip circumference ratio, but it is unclear whether this has any advantage over a simple waist circumference. Fat deposition at other sites, particularly muscle, liver and islets, may contribute to metabolic defects and insulin resistance (so-called lipotoxicity).

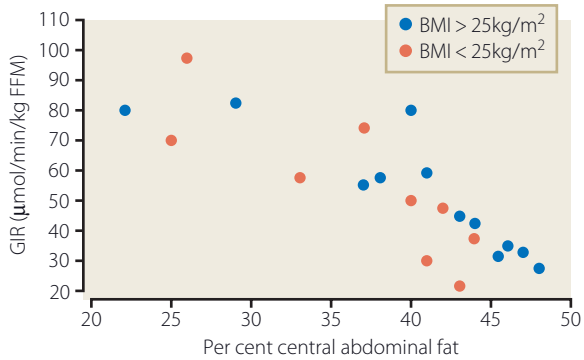


Figure 7.3 Insulin resistance (as assessed by glucose infusion rate (GIR) to maintain constant blood glucose during simultaneous insulin infusion) is proportional to visceral fat mass, independent of BMI. FFM, fat-free mass. Data from Pan et al. Diabetes 1997; 46: 983–988.

Physical exercise and diet

Low levels of physical exercise also predict the development of type 2 diabetes, possibly because exercise increases insulin sensitivity and helps prevent obesity (Figure 7.4). Subjects who exercise the most have a 25–60% lower risk of developing type 2 diabetes regardless of other risk factors such as obesity and family history.

There has been extensive research into the role of diet as a risk factor for type 2 diabetes. A study in over 10,000 35–55 year olds found that a diet containing large quantities of soft drinks, burgers, sausages and low fibre explained 5.7% of insulin resistance as assessed by the HOMA model. There were 77,440 person-years in the study with 427 incident cases of type 2 diabetes.

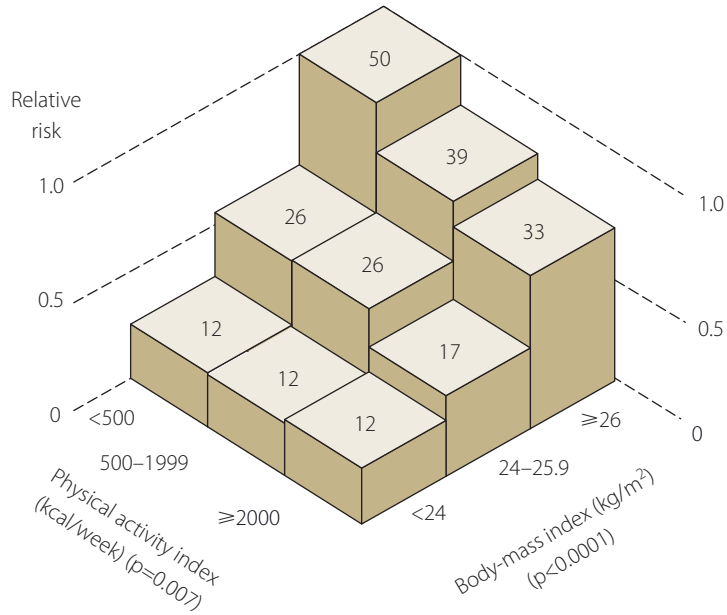


Figure 7.4 Age-adjusted risk of type 2 diabetes among 5990 men. The figure shows data for the physical activity index in relation to BMI. Each block represents the relative risk of type 2 diabetes per 10,000 man-years of follow-up, with the risk for the tallest block set at 1.0. The numbers on the blocks are incidence rates of type 2 diabetes per 10,000 man-years. From Helmrich et al. N Engl J Med 1991; 325: 147–152.

The Diabetes Prevention Programme and Diabetes Prevention Study in the USA and Finland have shown that lifestyle modifications with moderate exercise and modest weight loss can dramatically reduce the number progressing from IGT to type 2 diabetes and reinforce the importance of lifestyle factors in the cause of diabetes.

Insulin resistance

Insulin resistance can be estimated from the amount of glucose that is infused intravenously in order to maintain a constant blood glucose during a simultaneous intravenous insulin infusion. This method is cumbersome, however, and for population purposes it has been largely superseded by the HOMA (homeostasis model assessment)

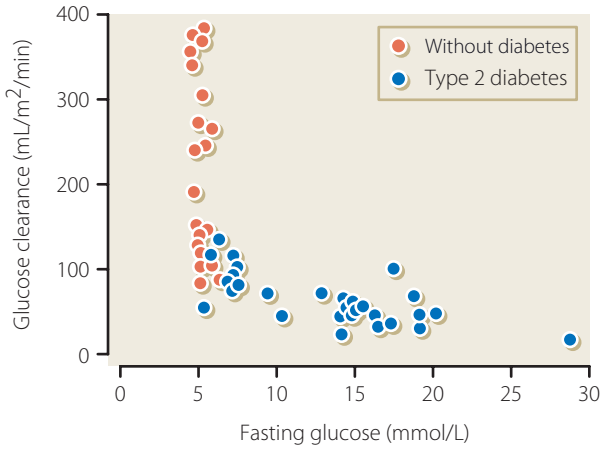


Figure 7.5 The relationship between fasting plasma glucose concentration and glucose metabolic clearance rates (insulin sensitivity) observed during hyperinsulinaemic, glucose-clamp studies in subjects without diabetes and patients with type 2 diabetes. Courtesy of Dr G Reaven, Stanford University School of Medicine, USA.

CASE HISTORY

A 25-year-old single, male postgraduate student, whose parents were from Bangladesh, presented to the local genitourinary clinic with penile candida, and was worried he may have contracted a sexually transmitted disease. Urinalysis confirmed glycosuria and a random capillary blood glucose was 13.2 mmol/L. On direct questioning, he said he had been a bit more thirsty lately. He added that his father had just been diagnosed with type 2 diabetes. He used to play first team hockey as an undergraduate but had stopped following a knee injury 18 months ago. Since then his life had become more sedentary, he ate convenience foods more than four times a week and had gained about 12 kg in weight. He now had a waist circumference of 100 cm and a BMI of 30 kg/m^2 (weight 86.7 kg, height 1.7 m).

Comment: This young man has multiple risk factors for type 2 diabetes. His ethnic background and family history, recent weight gain, dietary changes and lack of exercise are all well validated. We are not given his birthweight but if this was low then he would also fit the picture of the 'thrifty phenotype'. Although his BMI is definitely raised, his height makes this a less reliable measure of obesity than his waist circumference. He also shows the phenomenon of genetic anticipation in that his age at diagnosis is much earlier than that of his father.

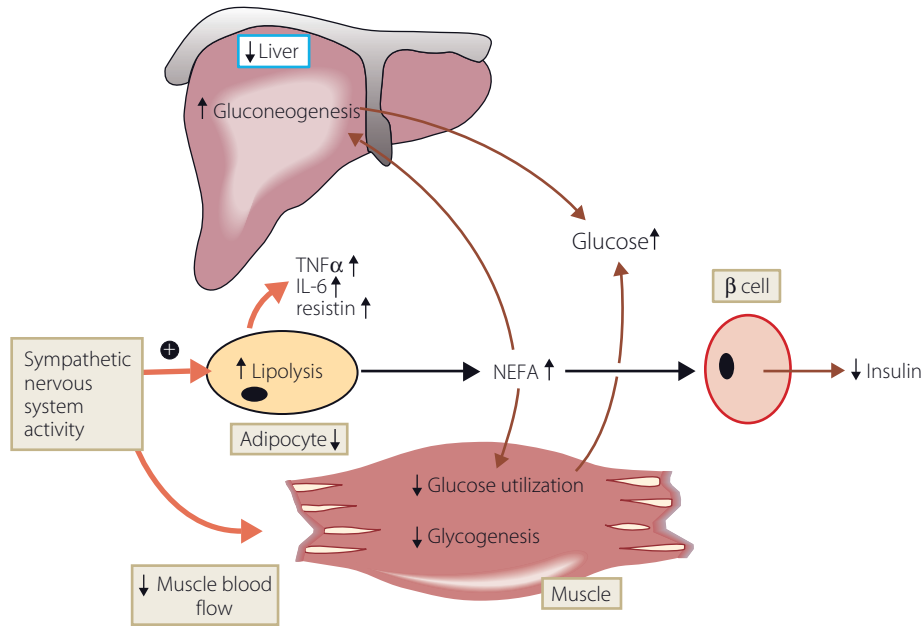


Figure 7.6 Mechanisms of insulin resistance in type 2 diabetes.

estimate of steady-state β cell function (HOMA B) and insulin sensitivity (HOMA S) as percentages of normal. These can be derived from a single fasting plasma C peptide, insulin and glucose concentration. Insulin resistance (or, more correctly, diminished insulin sensitivity) precedes the onset of diabetes and can worsen with increasing duration.

Hormones and cytokines

Visceral fat liberates large amounts of non-esterified fatty acids (NEFAs) through lipolysis, which increases gluoconeogenesis in the liver and impairs glucose uptake and utilization in muscle. NEFAs may also inhibit insulin secretion, possibly by enhancing the accumulation of triglyceride within the β cells. In addition, adipose tissue produces cytokines, such as TNF-α, resistin and IL-6, all of which have been shown experimentally to interfere with insulin action. TNF-α has been shown to inhibit tyrosine kinase activity at the insulin receptor and decrease expression of the glucose transporter GLUT-4.

Adiponectin is a hormone with anti-inflammatory and insulin-sensitising properties that is secreted solely by fat cells. It suppresses hepatic gluconeogenesis and stimulates fatty acid oxidation in the liver and skeletal muscles, as well as increasing muscle glucose uptake and insulin release from the β cells. Circulating adiponectin is reduced in obesity and a recent meta-analysis showed that the relative risk for diabetes was 0.72 for every 1-log μg/mL increment in adiponectin level.

Resistin is an adipocyte-secreted hormone that increases insulin resistance and was first described in rodents, being found in increased levels in experimental obesity and diabetes. In humans, it appears to be derived largely from macrophages, however, and its precise role in human diabetes is uncertain, although higher circulating levels have been found in some people with type 2 diabetes.

Leptin is an adipokine that was found to be absent in the ob/ob mouse model of obesity and diabetes. Its normal function is to suppress appetite, thus providing a candidate mechanism linking weight gain and appetite control. Although abnormal leptin function has been described in humans, these defects are very rare and paradoxically high levels have been found in type 2 diabetes.

Ghrelin is a recently described peptide secreted from the stomach and may act as a hunger signal. Circulating levels are negatively correlated with BMI and are suppressed by food intake. It has no known role in human diabetes but antagonism may provide a therapeutic target.

Finally there is often increased sympathetic nervous system activity in obesity, which might also increase lipolysis, reduce muscle blood flow and thus glucose delivery and uptake, and therefore directly affect insulin action.

Inflammation

Many of these cytokines are involved in the acute-phase response and it is therefore not surprising that circulating markers such as C-reactive protein and sialic acid are increased in type 2 diabetic patients, as well as in those who later go on to develop the condition. Because these markers have also been found to be elevated in patients with atherosclerosis, a unifying hypothesis has evolved proposing that inflammation may be a common precursor and link between diabetes and coronary artery disease.

Genetics

Evidence for a genetic basis for type 2 diabetes comes from a clear familial aggregation, but it does not segregate in a classic Mendelian fashion. About 10% of patients with type 2 diabetes have a similarly affected sibling. The concordance rate for identical twins is variously estimated to be 33–90% (17–37% in non-identical twins), but the interpretation of this is controversial as part of the explanation for the high concordance may be environmental rather than genetic.

Unlike type 1, type 2 diabetes is not associated with genes in the HLA region. So far, 19 gene variants have been described and validated as being associated with type 2 diabetes. Of these, the strongest is TCF7L2; 15% of European adults carry two copies of the abnormal gene and they have double the lifetime risk of developing type 2 diabetes compared to the 40% who carry no copies. Carriers of the T risk allele have impaired insulin secretion and enhanced hepatic glucose output. Nearly all of the other described genes affect either β cell mass or function; few appear to have potential effects on insulin resistance.

Thrifty phenotype hypothesis

A link between low birthweight and later development of type 2 diabetes in a UK population has led to a hypothesis linking foetal malnutrition to impaired β cell development and insulin resistance in adulthood. Abundant adult nutrition and consequent obesity would then expose these problems, leading to IGT and eventually type 2 diabetes. This has been called the thrifty phenotype hypothesis (Figure 7.7).

A meta-analysis of 31 populations involving 152,084 individuals from varying ethnic groups and 6090 cases of diabetes was published in 2008. This confirmed a negative association between birthweight and diabetes in 23, but found a positive association in eight studies. The combined odds ratio for type 2 diabetes was 0.8 (95% CI 0.72–0.89) for each 1 kg increase in birthweight. This relationship was strengthened if macrosomic (birthweight >4 kg) and offspring of mothers with known type 2 diabetes were excluded (odds ratio (OR) 0.67, 95% CI 0.61–0.73). Notably there was a tendency for a positive relationship in North American populations largely due to higher rates of maternal obesity and gestational diabetes. Adjustment for socio-economic

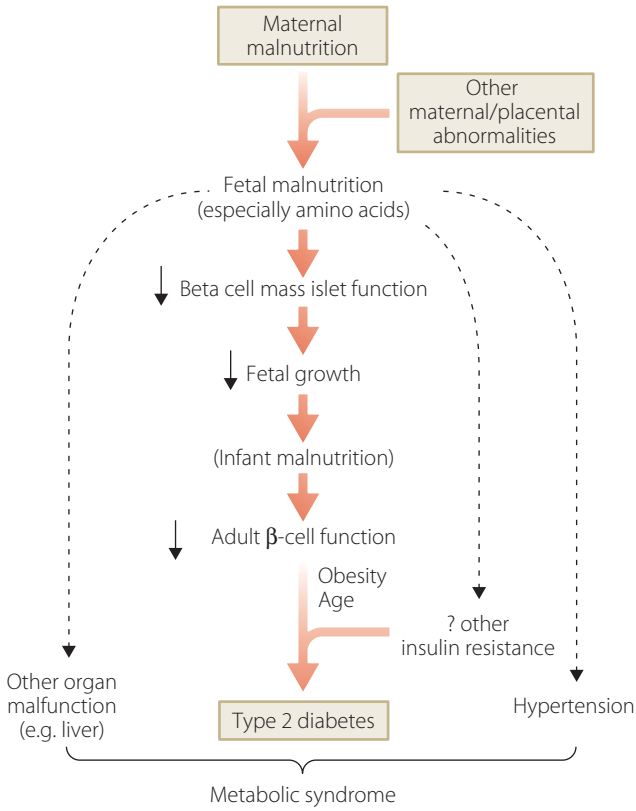


Figure 7.7 The 'thrifty phenotype' hypothesis.

status had no effect, but adjustment for achieved adult BMI attenuated the relationship.

With increasing maternal obesity and gestational diabetes mellitus (GDM), it is conceivable that the relationship will change to the pattern currently seen in Native Americans which is more U shaped. However, it is still unclear whether low birthweight is a causative factor or a sign of other potential mechanisms which may predispose to later diabetes.

Accelerator hypothesis

This is a proposal that type 1 and type 2 diabetes are essentially the same in that both result ultimately from β cell failure. The aetiology obviously differs but superimposed insulin resistance drives the process. Three accelerators are proposed: constitution – individuals have increased β cell apoptosis; insulin resistance – underpinned by physical inactivity and visceral adiposity; and autoimmunity – mainly operative in younger patients and linked to HLA susceptibility alleles. The overlapping driver of obesity would explain increasing rates of 'type 1' and 'type 2' diabetes. This intriguing idea is currently widely debated and awaits confirmatory studies.

Metabolic syndrome

The aggregation of obesity, hyperglycaemia, hypertension and hyperlipidaemia in people with both type 2 diabetes and cardiovascular disease is now termed the metabolic syndrome (Table 7.1). This concept is not new, it is said to have been first described in 1923, but latterly there have been attempts to standardise its definition.

Table 7.1 Definition of metabolic syndrome

Risk factor	Defining level	
	NCEP ATP III	IDF
Abdominal obesity (waist circumference)		
Men	>102 cm	≥94 cm (Europid) ≥90 cm (others)
Women	>88 cm	≥80 cm for all
Plasma triglycerides	≥1.7 mmol/L	≥1.7 mmol/L
Plasma HDL cholesterol		
Men	<0.9 mmol/L	<1.03 mmol/L
Women	<1.1 mmol/L	<1.29 mmol/L
Blood pressure	≥130/≥85 mmHg	≥130/≥85 mmHg or on treatment
Plasma fasting glucose	≥6.1 mmol/L	≥5.6 mmol/L or pre-existing type 2 diabetes
Diagnostic criteria	3 or more of the above	Obesity plus 2 others

NCEP ATP III, National Cholesterol Education Programme – 3rd Adult Treatment Panel; IDF, International Diabetes Federation.

Since these definitions appeared, there has been considerable debate as to their relative strengths and weaknesses. Indeed, there is some debate as to whether this constitutes a true syndrome at all and whether they add anything to predictive models for type 2 diabetes and coronary artery disease. A major problem is the correlation of many of the features. In prospective studies, fasting plasma glucose (FPG) is overwhelmingly linked to subsequent development of diabetes, but much less so with coronary artery disease. Thus the predictive utility of the metabolic syndrome as a concept adds little to its constituent risk factors when they are used individually. The long-term usefulness of the definition of the metabolic syndrome for identification and intervention in order to prevent diabetes and cardiovascular disease has yet to be demonstrated.

β cell dysfunction

Type 2 diabetes develops because of a progressive deterioration of β cell function, coupled with increasing insulin resistance for which the β cell cannot compensate. At the time of diagnosis β cell function is already reduced by about 50% and continues to decline regardless of therapy (Figure 7.8).

The main defects in β cell function in type 2 diabetes are a markedly reduced first- and second-phase insulin response to intravenous glucose, and a delayed or blunted response

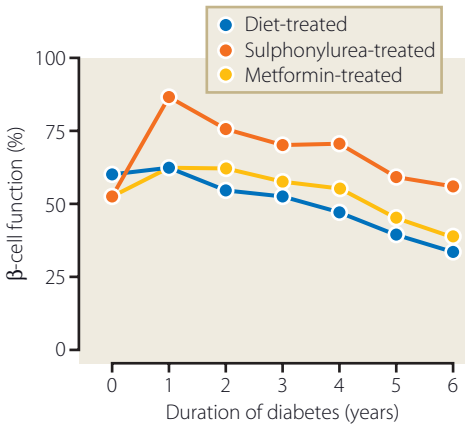
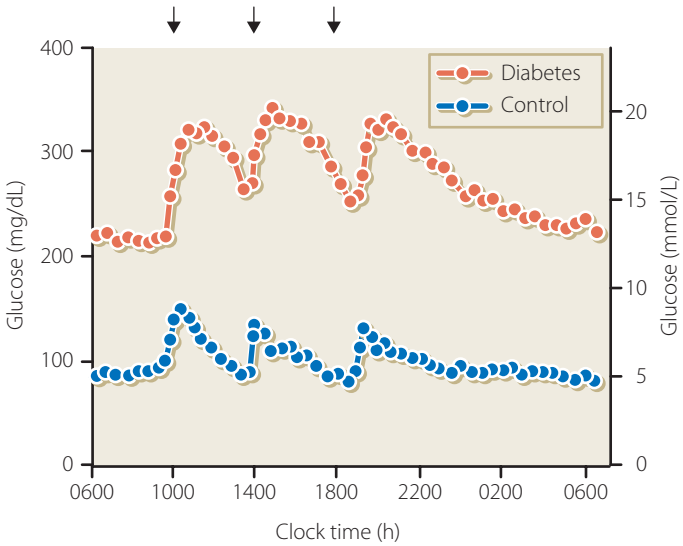


Figure 7.8 β-cell function as measured by the homeostasis model assessment (HOMA) method (calculated from the fasting blood glucose and insulin concentrations) in patients with type 2 diabetes from the UKPDS. β cell function is already reduced to 50% at diagnosis and declines thereafter, despite therapy. Data from Hales & Barker. Diabetologia 1992; 35: 595–601.



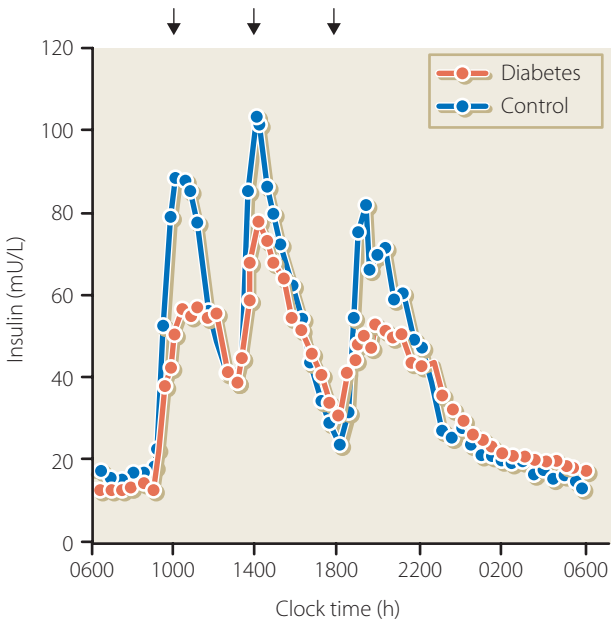


Figure 7.9 Plasma concentrations of glucose and insulin in subjects with type 2 diabetes and control subjects without diabetes in response to mixed meals. Data from UK Prospective Diabetes Study Group. Diabetes 1995; 44:1249–1258.

to mixed meals (Figure 7.9). There are also alterations in pulsatile and daytime oscillations of insulin release. Some researchers have found increases in the proportions of plasma proinsulin and split proinsulin peptides relative to insulin alone. Many of these abnormalities can be found in people with IGT and even in normoglycaemic first-degree relatives of people with type 2 diabetes, indicating that impaired β cell function is an early and possibly genetic defect in the natural history of type 2 diabetes (Figure 7.10).

The most common histological abnormality found in the islets of patients with type 2 diabetes is the presence of insoluble amyloid fibrils lying outside the cells. These are derived from islet amyloid polypeptide (IAPP, also sometimes known as amylin). This is co-secreted with insulin in a molar ratio of 1:10–50. Although IAPP is reported to impair insulin secretion and to be toxic to the β cell, its precise role in the pathogenesis of type 2 diabetes is uncertain because deposits can be found in up to 20% of elderly people who had completely normal glucose tolerance in life.

β Cell mass is thought to be decreased by only 20–40% in type 2 diabetes and this clearly cannot explain the >80% reduction in insulin release that is observed. There must therefore be additional functional defects in the β cell, perhaps mediated by glucose or lipid toxicity. It is likely that IAPP contributes to this process.

Conclusion

Both insulin resistance and β cell dysfunction are early features of glucose intolerance, and there has been much debate as to whether one is the primary defect and precedes the other. In practice, the contribution of insulin resistance and β cell dysfunction varies considerably between patients,

LANDMARK CLINICAL TRIALS

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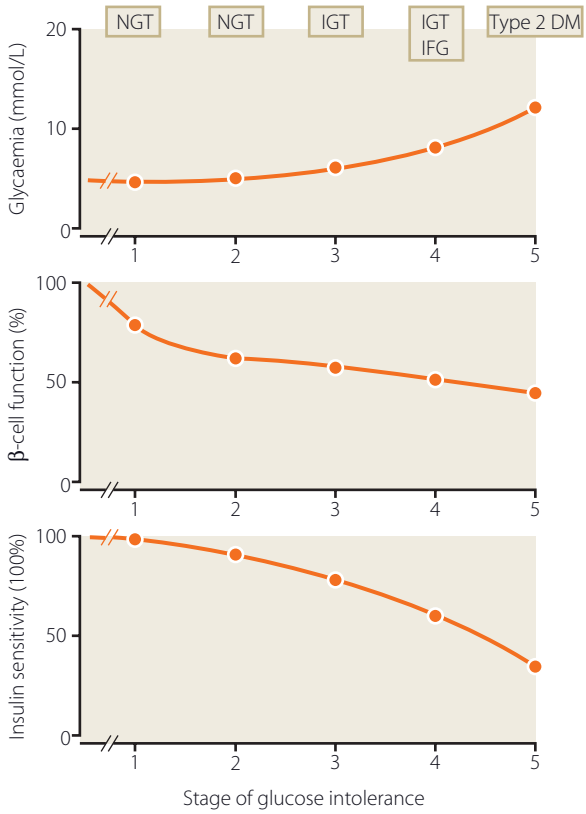

Figure 7.10 The stages of glucose tolerance and associated β cell function and insulin sensitivity, from normal glucose tolerance (NGT) through impaired glucose tolerance (IGT), with or without impaired fasting glucose (IFG), and finally type 2 diabetes mellitus (DM). Courtesy of Dr H Lewis Jones, Liverpool University, UK.

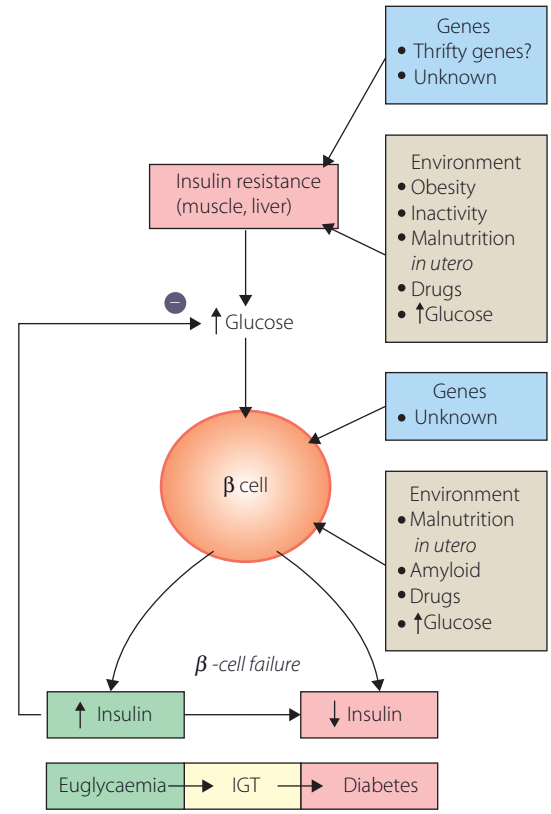

Figure 7.11 Pathogenesis of type 2 diabetes. Both genetic and environmental factors contribute to both insulin resistance and β cell failure.

as well as during the course of the disease. Usually, there is a decline in both insulin sensitivity and insulin secretion in patients who progress from IGT to diabetes and undoubtedly environmental and genetic factors contribute to this process (Figure 7.11).

KEY WEBSITES

- Diabetes atlas for prevalence/incidence: www.eatlas.idf.org
- HOMA calculator: www.dtu.ox.ac.uk

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Chapter 8

Other types of diabetes

KEY POINTS

- Other causes of diabetes can be of genetic, pancreatic, metabolic or endocrine origin.
- Of the genetic causes, maturity-onset diabetes of the young is probably the best characterised, but abnormalities in mitochondrial DNA and other genes are also important.
- Secondary pancreatic dysfunction due to pancreatitis, calculous disease, cystic fibrosis and haemochromatosis can also occur.
- Excess of counter-regulatory hormones such as glucocorticoids, growth hormone, catecholamines and glucagon is also associated with hyperglycaemia.

Maturity-onset diabetes of the young

Maturity-onset diabetes of the young (MODY) owes its name to a time when diabetes was defined by age of onset. The nomenclature has stuck, however, and MODY defines usually non-insulin dependent diabetes occurring before the age of 25 years and with a striking autosomal dominant inheritance. β cell dysfunction is usually present but in contrast to type 2 diabetes, obesity and insulin resistance are unusual. MODY accounts for about 1–2% of patients with diabetes in most white Europid populations. The diagnostic criteria which should suggest a diagnosis of MODY are listed in Box 8.1.

A recent survey of newly presenting non-type 1 diabetes in children <16 years of age in the UK revealed 17 cases of MODY, giving an incidence of 0.13/100,000 patient-years. This is almost certainly an underestimate as MODY 2 is often undetected for many years because it is largely asymptomatic.

The most common causes (accounting for >75% of cases) are mutations in nuclear transcription factors that control insulin production and secretion. They are listed in Table 8.1 together with associated clinical features. MODY 2 is a defect in the glucose-sensing glucokinase enzyme which means that insulin release occurs at higher than usual circulating blood glucose levels, usually leading to a raised fasting blood glucose. These patients are commonly detected either in pregnancy during screening for gestational diabetes, or as part of a health screening programme. MODY 2 needs no treatment, is largely benign and not associated with diabetes complications.

Box 8.1 Diagnostic criteria for MODY

- Early diagnosis of diabetes – usually before age 25 years in at least one family member
- Non-insulin requiring – shown by absence of insulin treatment 5 years after diagnosis or the demonstration of significant circulating C-peptide in a patient on insulin treatment
- Autosomal-dominant inheritance with vertical transmission through at least two generations (ideally three), with a similar phenotype in affected individuals

Other forms of MODY, however, are progressive and require treatment. Sulphonylureas are often initially effective but many patients ultimately need insulin. Because blood glucose levels are higher than MODY 2, these patients are prone to both micro- and macrovascular complications.

Pancreatic disease

Many pancreatic diseases can cause diabetes, but in total they account for <1% of all cases. Acute pancreatitis (commonly associated with alcoholism or gallstones) (Figure 8.1)

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Table 8.1 Different genetic aetiologies of MODY

Genetic basis	Clinical and biochemical features	Frequency
HNF4α (MODY1)	Low fasting triglycerides. Increased birthweight. Reduced apolipoproteins apo A11 and apo C111. Responds to sulphonylureas	3%
Glucokinase (MODY 2)	β cell response to high blood glucose impaired. Mild fasting hyperglycaemia, can present as gestational diabetes. Usually does not require treatment	14%
HNF1α (MODY 3)	Raised HDL cholesterol. Responds well to sulphonylureas	69%
IPF-1 (MODY 4)	Pancreatic agenesis with homozygous mutations	<1%
HNF1-β (MODY 5)	Renal abnormalities (cysts, dysplasia). Uterine and genital abnormalities. Short stature and low birthweight. Pancreatic atrophy	3%
NEURO D1 (MODY 6)	None described but probably reduced β cell formation	<1%
KLF 11 (MODY 7)	None described	<1%
CEL (MODY 8)	Pancreatic atrophy with exocrine deficiency	<1%
MODY X	Unknown and gene defect yet to be determined	10%

HNF, hepatocyte nuclear factor; IPF, insulin promotor factor; NEURO D1, neurogenic differentiating factor 1; KLF, Kruppel-like factor; CEL, carboxyl-ester-lipase.

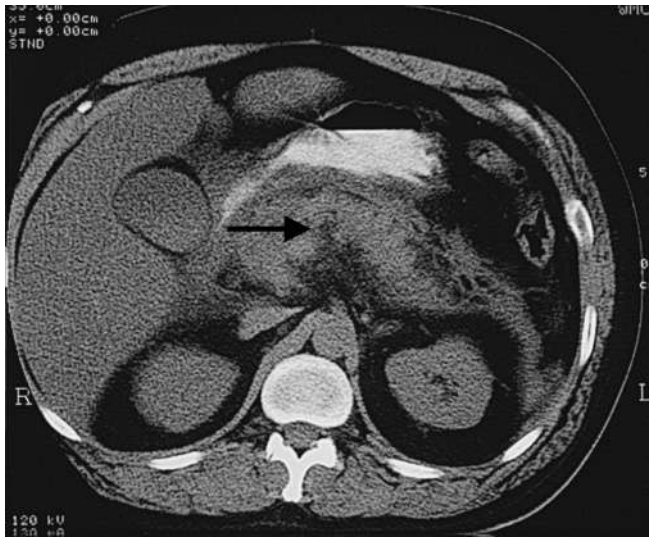
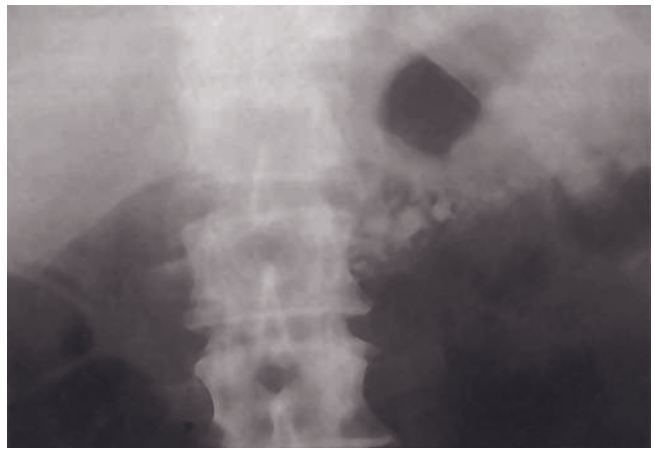


Figure 8.1 Acute pancreatitis. CT scan of the abdomen, showing marked oedema and swelling of the gland (arrow). Subsequently, a pancreatic pseudocyst developed.

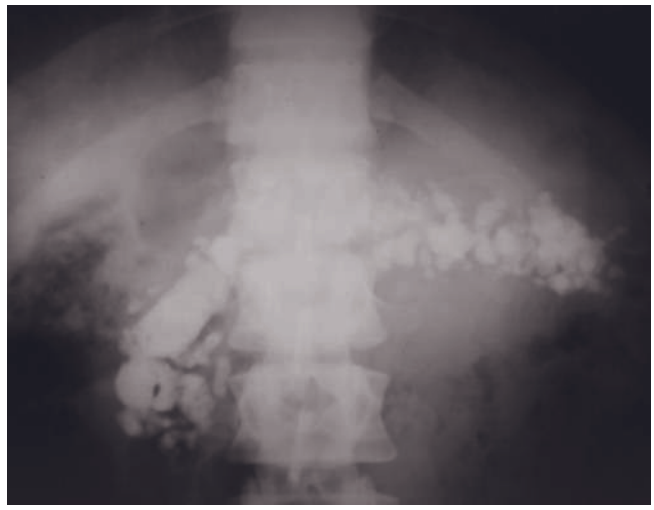
usually results in transient hyperglycaemia, but permanent diabetes occurs in up to 15% of patients.

Chronic pancreatitis, which is commonly caused by alcoholism in Western countries, leads to IGT or diabetes in 40–50% of cases. Intraductal protein plugs subsequently calcify as characteristic calcite stones, with cyst formation, inflammation and fibrosis. One-third require insulin, but ketoacidosis is rare. Many patients are extremely insulin sensitive, requiring small doses to prevent ketosis; higher doses are often associated with hypoglycaemia.

Tropical calcific pancreatitis is confined to India and developing nations, and results in diabetes in 90% of cases. Even in these countries, it accounts for only 1% of diabetes.



(a)



(b)

Figure 8.2 Pancreatic calculi, showing characteristic patterns in alcoholic chronic pancreatitis (a), and fibrocalculous pancreatic diabetes (b).

It is often associated with malnutrition, its aetiology is not understood and most patients require insulin.

Cystic fibrosis

This is a common autosomal recessive condition which results in abnormal chloride and water transport across epithelial membranes. Over 1500 mutations in the cystic fibrosis transmembrane conductance regulator gene have been described and they result in differing severities of the condition. Pancreatic and pulmonary disease predominate and better treatment has resulted in much improved survival. Diabetes results from β cell failure secondary to exocrine pancreatic damage. A recent UK survey of 8029 patients on the cystic fibrosis register studied from 1996 to 2005 revealed an annual incidence of diabetes of 3.5%, but this was 1–2% in the first decade of life, and 6–7% in the fourth. Female sex, more severe lung dysfunction, liver disease, exocrine pancreatic insufficiency, steroid use and severity of gene expression were all positively related to diabetes development.

The earliest biochemical abnormality tends to be postprandial hyperglycaemia. The majority of patients require insulin treatment.

Haemochromatosis

This is an autosomal recessive inborn error of metabolism, usually caused by a mutation in the haemochromatosis gene, HFE, on chromosome 6. The HFE protein is expressed on duodenal enterocytes and modulates iron uptake. Haemochromatosis is associated with increased iron absorption and tissue deposition, notably in the liver, pancreatic islets, skin and pituitary glands. The classic clinical triad is one of hepatic cirrhosis, glucose intolerance with insulin-requiring diabetes in 25%, and skin hyperpigmentation, which has led to the term 'bronzed diabetes'. Serum iron and ferritin concentrations are raised. Secondary haemochromatosis may occur in patients who undergo frequent blood transfusions, for example those with β-thalassaemia or other haemoglobinopathies.

Pancreatic cancer

Rarely, diabetes can be a presenting feature of pancreatic cancer. Usually, however, there are other features such as profound weight loss and back pain. The prognosis is very poor; insulin treatment is usual.

Neonatal diabetes

Permanent neonatal diabetes (PNDM) is caused by a mutation in the gene coding the Kir 6.2 and SUR1 sub units of the KATP channel on the β cell. This defect results in an inability to release insulin and consequent ketoacidosis, usually occurring before 6 months of age. Sulphonylureas close this channel by an ATP-independent route and are effective in over 50% of cases of PNDM.

Mitochrondrial diabetes

Mitochrondrial DNA is inherited maternally. A heteroplasmic mutation at position 3243 results in type 2 diabetes and sensorineural deafness. Other features include myopathy, pigmented retinopathy, cardiomyopathy and neurological abnormalities. Its most severe form comprises the MELAS syndrome (Myopathy, Encephalopathy, Lactic Acidosis and Stroke-like episodes). Prevalence studies suggest that Mt 3243 accounts for 1–2% of Japanese and 0.2–0.5% of European type 2 diabetes.

Wolfram syndrome

This rare autosomal recessive disorder was first described in 1938. The most common features are Diabetes Insipidus, type 1 Diabetes Mellitus, Optic Atrophy (Figure 8.3) and Deafness (DIDMOAD). There are many other features, notably psychiatric illness. A gene defect on chromosome 4 coding for a transmembrane protein (wolframmin) has been described, together with some mitochondrial DNA abnormalities (but not 3243). Diabetes usually occurs in the second decade and prevalence has been estimated as between 1 in 100,000 – 800,000 of the population.

Lipodystrophies

These are rare inherited conditions characterised by a partial or total absence of adipose tissue and have an associated

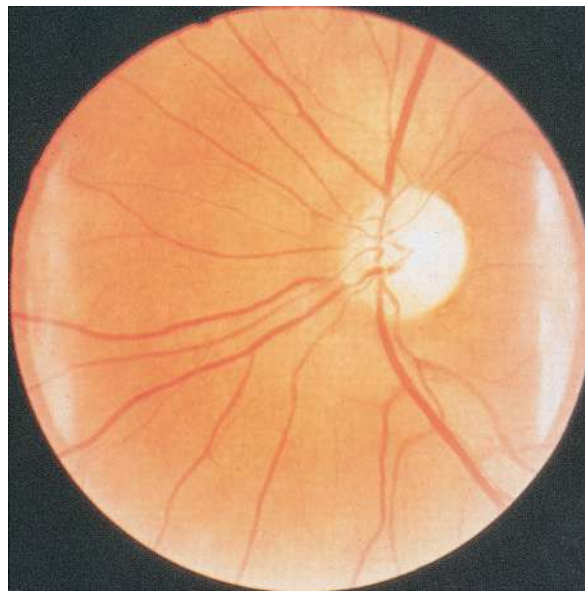


Figure 8.3 Optic atrophy (note white optic disc) in a patient with Wolfram's syndrome.

insulin resistance. In many cases, the genetic basis has been discovered, leading to new insights into the causes of insulin resistance. Patients with partial lipodystrophy (sometimes called the Kobberling–Dunnigan syndrome) have an abnormality in the LMNA (encoding lamin A/C which is a constituent of nuclear lamina) or PPAR γ gene. These changes result in defective adipocyte differentiation and/or cell death. Apart from type 2 diabetes, some of these patients also have problems with severe hypertriglyceridaemia, hepatic steatosis and pancreatitis.

Generalised lipoatrophy usually presents in early childhood and several different genetic causes have been described for this. Severe insulin resistance, diabetes and hyperlipidaemia are the norm.

Myotonic dystrophy

This autosomal dominant disorder is the most common adult form of muscular dystrophy (prevalence 1 in 8000 population) and is characterised by abnormal insulin secretion, insulin resistance and type 2 diabetes. The abnormal mutation is in the protein kinase gene on chromosome 19 and this may affect insulin receptor RNA and protein expression or perhaps calcium-dependent insulin release from the β cells.

Abnormalities of the insulin receptor or insulin molecule

Genetic abnormalities in the insulin receptor can give rise to rare but well-described syndromes characterised by severe insulin resistance. Clinically these patients have acanthosis nigricans (hyperpigmented velvety skin in the flexures of the neck, axillae or groin) (Figure 8.4) and hyperandrogenism.

Mutations of the gene encoding the α subunit of the insulin receptor can lead to leprechaunism or the less severe Rabson–Mendenhall syndrome (Figure 8.5).

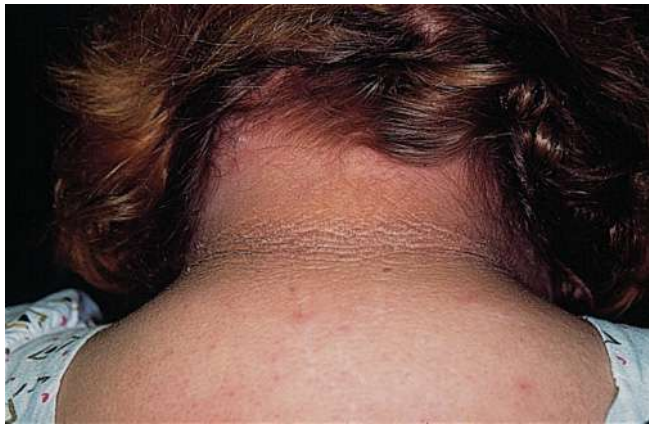


Figure 8.4 Acanthosis nigricans on the nape of the neck of a 26-year-old woman with the type A insulin resistance syndrome.

CASE HISTORY

A 22-year-old woman was referred to the medical obstetrics clinic for booking at 6 weeks gestation of her first pregnancy. She had had diabetes for 10 years, initially on sulphonylureas for 6 months but now on insulin. She had never been ketotic. Her control was fair (HbA_{1c} 8.2%). She had a strong family history of diabetes; her mother had type 2 diabetes and was now on insulin and currently an inpatient, having required a below-knee amputation for neuroischaemia and gangrene. Her brother was in the army and had recently been diagnosed with type 2 diabetes at the age of 19 years. Another brother aged 24 years had had diet-controlled diabetes for 6 years.

DNA testing revealed a mutation in the HNF1α gene, confirming a diagnosis of MODY 3. During pregnancy her glycaemic control improved dramatically but unfortunately she developed rapidly progressive retinopathy requiring laser photocoagulation. Postpartum she was tried again on sulphonylureas but her glycaemia worsened and she was recommenced on insulin. Three years later she has established nephropathy and has required vitreoretinal surgery.

Comment: This case shows many of the typical features of MODY as outlined in Box 8.1. Not all can be managed on oral agents and many are prone to severe complications. This woman and her family have received counselling from the UK Regional MODY Service.

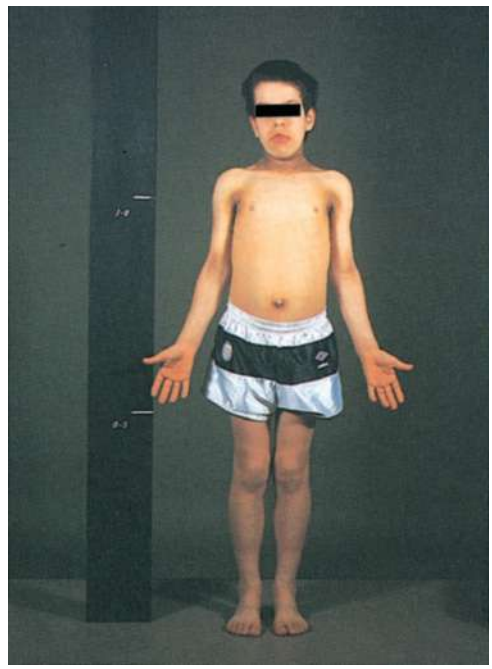


Figure 8.5 Rabson–Mendenhall syndrome in a 12-year-old boy, showing growth retardation, prominent acanthosis nigricans affecting the axillae, neck and antecubital fossae, and typical facies.

Type A insulin resistance affects mainly adolescent girls and shares many features with the polycystic ovary syndrome (Figure 8.4). In 25% of cases there is a mutation of the tyrosine kinase domain of the β subunit of the insulin receptor.

Rare mutations of the human preproinsulin gene can lead to abnormal levels of insulin precursors. Such patients are heterozygous (homozygosity would be incompatible with life), and develop diabetes in later life in response to other factors such as obesity.

Autoimmune insulin resistance

Type B insulin resistance is very rare and the result of circulating antibodies to the insulin receptor. There is a link with other autoimmune diseases and with these shares a female preponderance. Patients may have fluctuating hyper- and hypoglycaemia and are very difficult to treat.

Diabetes complicating other endocrine diseases

Several endocrine conditions are associated with diabetes mellitus. Cushing's syndrome is the result of glucocorticoid excess from any cause, including steroid drug induced, pituitary adenomas, adrenal tumours and ectopic ACTH production. Glucocorticoid excess results in central obesity which causes insulin resistance. This in turn stimulates hepatic gluconeogenesis, peripheral adipose tissue lipolysis and NEFA release. All of these inhibit peripheral glucose uptake and the net result is hyperglycaemia. Most patients have some degree of glucose intolerance, with overt diabetes in 10–20% of cases.

Acromegaly is a condition of growth hormone excess almost always arising from an anterior pituitary tumour. This causes glucose intolerance by inducing insulin resistance. Overt diabetes and impaired glucose tolerance each affect around one-third of patients with acromegaly. Glucose tolerance returns to normal with effective treatment and reduction of circulating growth hormone levels.

Phaeochromocytomas are tumours that arise from the chromaffin cells of the sympathetic nervous system, usually in the adrenal medulla but they can occur anywhere along the sympathetic nervous chain. They secrete excess catecholamines, and typically the clinical presentation is that of high blood pressure, headache, tachycardia and sweating, sometimes occurring in paroxysms. Up to 75% have evidence of glucose intolerance but this rarely needs treatment with insulin. Resolution is usual with removal of the tumour.

Glucagonomas are rare tumours of the islet α cells (Figure 8.6). They are slowly growing but often malignant. The most striking clinical features are weight loss and a characteristic rash, termed 'necrolytic migratory erythema' affecting skin flexures and the perineum. There is also a tendency to thromboembolism and neuropsychiatric disorders. Diabetes is common and the result of enhanced gluconeogenesis and glycogenolysis induced by high circulating glucagon levels. It usually resolves with removal of the tumour.

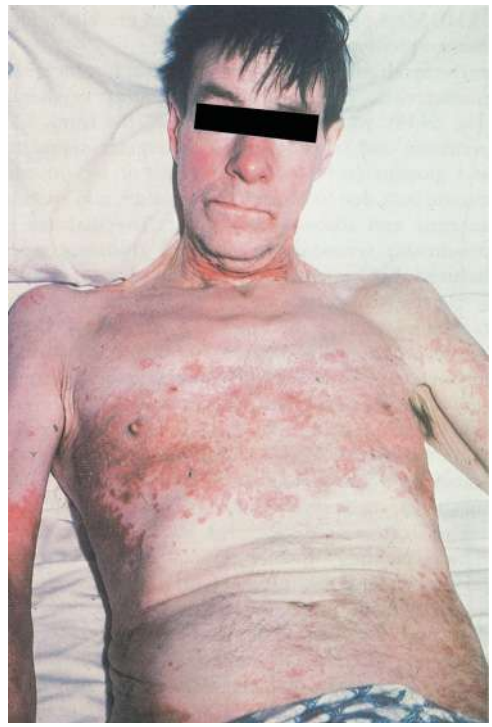


Figure 8.6 A patient with glucagonoma, showing characteristic necrolytic migratory erythema. Non-ketotic diabetes was controlled with low doses of insulin.

KEY WEBSITES

- Diagnostic criteria and details of how to request genetic tests for MODY in the UK: http://projects.exeter.ac.uk/diabetesgenes/mody/
- Information on monogeneic form of diabetes: http://diabetes.niddk.nih.gov/dm/pubs/mody/

FURTHER READING

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Part 2

Metabolic control and complications

Chapter 9

Diabetes control and its measurement

KEY POINTS

- Assessment of diabetic control is usually based upon estimates of glycaemia. Capillary blood glucose monitoring is relatively convenient and easy to perform and is a critical adjunct to modern insulin treatment regimens. Its role in diet- or tablet-controlled type 2 diabetes is less certain.
- Glycated haemoglobin concentrations estimate average blood glucose over the preceding 8–12 weeks. Its measurement is now subject to international standardisation and the units will change from percent to mmol/mol. Many national bodies are recommending the use of an HbA_{1c}-derived estimated average blood glucose.
- Continuous glucose monitoring systems are now widely available but their role in management has yet to be clarified.

'Diabetic control' defines the extent to which the metabolism in the person with diabetes differs from that in the person without diabetes. Measurement usually focuses on blood glucose: 'good' control implies maintenance of near-normal blood glucose concentrations throughout the day. However, many other metabolites are disordered in diabetes and some, such as ketone bodies, are now more easily measurable and clinically useful, particularly during acute illness or periods of poor blood glucose control (Figure 9.1).

In addition to blood and urine glucose concentrations, there are indicators of longer term glycaemic control over the preceding weeks using plasma glycated haemoglobin (HbA_{1c}) or fructosamine concentrations (Table 9.1).

Capillary blood glucose monitoring

Single blood glucose measurements are of little use as an assessment of overall control in type 1 diabetes because of unpredictable variations throughout the day and from day to day, although they are important in order to detect hypoglycaemia. In order to assess control more meaningfully, serial, timed blood glucose samples are usually needed. In diet- or stable tablet-controlled type 2 diabetes, although blood glucose levels are elevated they tend not to vary widely throughout the day. In these patients a fasting or random blood glucose relates reasonably well to mean blood glucose concentration and to glycated haemoglobin and is probably adequate.

Self-monitoring of capillary blood glucose by patients at home using special enzyme-impregnated reagent strips and a meter is now an integral part of modern diabetes management, especially for those who are on insulin therapy (Figure 9.2). Strips usually contain a combination of glucose oxidase and peroxidase. Colorimetric tests have now largely been superceded by newer electrochemically based strips which generate a current rather than a colour change. Meters vary in their need for standardisation, their memory and their ability to generate blood glucose profiles when connected to a computer. Some contain algorithms that can give advice on insulin dosage prior to a meal, depending on its carbohydrate content. Some meters require more blood than others. Meters are often made freely available by the manufacturers in the UK.

It is worth remembering that all meters tend to be less accurate at lower blood glucose values and usually have an upper limit of detection following which they read 'high'.

There are many devices which contain a spring-loaded lancet in order to obtain a capillary blood sample (Figure 9.2). This is usually obtained from the fingers; the sides of the fingertip are less sensitive than the pulp. A major reason for poor compliance and low frequency of testing is finger

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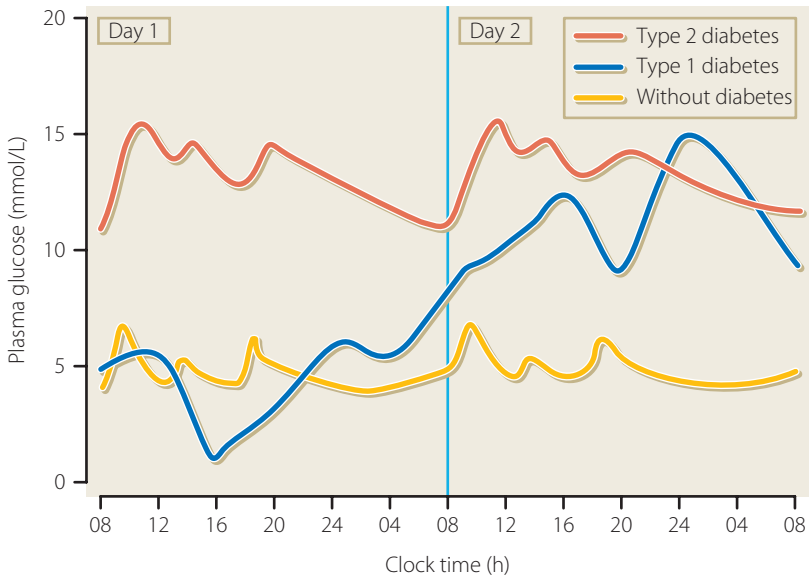

Figure 9.1 Variations in plasma glucose concentrations over 2 days in a person without diabetes, a patient with type 1 diabetes (wide swings in glucose levels with little day-to-day consistency) and a patient with type 2 diabetes (similar profile to a subject without diabetes, but at a higher level and with greater postprandial peaks; fairly consistent from day to day). From Pickup & Williams. *Textbook of Diabetes*, 3rd edition. Blackwell Publishing Ltd, 2003.

Table 9.1 Indicators of glycaemic control

Indicator	Main clinical use
Urine glucose	Poor index of BG, useful for surveillance in stable non-insulin treated type 2 diabetes
Blood glucose	
• Fasting	Correlates with mean daily BG and HbA_{1c} in type 2 diabetes
• Diurnal/circadian profiles	Self-monitoring of BG, hospital assessment
Glycated haemoglobin	Glycaemic control (mean) over preceding 1–3 months
Glycated serum protein, e.g. fructosamine	Glycaemic control (mean) over preceding 2 weeks
Urine and blood ketones	Insulin deficiency, warning of DKA, monitoring during intercurrent illness
Other blood metabolites/ hormones	
• Cholesterol (total and HDL) and triglyceride	Cardiovascular risk factors

BG, blood glucose; DKA, diabetic ketoacidosis; HbA_{1c}, glycated haemoglobin.

Figure 9.2 Meters and blood sampling devices for home blood glucose monitoring.

discomfort. In recent years strips require less blood and many devices have a depth adjustment. Some offer the option of testing at alternative sites to the fingers such as the forearm, abdomen, calf and thigh. However, there can be discrepancies in values measured at the finger and these sites, particularly during times of rapid change in blood glucose such as after meals or exercise.

Frequency of testing

Initial trials of home blood glucose monitoring were nothing short of revelatory for patients used to urine tests. Latterly, as part of clinical trials (e.g. Diabetes Control and Complications Trial (DCCT) in type 1 and UK Prospective Diabetes Study (UKPDS) in type 2) and structured educational programmes (e.g. Diet Adjustment For Normal Eating (DAFNE) in the UK), they have been shown to help patients achieve sustained long-term improvements in glycaemic control. However, systematic reviews have failed to confirm that home blood glucose monitoring alone results in significant glycaemic improvement. Many patients, though, prefer it to urinalysis, and it is hard to see how multiple daily insulin injection regimens can be used without it. NICE guidance uses it as an essential component of care management in type 1 diabetes with a frequency dependent upon the clinical circumstances, whereas for type 2 diabetes home blood glucose monitoring should be available for the indications

listed in Box 9.1. Both NICE type 1 and type 2 guidelines suggest that knowledge and skills of interpretation, and action based upon home blood glucose monitoring results should be assessed annually. The American Diabetes Association guidelines suggest three or more tests per day in type 1 diabetes on multiple daily injections or pump therapy and for pregnant women. Otherwise their advice is concordant with that from NICE.

Urine glucose monitoring

Glycosuria occurs when blood glucose levels exceed the renal threshold for glucose (usually 10 mmol/L–180 mg/dL). However, urine glucose testing is unreliable in the assessment of blood glucose control because renal threshold varies between and within patients (Box 9.2). Fluid intake can affect urine glucose concentrations and importantly, the result does not reflect blood glucose at the time of the test but over the duration that the urine has accumulated in the bladder. A negative urine test cannot distinguish between hypoglycaemia, normoglycaemia and modest hyperglycaemia.

However, urine testing still remains a reasonable option in stable type 2 diabetic patients treated with diet or oral agents, particularly in those who are unable or unwilling to perform blood glucose monitoring. It should be supplemented by glycated haemoglobin tests once or twice a year. It is worth noting that there is no benefit in terms of assessment of control in using freshly voided urine samples.

Box 9.1 Indications for capillary blood glucose monitoring in type 2 diabetes

- Insulin therapy
- On oral therapy with a risk of hypoglycaemia (e.g. sulphonylureas, glitinides)
- Assessment of response of glycaemia to changes in management or lifestyle
- Monitoring of glycaemia during intercurrent illness
- Avoidance of hypoglycaemia during driving, employment or physical activity

Box 9.2 Limitations of urine testing for glucose

- Variations in renal threshold, especially in pregnancy
- Variable result depending on urinary output/concentration
- No immediate relationship to current blood glucose
- Negative test unhelpful for detection of hypoglycaemia
- Visual reading of colour required
- Accuracy may not be as precise at urine concentrations around 5.5 mmol/L
- Some drugs may interfere with the test

Glycated haemoglobin

Haemoglobin A comprises over 90% of most adult haemoglobin and is variably glycated by the non-enzymatic attachment of sugars. HbA_{1c} comprises the major glycated component and has been shown in numerous studies to correlate with average blood glucose (Figure 9.3).

As the average life span of the red cell is 90–120 days, the percentage glycated haemoglobin is a reflection of glycaemic control over the 8–12 weeks preceding the test. However, the level of glycation is not linear with time – 50% of the value reflects the 30 days prior to the test, and only 10% the initial 30 days of red cell life.

It is important to remember this because if the life span of a patient's red cell is less than 90 days then theoretically the HbA_{1c} could be 50% of the expected value. Although high-pressure liquid chromatography (HPLC) methodology and the new International Federation for Clinical Chemistry and Laboratory Medicine (IFCC) standard have largely eliminated the confounding problems of aberrant haemoglobins, these can still cause falsely high values in some populations where they exist in high prevalence. It is important to check local assays in order to be aware of potential confounding factors.

The more common causes of misleading HbA_{1c} values are shown in Box 9.3. Carbamylation due to uraemia increases HbA_{1c} by 0.063% for every 1 mmol/L increase in plasma urea concentration so is of relatively minor consequence.

Of more importance is the observation that there is considerable interindividual variation in the correlation between average blood glucose and HbA_{1c}. Analysis of the DCCT

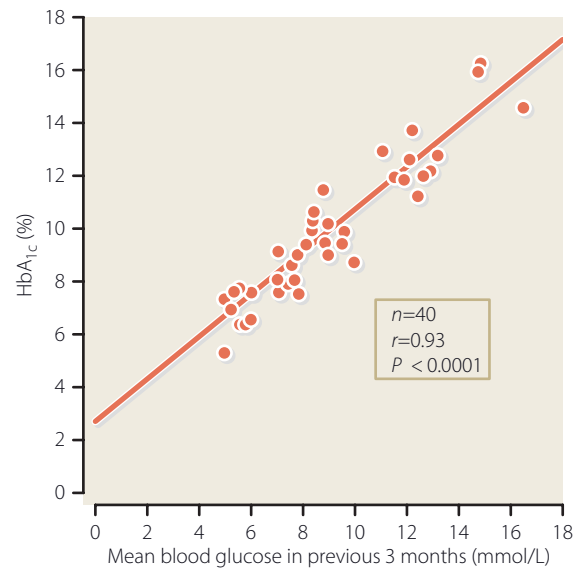

Figure 9.3 Correlation in patients with type 1 diabetes between blood glucose concentration over the preceding 3 months and glycated haemoglobin (HbA_{1c}) level. Adapted from Paisey. Diabetologia 1980; 19: 31–34.

Box 9.3 Potential reasons for a misleading HbA_{1c}

Altered red blood cell turnover
- Blood loss
- Haemolysis
- Haemoglobinopathies and red cell disorders
- Myelodysplasia
- Pregnancy
- Iron deficiency

Interference with assay
- Persistent foetal haemoglobin
- Haemoglobin variant
- Carbamylation

Timing
- Too frequent testing

Imprecision
- Differences of approximately 0.4% reflect ± 2 SD for most modern assays

Variability in red blood cell membrane transport (slow/rapid glycators)

cohort showed that for a mean blood glucose of 10 mmol/L based upon 7-point home blood glucose monitoring profiles over 24 hours, the HbA_{1c} can range from 6% to 10%. A concept of rapid and slow glycators has been proposed to explain this phenomenon, but it is more likely to reflect variable red blood cell membrane transport of glucose. Recent research has shown a range of approximately 0.7–1.0 for this property between individuals and could explain HbA_{1c} differences of 1.5–2.3% for any given mean blood glucose value. These observations question whether a single target HbA_{1c} should be used and perhaps explains some of the often observed discrepancy between recorded home blood glucose tests and glycated haemoglobin concentrations.

The recommended frequency of testing of HbA_{1c} is twice per year in stable patients and 4–6 times for those undergoing treatment changes.

Estimated average glucose (eAG)

Because many patients have difficulty relating HbA_{1c} to their results of home blood glucose monitoring, glycated haemoglobin levels are now often reported together with an estimated average blood glucose (eAG). The initial equations were based upon the DCCT cohort but the more recently used conversion has come from the A1c-Derived Average Glucose (ADAG) Trial (Table 9.2) utilising frequent capillary blood glucose measurements and continuous subcutaneous blood glucose monitoring. The strongly positive correlation

Table 9.2 Correlation of HbA_{1c} with average blood glucose (r = 0.92) (based upon ADAG Trial)

HbA_{1c} %	Mean blood glucose	
	mmol/L	mg/dL
6	7.0	126
7	8.6	154
8	10.2	183
9	11.8	212
10	13.4	240
11	14.9	269
12	16.5	298

(r = 0.92) has not been reproduced in children and there may also be differences in African Americans. There is ongoing debate about the utility of eAG and there are as yet no data to suggest it has clinical benefit over and above HbA_{1c}. It is also important to remember that eAG relates to plasma, not whole blood, so there will inevitably be some discrepancy with meter-based home blood glucose measurements. However, eAG could provide a more accessible estimate of control for patients and create the basis for more meaningful discussions about management.

Glucose variability

Attempts have been made to obtain an estimate of blood glucose variability based upon the ranges or standard deviations of the mean of profiles, or continuous subcutaneous monitoring. So far, these analyses using the DCCT and other data sets have not been shown to provide advantages over HbA_{1c} alone.

IFCC standard

Most HbA_{1c} assays have been standardised to that used in the DCCT as part of work carried out by the National Glycohaemoglobin Standardisation Programme (NGSP) in the USA. However, Sweden and Japan have each had their own standard. The IFCC has developed a new reference method that specifically measures only one molecular species of HbA_{1c} and relates this to total haemoglobin. This method is expensive and laborious and can only be used to standardise local assays. It reports in units of mmol/mol and the absolute values will be quite different from the current familiar percentage. However, it has been decided internationally that there should be a gradual switch to the IFCC standard with its new units. An international consensus agreed the following.
- HbA_{1c} results would be standardised worldwide to the new IFCC standard.
- The IFCC method is currently the only valid anchor that permits such standardisation.

Table 9.3 Guide to new values of HbA_{1c} (IFCC) and DCCT (NGSP) standardised assay

DCCT %	New IFCC method (mmol/mol)
4.0	20
5.0	31
6.0	42
6.5	48
7.0	53
7.5	58
8.0	64
9.0	75
10.0	86

Conversion equation IFCC HbA_{1c} (mmol/mol) = [DCCT HbA_{1c} (%) − 2.15] × 10.929.

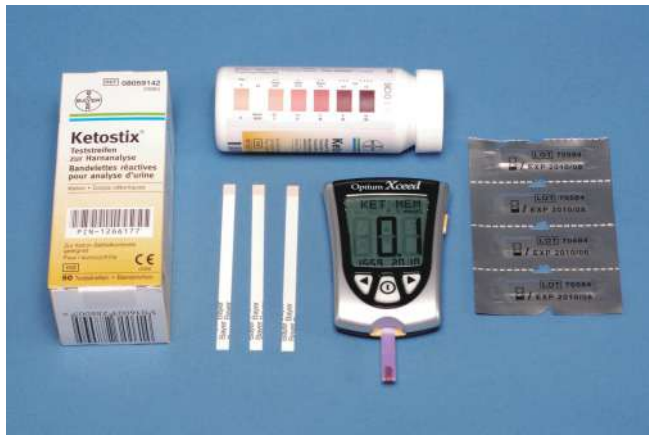

Figure 9.4 Urine testing strips (Ketostix®) and blood testing meter for ketones. NB urine tests detect acetoacetate; blood tests detect β hydroxybutyrate.

- HbA_{1c} would be reported in both new and old units for the time being (probably until 2011) together with eAG.
- Glycaemic goals should be expressed in IFCC units, NGSP percent and eAG mmol/L or mg/dL.

Fructosamine

Serum fructosamine is a measure of glycated serum protein, mostly albumin, and is an indicator of glycaemic control over the preceding 2–3 weeks (the lifetime of albumin). Colorimetric assays for fructosamine, which are now adapted for automated analysers, give a normal reference range of 205–285 µmol/L. Fructosamine generally correlates well with HbA_{1c}, except when control has changed recently.

It has potential advantages over HbA_{1c}, particularly in situations such as haemoglobinopathies or pregnancy when the glycated haemoglobin is hard to interpret. However, standardisation is difficult: uraemia, lipaemia, hyperbilirubinaemia and vitamin C use can affect the assay, and there may be an effect of high or low circulating blood proteins.

Urine and blood ketone measurements

Ketones can be measured in urine using a colorimetric test or in capillary blood using an electrochemical sensor similar to those now used for glucose (Figure 9.4).

Acetoacetate and acetone are detected by the urine test, β hydroxybutyrate by the blood sensors. As the ratio of β hydroxybutyrate to acetoacetate is around 6:1 in human ketoacidosis, the blood sensor offers a convenient way to monitor diabetes control during intercurrent illness or in situations that may predispose to ketoacidosis, such as pregnancy, or where it can occur relatively quickly, such as in patients using continuous subcutaneous insulin infusion pump therapy. As yet there is little evidence on which to form a consensus but blood ketone testing should be available in acute medical and obstetric assessment units as well as for inpatients with diabetes with intercurrent illnesses and perhaps as a means of monitoring response to treatment for diabetic ketoacidosis. Many units also provide their insulin pump users with blood ketone monitoring.

CASE HISTORY

A 24-year-old white Europid man developed classic symptoms of type 1 diabetes and was commenced upon insulin as a basal–bolus regimen. His initial HbA_{1c} was 9.7%. Six months later at regular review his home blood glucose monitoring showed excellent control with readings between 3.8 and 8.9 mmol/L (68–160 mg/dL) and he only reported occasional, mild, effort-related hypoglycaemia. However, his HbA_{1c} value came back the next day at 8.3%. He was contacted at home and an increase in his insulin of 2 units per dose was recommended and a repeat HbA_{1c} ordered for 6 weeks time.This was 8.1% and further insulin increase was instituted. Five days later he was admitted to hospital following a profound nocturnal hypoglycaemic episode during which he was found fitting.

Haemoglobin electrophoresis revealed the presence of HbS. The laboratory used an HbA_{1c} assay that was sensitive to HbS, particularly at lower HbA_{1c} concentrations. On direct questioning, it transpired that his parents were from the Mediterranean area.

Comment: Several learning points emerge. HbS can occur in non-African populations, so a family history in all people with diabetes is important. Secondly, it is important to know the limitations of the assays used by local laboratories. Lastly, in the presence of discrepancies between home monitoring and laboratory, do not always assume the patient's tests are incorrect.

Continuous glucose monitoring systems

A major objective of diabetes research has been to provide continuous real-time monitoring of blood glucose so that insulin therapy can be matched to glycaemia. Ideally such a system would be linked to an insulin delivery device automatically, thus 'closing the loop'. In the last decade, huge strides have been made to achieve this goal but the current systems based upon capillary blood glucose monitoring technology using electron transfer do have their drawbacks.

Firstly, they are based upon measures of interstitial fluid, not blood glucose (Figure 9.5). This inevitably means that there is a delay or lag between detecting changes in blood glucose (mean delay 6.7 minutes, range 2–45 minutes). This lag can be affected by level of blood glucose, exercise, food intake and blood flow to the interstitial sampling site. Accuracy of the current devices tends to be less good at lower blood glucose levels. Secondly, such systems are by definition invasive as they require subcutaneous sensor insertion, usually on the abdominal wall. Thirdly, linkage to subcutaneous insulin infusion pumps introduces a further time lag in responsiveness (that of insulin absorption from the subcutaneous site). Finally, they need intermittent calibration with capillary blood glucose tests. The technology is also expensive and requires replacement every 5 days or so.

Clinical trials have, however, shown modest improvements of around 0.5% HbA_{1c} at 6 months in young adults >25 years of age; children and adolescents in the same study showed no significant benefit. In a separate study, adults with an HbA_{1c} <7% had a significant reduction in the time spent in biochemical hypoglycaemia when randomised to continuous glucose monitoring compared to intermittent capillary blood tests. However, there was no difference in

LANDMARK CLINICAL TRIAL

Koenig RJ, Peterson CM, Jones RL, Saudek C, Lehrman M, Cerami A. Correlation of glucose regulation and hemoglobin A1c in diabetes mellitus. N Engl J Med 1976; 295: 417–420.

Although abnormal haemoglobin electrophoresis had been described in diabetes since the 1950s, this was the first correlation between change in glycaemia and change in HbA_{1c}. Five patients with a fasting blood glucose ranging from 280 to 450 mg/dL (15.6–25.0 mmol/L) were hospitalized and their values corrected to 70–100 mg/dL (3.9–5.6 mmol/L). HbA_{1c} was 6.8–12.1% initially, falling to 4.2–7.6% after glycaemic improvement. Later, much larger studies confirmed the linear relationship but the author's conclusion was spot on: 'Periodic monitoring of hemoglobin A_{1c} levels provides a useful way of documenting the degree of control of glucose metabolism in diabetic patients …'.

KEY WEBSITES

- National Glycohemoglobin Support Program. Excellent information on HbA_{1c}, eAG and the new IFCC standards: www.ngsp.org
- National Institute for Health and Clinical Excellence (NICE). All UK guidelines available on this site (Type 1 Clinical Guidance CG15, Type 2 CG 66): www.nice.org.uk
- Diabetes UK. Guidance on monitoring: www.diabetes.org.uk
- American Diabetes Association. Standards of care published in *Diabetes Care* as a supplement each January: http://professional.diabetes.org/
- SIGN Guidelines: www.SIGN.ac.uk

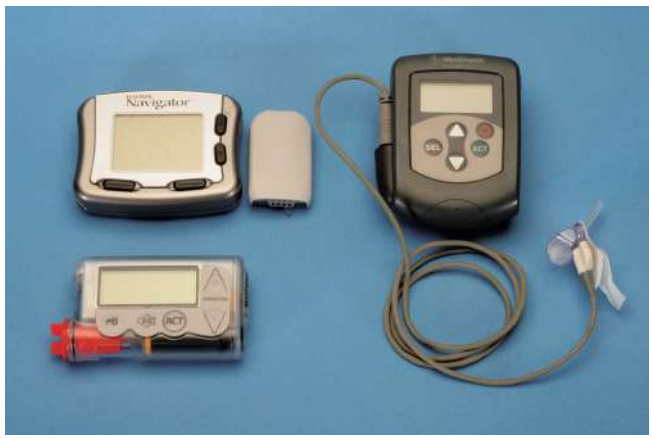

Figure 9.5 Examples of continuous interstitial glucose monitoring devices. Also shown is the Medtronic Veo subcutaneous insulin infusion pump with built in glucose sensor. Systems comprise a small subcutaneous sensor that communicates with a separate meter and screen or pump.

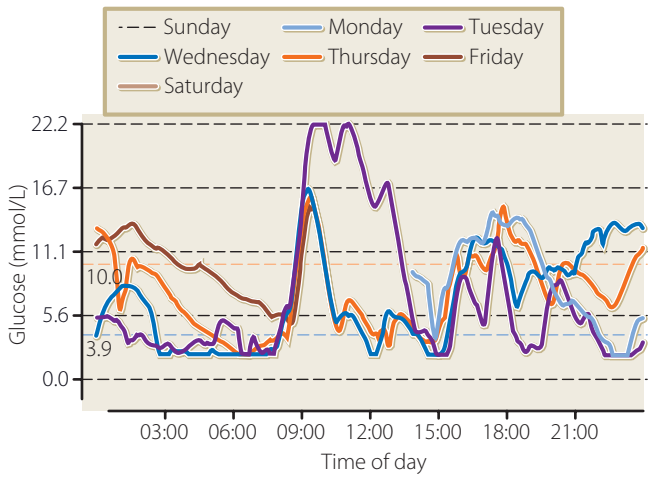

Figure 9.6 Sample print out of continuous glucose monitoring using Medtronic Gold sensor. Note the tendency for hypoglycaemia in early morning with large post prandial rise post breakfast and a smaller one post supper (1800 hours). Reduction in overnight insulin and increase in meal time boluses was initiated.

HbA_{1c} in this study. These trials have used open loop algorithms and results were highly dependent upon patient motivation, training and education. Those who used the devices more consistently and made regular adjustments to their insulin dose obtained most benefit.

Closed loop devices and truly non-invasive glucose monitoring systems are under intense research and there are certain to be rapid developments in the near future. Meanwhile, the existing systems based upon interstitial glucose sensing probably have a role for patients struggling with glycaemic control (particularly those with unpredictable and severe hypoglycaemia), who are either on an insulin pump or multiple daily injections, and who are looked after by specialist teams who are well versed in the technology (Figure 9.6).

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Chapter
10

Management of type 1 diabetes

KEY POINTS

- The objective of insulin treatment is to try and reproduce the physiological pattern of insulin production using subcutaneous injections. This usually entails multiple daily injections of short-, intermediate- or long-acting insulins, together with regular capillary blood glucose testing.
- There is no clear evidence-based superiority of the newer short- or long-acting insulin analogues in terms of glycaemic control.
- Continuous subcutaneous insulin infusion can improve glycaemia and reduce hypoglycaemia in patients struggling on conventional therapy.
- Islet transplantation (where it is available) could be considered for patients with severe disabling hypoglycaemia.

Modern management of type 1 diabetes comprises a package of measures including multiple daily injections for a more physiological insulin replacement; assessment of glycaemic control using blood glucose self-monitoring as well as clinic tests such as glycated haemoglobin (HbA_{1c}); insulin dosage adjustment according to diet and exercise; a healthy diet and carbohydrate counting; and intensive diabetes education. In the Diabetes Control and Complications Trial (DCCT) 1441 patients were randomised to either intensive treatment (including all the elements listed above plus regular contact with a named healthcare professional) or to conventional therapy with one or two injections of insulin a day. Significant improvements in HbA_{1c} and a reduction in microvascular complications were seen in the intensively managed group. In practice, it is difficult to sustain the level of intensive healthcare professional support in the DCCT. In the UK the Diet Adjustment For Normal Eating (DAFNE) Programme comprising a 5-day intensive education programme has been shown to significantly reduce HbA_{1c} at 6 and 12 months. Educational aspects of management such as these will be dealt with later (see Chapter 31).

Insulin replacement

The objective of insulin replacement is to mimic the insulin secretion pattern in the person without diabetes with multiple subcutaneous injections. In the person without diabetes, there is normally a rapid increase in plasma insulin after meals, triggered by glucose absorption into the bloodstream. This surge in insulin limits postprandial glycaemia by stimulating hepatic and peripheral glucose uptake. During fasting and between meals, insulin measurements drop to much lower levels (often called basal or steady state) which are sufficient to maintain blood glucose in the range 3.5–5.5 mmol/L. Even after a prolonged fast, it is possible to detect circulating insulin.

Basal insulin levels tend to be highest in the early morning, probably in response to the well-described surge in growth hormone and cortisol at that time of day (Figure 10.1). These counter-regulatory hormones tend to increase blood glucose and this has been termed the 'dawn phenomenon'.

For practical reasons, insulin is usually injected subcutaneously and regimens comprise short-acting (soluble, regular or analogue) insulin to simulate the normal mealtime surge, together with a longer acting insulin which is used to provide the background or basal concentration. This combination is called the 'basal-bolus' regimen or multiple daily injection (MDI) therapy (Figure 10.2).

Other routes of insulin administration such as intravenous infusion or intramuscular injection have not proven practical in the long term and despite intensive research, oral insulin preparations are not yet available.

Until the 1980s, insulin was extracted and purified from animal sources. Porcine and bovine insulins are still available

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but have been largely replaced by human sequence insulin produced from genetically engineered bacteria. Recently modified human insulin molecules (so-called analogues) have now been developed (Figure 10.3).

Essentially insulins can be divided up into short-acting and intermediate- to long-acting preparations and those currently available in the UK are listed in Table 10.1.

Short-acting insulins

Achieving normoglycaemia with insulin injections is frustrated by several pharmacological problems. Firstly, subcutaneously injected insulin is absorbed into the peripheral rather than the portal bloodstream; thus, effective insulinisation of the liver can be achieved only at the expense of systemic hyperinsulinaemia. Moreover, conventional short-acting insulins are absorbed too slowly to mimic precisely the normal prandial peaks, and must therefore be injected about 30 minutes before the meal so that the peak of blood insulin corresponds with postprandial glycaemia. Human insulin is absorbed more quickly and can be injected closer to eating (Figure 10.4). It is therefore much more convenient than animal insulins, although a systematic review has failed to demonstrate significant improvements in overall glycaemic control. Some patients who were well controlled on animal insulin felt less well when switched to the human preparation. Many complained that their warning signs of hypoglycaemia were lost. However, carefully controlled studies have failed to show significant differences in the glycaemic

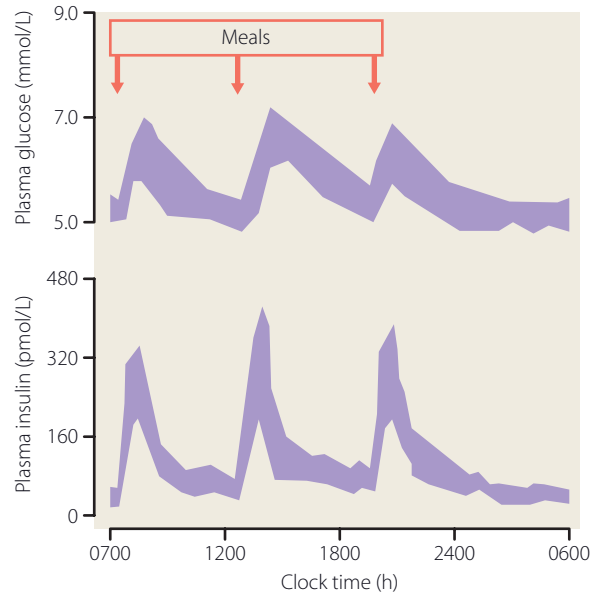

Figure 10.1 Normal plasma glucose and insulin profiles. Shaded areas represent mean ± 2 SD. From Owens et al. Lancet 2001; 358: 739–746.

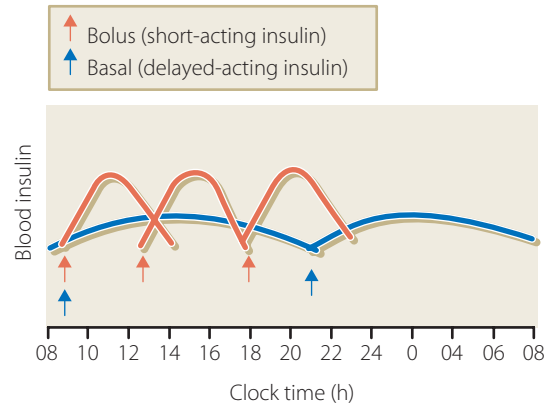

Figure 10.2 Basal-bolus insulin regimen.

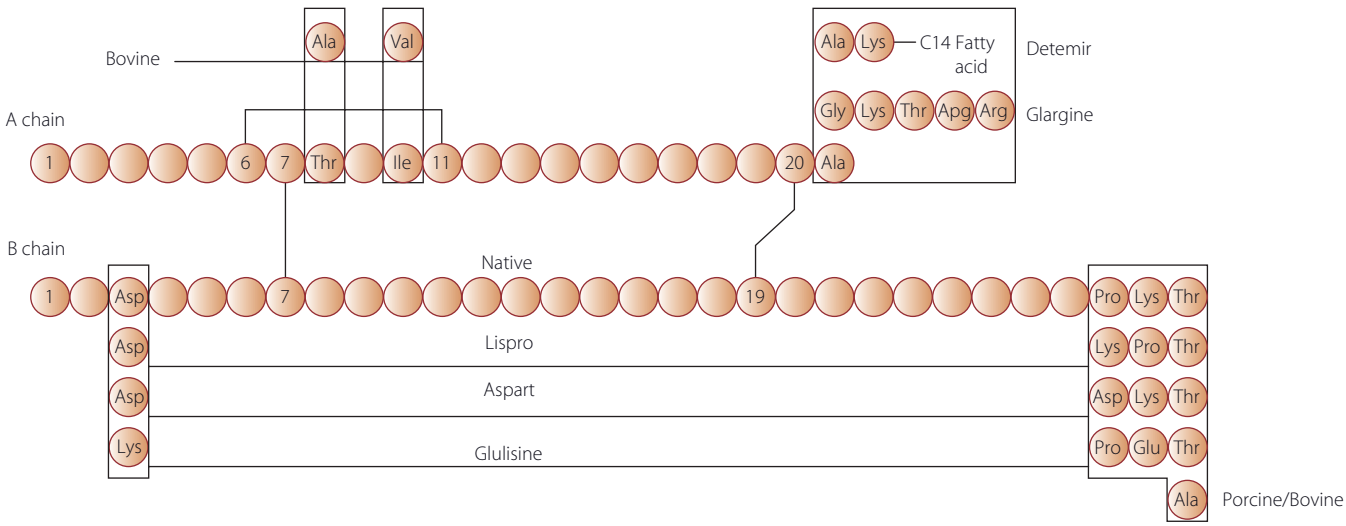

Figure 10.3 Schematic amino acid sequence of native human insulin; porcine and bovine insulin; the short-acting insulin analogues lispro, aspart and glulisine; and the long-acting analogues glargine and detemir. ALA, alanine; ARG, arginine; PRO, proline; LYS, lysine; ASP, aspartate; THR, threonine; GLU, glutamate; GLY, glycine; ILE, isoleucine; VAL, valine.

Table 10.1 Types of insulins and their preparations available in the UK in 2009 together with their indicative cost

Duration	Origin	Type	10 mL vial	5 × 3 mL cartridge	Disposable pen × 5
Short					
4–8 hours	Animal – bovine	Neutral	£18.48	£27.72	
	– porcine	Neutral	£16.80	£25.20	
	Human – genetic	Actrapid	£7.48		
		Humulin S	£16.50	£28.12	
		Insuman Rapid		£23.43	£27.90
3–4.5 hours	Analogue	Aspart	£17.27	£29.43	£32.00
		Lispro	£17.28	£29.46	£29.46
		Glulisine	£17.27	£29.45	Optiset £29.45 Solostar £25.00
Intermediate					
8–12 hours	Animal – bovine	NPH	£18.48	£27.72	
	– porcine	NPH	£16.80	£25.20	
	Human Insulatard	NPH	£7.48	£20.08	£20.40
	Humulin I	NPH	£16.50	£29.94	£29.94
	Insuman Basal	NPH	5 mL £5.84	£23.45	£27.90
Long 8–14 hours	Animal – bovine	Lente	£18.48		
	– bovine	Protamine zinc	£18.48		
16–24 hours	Analogues	Detemir		£39.00	Flexpen £39.00 Innolet £44.85
		Glargine	£26.00	£39.00	Optiset £39.00 Solostar £42.00
Biphasic	Animal – porcine	30/70 (30% neutral, 70% NPH)	£16.80	£25.20	
	Human	Mixtard 30 (30% Actrapid, 70% Insulatard)	£7.48	£20.08	£19.87
		Humulin M3 (30% Humulin S, 70% Humulin I)	£16.50	£28.12	
		Insuman Comb 15 (15% Insuman rapid, 85% Insuman basal)			£27.90
		Insuman Comb 25 (25% Insuman rapid, 75% Insuman basal)	5 mL £5.84	£23.43	£27.90
		Insuman Comb 50 (50% Insuman Rapid, 50% Insuman Basal)		£23.43	£27.90
	Analogue	Novomix 30 (30% Aspart, 70% Aspart NPH)		£29.43	£32.00
		Humalog Mix 25 (25% Lispro, 75% Lispro NPH)		£29.46	£30.98
		Humalog Mix 50 (50% Lispro, 50% Lispro NPH)		£29.46	£30.98

NPH, neutral protamine Hagedorn (Isophane).

response to the two insulins and under blinded conditions patients were unable to distinguish between them.

The delay in absorption of subcutaneous insulin is a result of the formation of hexamers following injection (Figure 10.4). The hexamers need to dissociate into dimers or monomers so that insulin can be absorbed into the bloodstream.

In order to get around this problem, the insulin molecule has been modified using genetic and protein engineering techniques. These changes in amino acid sequence reduce the tendency to self-associate into hexamers and therefore speeds absorption. The first short-acting analogue to be marketed was lispro closely followed by aspart and glulisine (see Figure 10.3). Their peak action occurs 1–2 hours after injection (compared to 2–4 hours for conventional soluble and slightly less for unmodified human) and they can therefore be injected at the start or even during a meal. Although this is highly convenient for patients, systematic reviews of short-acting analogues versus unmodified human insulin have failed to demonstrate consistent advantages in terms of glycaemic control, although a fairly consistent pattern of reduced nocturnal hypoglycaemia, lower postprandial and higher preprandial blood glucose levels is seen.

Intermediate- and long-acting insulins

There are three main types of intermediate- and long-acting insulins. Isophane (or NPH, neutral protamine Hagedorn, named after its inventor) is an insoluble suspension of insulin made by combining it with the highly basic protein

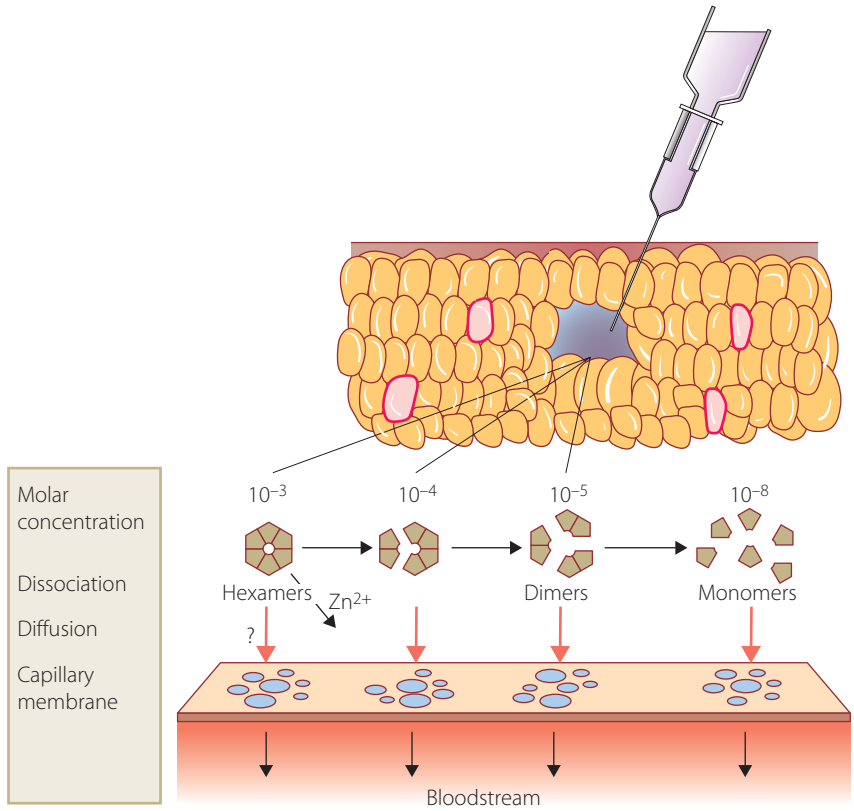

Figure 10.4 Putative events in the subcutaneous tissue after subcutaneous injection of regular human insulin.

protamine, together with zinc, at a neutral pH. NPH insulin can be derived from animal, unmodified human or analogue insulins. Lente insulins are made by adding excess zinc to soluble insulin. There is also a combination of protamine and zinc suspended insulin available. NPH and lente insulins have a duration of action of between 8 and 16 hours after injection. So-called ultralente insulins are no longer available in the UK.

Because of the duration of action of NPH insulin there was a tendency for patients to develop nocturnal hypoglycaemia. As a result of this, two longer-acting insulin analogues have been developed which have a flatter absorption profile. The first of these (insulin glargine) was made by adding two arginine molecules to the C-terminal of the B chain and substituting a glycine for alanine at A21 (Figure 10.3). This modification altered the isoelectric point (which is when proteins are least soluble) from pH 5.4 to 7.4. This means that at a slightly acidic pH in the vial, glargine is soluble and clear (in contrast with NPH and lente which are both cloudy solutions) but after subcutaneous injection it precipitates as microcrystals and is gradually absorbed (Figure 10.5). Detemir is human insulin where the C-terminal amino acid on the B chain is substituted with a C14 fatty acid (see Figure 10.3). This binds to albumin which slows absorption and also prolongs circulation.

The duration of action of both of these analogues is longer than that of NPH and lente (Figure 10.5), but despite this no consistent benefit in terms of HbA_{1c} has been found. However, fasting glycaemia and rates of nocturnal hypoglycaemia tend to be reduced and current NICE guidance suggests that insulin glargine be considered instead of NPH if there are problems with night-time glycaemic control.

Premixed or biphasic insulins

A number of these are available (see Table 10.1) but those most commonly in use in UK have 30% human soluble and 70% human NPH although the newer analogues come in 25:75, 30:70 or 50:50 mixtures. These fixed rate combinations give less flexibility than MDI. Moreover, the early evening injection of the NPH component may not be adequate to provide overnight glycaemic control, particularly if the patient exhibits the dawn phenomenon.

Injection sites

The recommended injection sites are the subcutaneous tissue of the abdomen, upper outer thighs, upper outer arms, and buttocks (Figure 10.6). Disposable plastic syringes with a fine needle can be reused for several injections, although these have been largely superseded in the UK by insulin pens (see below). There is no need to pinch up the

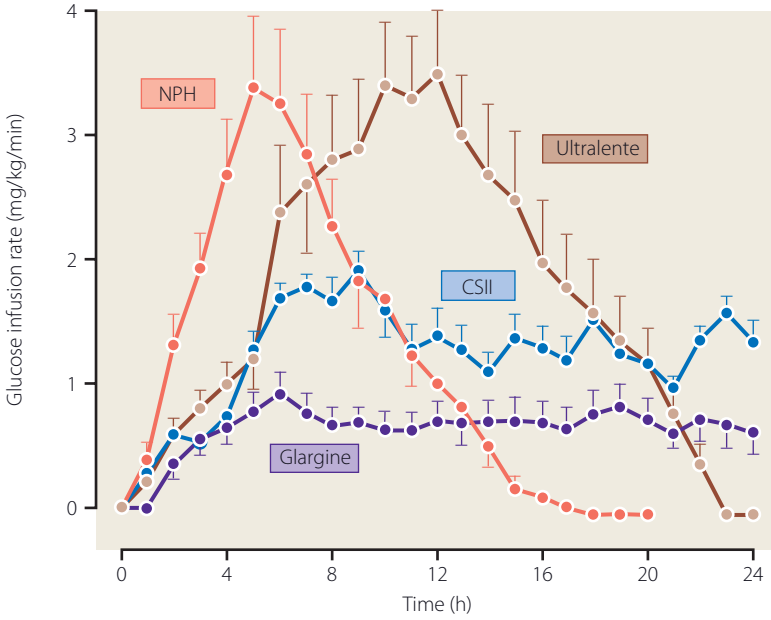

Figure 10.5 Action profiles of neutral protamine Hagedorn (NPH), ultralente, glargine and continuous subcutaneous insulin infusion (CSII). From Lepore et al. Diabetes 2000;49:2142–2148.

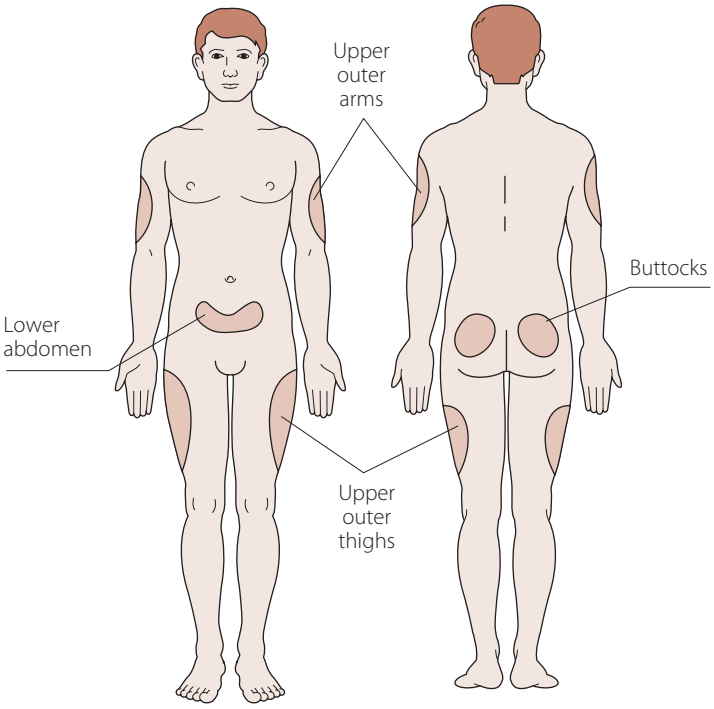

Figure 10.6 Suitable sites for subcutaneous insulin injection.

skin prior to injection (in fact, this probably causes more discomfort). Care should be taken to avoid inadvertent intramuscular injection which can be a particular risk in the upper arms and legs of slim people or children.

Insulin absorption is fastest in the abdomen and slowest in the thigh and buttocks although it can be accelerated from these sites by exercise or taking a sauna or warm bath. Short-acting insulin is usually given into the abdomen, which is less affected by exercise, and longer acting insulins into the thigh.

Repeated injection into the same subcutaneous site may, in the long term, give rise to an accumulation of fat (lipohypertrophy) because of the local trophic action of insulin (Figure 10.7). Lipohypertrophy can be unsightly and can affect insulin absorption. In order to prevent lipohypertrophy, patients should be advised to rotate the site of injection.

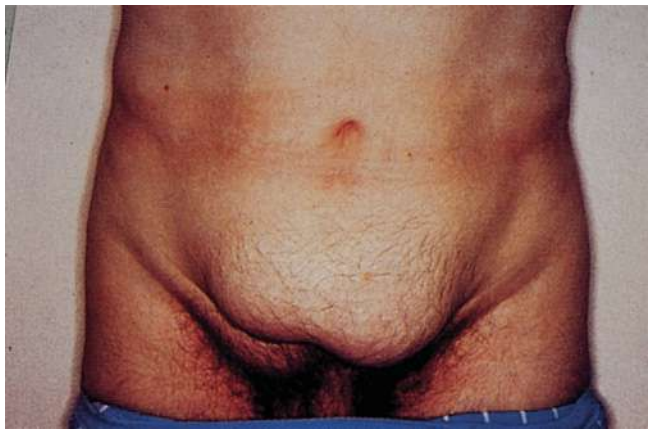

Figure 10.7 Lipohypertrophy at a habitually used insulin injection site.

Figure 10.8 A selection of insulin pens available in the UK. Also shown are two cartridges and pen needles.

Table 10.2 Available insulin pens and their cost in the UK

Device	Dose (units)	Max. dose (units)	Insulin	Cost
Autopen 24	1 or 2	21 or 42	Glargine, Glulisine, Insuman	£15.55
Autopen classic	1 or 2	21 or 42	Animal, Humalog, Lispro, Humulin	£15.79
Humapen Luxura	1	60	Humalogs, Lispro, Humulin S	£26.36
Humapen HD	0.5	30	Humalogs, Lispro, Humulin S	£26.36
Novopen Junior/Demi	0.5	35	Aspart, Insulatard, Detemir, Mixtard	£25.60/£25.03
Novopen 4	1	60	Aspart, Insulatard, Detemir, Mixtard, Novomix	£25.60/£25.03
Opticlick	1	80	Glargine, Glulisine	£20.13
Optipen	1	60	Insuman	£22.00

It is important to remember that lipohypertrophic areas become relatively painless and are thus often favoured by patients who may inadvertently make the problem worse. For this reason inspection of injection sites is an important part of the annual patient review.

Insulin pens

Pen needle devices have become a popular option for insulin therapy in recent years (Figure 10.8). There are at least eight currently available in the UK (Table 10.2). Whilst they differ slightly, the principles are the same. Insulin is contained in a 3 mL cartridge in the barrel of the pen. There is an adjustable dosage device which drives a plunger in the cartridge and insulin is delivered through a removable fine needle which screws on at the opposite end of the pen. The advantages of pens are their convenience, the needles are often finer than conventional syringes and needles, and they tend to keep their sharpness longer because they are not being continually inserted through the rubber bung of a 10 mL vial. It is also possible to get pen needles of different lengths which means it is easier to avoid inadvertent intramuscular injection.

Intensive insulin therapy

Multiple daily injections (MDI) of insulin are only part of intensive or optimised treatment. The other components are patient education, dietary advice and carbohydrate counting and continual insulin adjustment. Moreover, patients need to be in a systematic programme of care and medical surveillance. These aspects will be covered later (see Chapter 31).

Multiple daily injections consist of short-acting, regular or rapid-acting analogue insulins given with meals at a variable dose, depending on the carbohydrate content. Patients are encouraged to monitor carefully and learn by checking the postprandial blood glucose 1½–2 hours after meals to see if their first estimation was correct.

Isophane or lente insulins or long-acting analogues can be given at night or twice daily. As previously mentioned, insulin sensitivity decreases in the few hours before breakfast because of surges of growth hormone and cortisol during sleep. The effect of this, together with the waning of the previous evening's insulin dose, results in fasting hyperglycaemia (the 'dawn phenomenon') (Figure 10.9). This

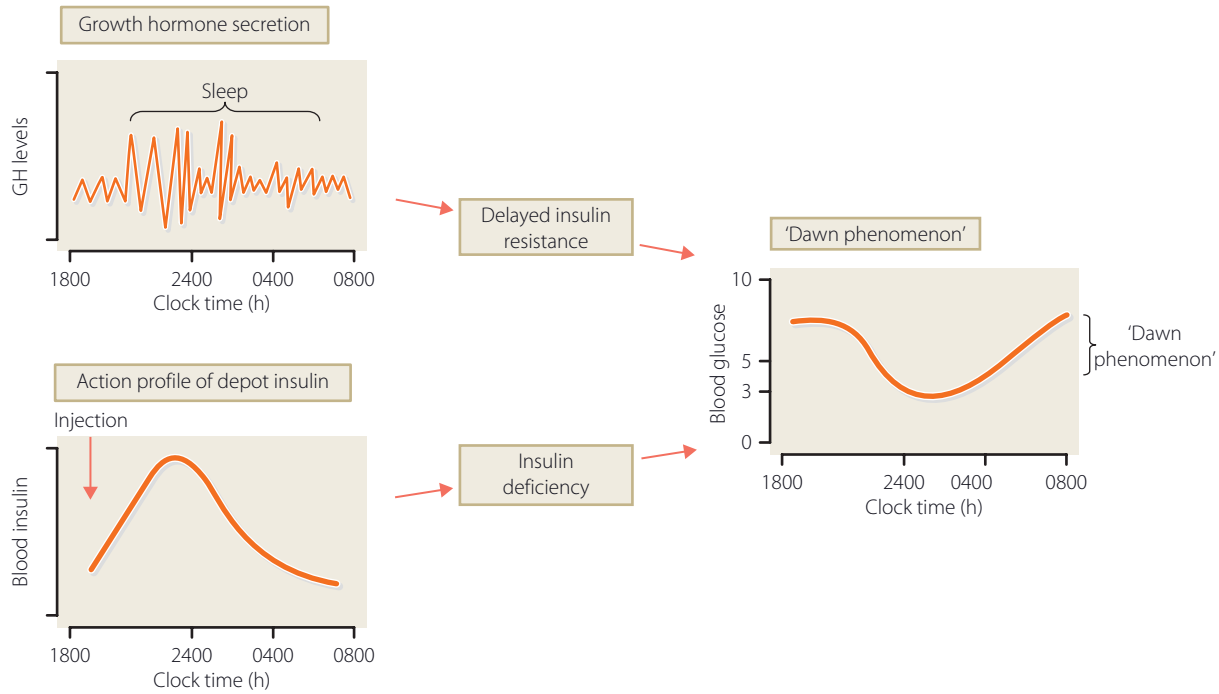

Figure 10.9 The 'dawn phenomenon'. A prebreakfast rise in blood glucose levels occurs because the growth hormone (GH) surges during sleep induce delayed insulin resistance. This effect can be accentuated if insulin levels run out overnight (e.g. from intermediate-acting insulin injected in the early evening).

Table 10.3 Target levels for glycaemia for type 1 diabetes

	Diabetes UK	NICE	American Diabetes Association
Pre-meal/fasting	Adult 3.5–5.5 mmol/L	<8.0 mmol/L	3.9–7.2 mmol/L (70–130 mg/dL)
	Child 4.0–8.0 mmol/L	4.0–8.0 mmol/L	6–12 years 5.0–10.0 mmol/L (90–180 mg/dL) 13–19 years 5.0–7.2 mmol/L (90–130 mg/dL)
Post meal (1.5–2.0 hours)	Adult <8.0 mmol/L	<10.0 mmol/L	<10.0 mmol/L (<180 mg/dL)
	Child <10.0 mmol/L	<10.0 mmol/L	None
Bedtime/overnight	Child: none	None	6–12 years 5.6–10.0 mmol/L (100–180 mg/dL) 13–19 years 5.0–8.3 mmol/L (90–150 mg/dL)
HbA_{1c}	Adult <6.5% Child <6.5%	<7.5% (<6.5% if complications) <7.5%	<7.0% 6–12 years <8.0% 13–19 years <7.5%

problem can often be countered by moving the longer-acting insulin injection to bedtime.

Deciding which insulins to use can often be a case of trial and error based upon the patient's lifestyle and needs, employment, etc. Current evidence would suggest that NPH plus a short-acting human insulin (or possibly an analogue) is the logical starting point.

Glycaemic targets

Glycaemic targets published in the UK and the USA are shown in Table 10.3. These will need to be discussed and agreed with individual patients. For example, those with existing microvascular complications may need a lower target HbA_{1c} (NICE recommends <6.5%) whereas patients suffering from regular hypoglycaemia (particularly if their

warnings are blunted) may need more relaxed targets. Recently Diabetes UK has come up with the phrase '4 is the floor', suggesting a minimum blood glucose of 4 mmol/L.

Continuous subcutaneous insulin infusion

Continuous insulin delivery systems can be either 'open loop', in which insulin infusion rates are preselected by the patient, or 'closed loop' in which there is continuous glucose sensing and a computer-regulated feedback control of insulin delivery (the so-called 'artificial pancreas').

Continuous subcutaneous insulin infusion (CSII) was developed over 30 years ago. This is an open-loop delivery system in which a portable pump infuses insulin subcutaneously at variable rates via an implanted cannula (Figures 10.10 and 10.11). This is meant to mimic basal insulin. At mealtimes patients activate a bolus dose. This combination is meant to reproduce the insulin secretory pattern seen in non-diabetic people. Because only short-acting (usually analogue) insulin is used, the problem of variable absorption of intermediate-acting preparations is overcome. Moreover, basal rates can be changed hour by hour and this is particularly useful in individuals who have the dawn phenomenon.

Closing the loop using subcutaneous interstitial glucose sensing connected to an insulin pump is now available but at the time of writing was not yet funded on the NHS in the UK (see Chapter 9).

There are now several different insulin pumps available; they cost between £2500 and £3000 with running costs of approximately £800–1000 per year.

All pumps comprise a chamber where usually 3 mL of insulin is drawn up into a special syringe. A motor drives a plunger which delivers insulin from the syringe via a cannula under the skin.

A typical strategy for commencing pump therapy is to reduce the patient's total daily insulin dose on injections by 20% and then allocating the remainder, one half to the basal rate and the other split equally between the three main meals. In order to fine-tune insulin delivery, multiple capillary blood glucose tests are required. In addition, patients are taught how to estimate the carbohydrate content of their meals and generally one unit of insulin is given for every 10 g portion. Higher doses may be required in patients who may be insulin resistant (e.g. adolescents, pregnancy, obesity, where 1.25 units/10 g may be required). Conversely, for smaller children who tend to be more insulin sensitive, 0.5 units/10 g is a useful starting dose.

The best-established clinical indication for CSII is in patients who have failed to achieve glycaemic targets on MDI or who have problematic, frequent and unpredictable hypoglycaemia. In addition, there may be particular indications for patients who have a marked dawn phenomenon or for those women who are considering pregnancy or who are pregnant and have difficulty achieving glycaemic control, and for those rare patients who have a true insulin allergy.

Psychological problems should not preclude a trial of CSII; one centre reported significant benefit in terms of reduction of hospital admission rates with diabetic ketoacidosis, together with a reduction in HbA_{1c} even though the level on CSII was less than ideal at >9% (75 mmol/mol). Estimates of the numbers of patients in the UK who might want or

Figure 10.10 Examples of three currently available insulin pumps in the UK. All comprise a motor driven plunger, insulin cartridge and cannula with connecting tube.

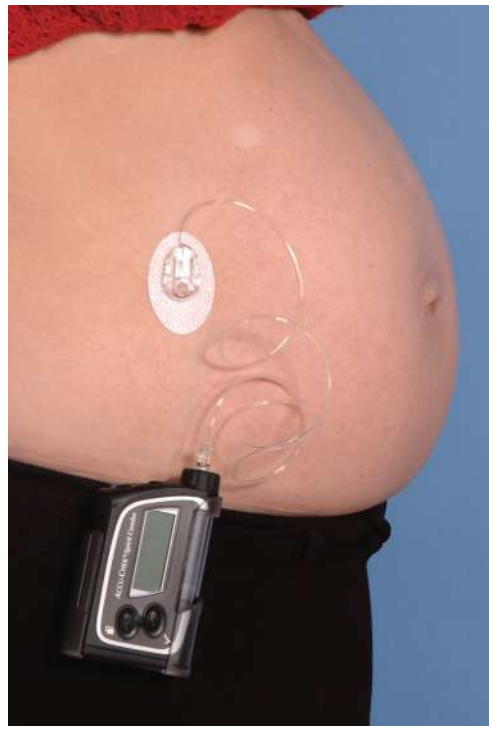

Figure 10.11 Insulin infusion pump attached to a pregnant woman with type 1 diabetes. The tubing can be detached for bathing, leaving a waterproof cannula in situ.

CASE HISTORY

A 40-year-old manager with type 1 diabetes had noticed a gradual deterioration in his glycaemic control. He developed diabetes aged 25 when working offshore and had to change career. He was managed on a twice-daily regimen of soluble and lente insulins. His doses of insulin had increased such that he was taking >120 units/day (~1.4 units/kg bodyweight) and he periodically experienced severe hypoglycaemia with little warning. His HbA_{1c} was 8.2%. He exercised regularly but was finding this more difficult because of general fatigue and hypoglycaemia. Investigations showed normal thyroid function and negative insulin antibodies.

He was commenced upon CSII using human insulin and his total daily dose fell to 60 units. His fatigue and hypoglycaemic episodes disappeared and his HbA_{1c} fell to 6.9%. He has now been on CSII for 9 years and remained in stable control with minimal retinopathy only.

Comment: Lente insulins could be associated with unpredictable hypoglycaemia. Part of the problem is the excess zinc in these preparations and the potential for this to accumulate under the skin. The cause of the fatigue was probably a combination of poor glycaemic control and hyperinsulinaemia. Insulin doses often fall on CSII, on average 15%, so the 50% reduction in this case is exceptional. It is also noteworthy that hypoglycaemia rates diminished despite a reduction in HbA_{1c}. This man was converted to CSII pre glargine. He declined a trial of this analogue although current NICE guidance now suggests it prior to commencing CSII.

benefit from CSII vary but it is probable that 10–20% would accept the treatment and achieve benefit.

As is the case with many medical technologies, the evidence base for the effectiveness or otherwise of CSII is not as strong as we would like. A Health Technology Appraisal from NICE in the UK was updated in 2008 and approved CSII for adults and children with type 1 diabetes provided certain conditions have been met (see Box 10.1). As a result, CSII has become much more widely available in the UK, although absolute numbers of patients using pumps are far fewer than those in other European countries and North America.

A meta-analysis in 2008 confirmed glycaemic improvement in terms of both HbA_{1c} (average reduction 0.61%) and severe hypoglycaemic rates (4.19 times less likely) on pump therapy compared to MDI (Figure 10.12). NICE found that patients with a higher HbA_{1c} on MDI obtained most benefit in terms of glycaemic control on CSII. Moreover, CSII was effective in terms of cost per QALY (quality adjusted life year) with a range of £16,842 to £34,330; this fell to less than £29,000 when improvement associated with the reduction in severe hypoglycaemic rates was taken into account.

Totally implantable pumps that deliver insulin into the peritoneal cavity have been used in Europe and the USA for many years. Overall glycaemic control tends to be similar to that during MDI or CSII but with reduced fluctuations and fewer hypoglycaemic episodes. These pumps need to be implanted subcutaneously with a catheter placed in the peritoneal cavity; requiring a general anaesthetic. The insulin pump reservoir is topped up by using a syringe and needle via an injection port. The pump is programmed by a small external device which can be used to deliver variable basal rates and boluses. These devices are only funded in the UK on an individual patient basis and their use is really confined to patients with severe brittle diabetes who have not responded to CSII.

Box 10.1 NICE Technology Guidance 151 on continuous subcutaneous insulin infusion

Continuous subcutaneous insulin infusion is:

1) Recommended for adults and children over 12 years of age provided that:
   a) attempts to achieve target HbA_{1c} on MDI result in disabling hypoglycaemia *or*
   b) HbA_{1c} levels remain ≥8.5% on MDI despite high levels of care.
2) Recommended for children <12 years provided that:
   a) MDI is deemed impractical or inappropriate
   b) a trial of MDI should be considered between ages 12–18 years.
3) CSII should be initiated by a trained team comprising a physician with a specialist interest, a diabetes specialist nurse and a dietitian. Teams should provide structured education and advice on diet, lifestyle and exercise.
4) CSII should be continued if there is a sustained improvement in glycaemic control as evidenced by a reduction in HbA_{1c} and/or number of hypoglycaemic episodes.

LANDMARK CLINICAL TRIAL

Wang PH, Lau J, Chalmers TC. Meta-analysis of effects of intensive blood-glucose control on late complications of type 1 diabetes. Lancet 1993; 341: 1306–1309.

This analysis of 16 (six for longer than 2 years) trials of intensive blood glucose control on microvascular complications was published 6 months before the DCCT. A difference in HbA_{1c} of 1.4% (95% CI 1.8–1.1) between groups was found. There was a non-significant trend for retinopathy worsening within 6–12 months but for the six studies of 2 or more years duration, there was an OR of 0.49 (0.28–0.85) for retinopathy progression. For nephropathy, the results were more impressive: OR for progression 0.34 (0.20–0.58). This meta-analysis showed results remarkably similar to the DCCT and is an example of how powerful a tool this can be. The problem of acute worsening of retinopathy with rapid glycaemic correction (called by some normoglycaemic re-entry) was confirmed.

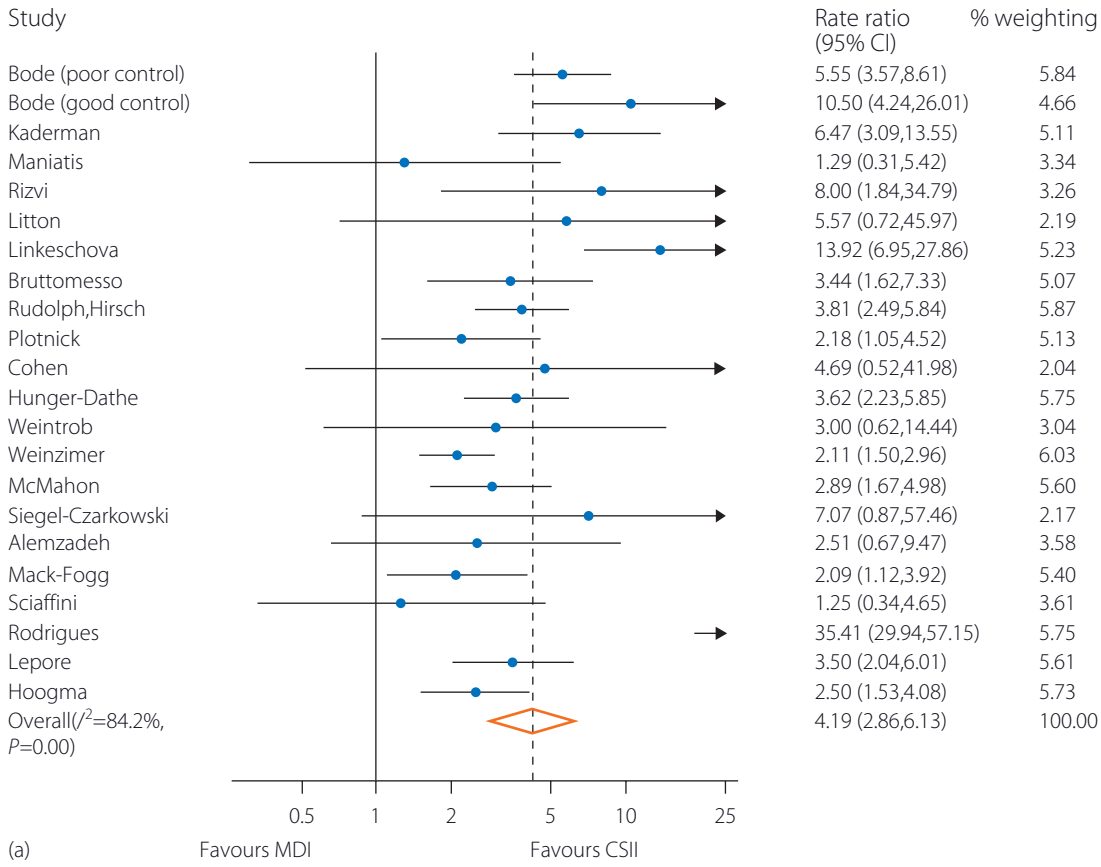

Figure 10.12 Forest plots of random effects meta analysis. (a) For severe hypoglycaemia rate ratio for multiple daily injections (MDI) versus CSII. (b) For mean difference in HbA_{1c} (%) for MDI (using an isophane/lente or glargine based regimen) versus CSII. CSII, continuous subcutaneous insulin infusion; CI, confidence interval. From Pickup & Sutton. Diabetic Med 2008; 25: 765–774.

Islet transplantation

Islet transplantation for type 1 diabetes was first attempted in the 1980s with very poor results – less than 10% of patients were insulin independent at 1 year. In the late 1990s a new protocol was developed by workers in Edmonton, Canada, which avoided the use of high-dose corticosteroids for immunosuppresion. The islets are infused directly into the hepatic portal vein percutaneously. The initial results were extremely promising with all of the first seven patients maintaining insulin independence at 1 year. However, more extensive experience from multicentre trials and transplant registries suggests that longer term insulin independence is much less good.

From 1999 to April 2008 the Collaborative Islet Transplant Registry (CITR) recorded 325 recipients of 649 islet infusions. At 3 years post first infusion, only 23% were insulin independent, with a further 29% showing some insulin secretion; 26% had lost function.

There are problems associated with longer term immunosuppression. Apart from the well-recognised complications of infection and cancer, the current protocols rely on agents that are nephrotoxic. Rates of decline in kidney function of 2–4 times that of non-transplanted controls have been reported. For this reason, patients with renal impairment are ineligible for islet transplantation. Moreover, islet recipients have developed sensitivity to HLA antigens, making subsequent kidney transplantation (if required) more difficult. Thus patients with nephropathy potentially needing a kidney graft in the future are also ineligible.

However, for patients with severe disabling hypoglycaemia with unawareness, islet transplantation has been life transforming and even those who lose their insulin independence continue to have fewer and much less severe hypoglycaemic episodes. In 2008 NICE approved allogeneic islet transplantation for patients with type 1 diabetes and severe hypoglycaemia with unawareness.

KEY WEBSITES

- National Institute for Health and Clinical Excellence: www.nice.org.uk
- NICE Interventional Procedure Guidance 257. Allogeneic pancreatic islet transplantation for type 1 diabetes mellitus. 2008: www.nice.org.uk/nicemedia/pdf/IPG257Guidance/pdf
- Diabetes UK Care Recommendation. Self-monitoring of blood glucose: www.diabetes.org.uk
- Collaborative Islet Transplant Registry: www2.niddk.nih.gov/Research/ScientificAreas/Pancreas/EndocrinePancreas/CITT.htm
- SIGN Guidelines: www.SIGN.ac.uk

FURTHER READING

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Chapter

11 Management of type 2 diabetes

KEY POINTS

- Key components of management include dietary and lifestyle adjustment to avoid or treat obesity; pharmacological and non-pharmacological strategies to lower glucose levels; and treatments to reduce CV risk, in particular BP and cholesterol reduction.
- Structured education programmes (e.g. DESMOND) have an important role.
- Regular exercise, independently of weight loss, improves insulin sensitivity and CV outcomes.
- Type 2 diabetes is metabolically progressive: HbA_{1c} rises with duration of disease, despite escalating therapy, mainly due to a progressive decline in β cell function.
- Glucose-lowering therapies work primarily by increasing insulin secretion (sulphonylureas, miglitinides, DPP-4 inhibitors) or increasing peripheral and hepatic insulin sensitivity (biguanides, glitazones).
- Insulin analogues, bariatric surgery and GLP-1 agonists (exenatide, liraglutide) are creating more choices as part of combination therapy to achieve lower HbA_{1c} targets in different patient subgroups.

Lifestyle modification

The starting points and mainstays of treatment for type 2 diabetes are diet and other modifications of lifestyle, such as increasing exercise and stopping smoking (Figure 11.1). The major aims are to reduce the weight of obese patients and improve glycaemic control, but also to reduce risk factors for cardiovascular disease (CVD), such as hyperlipdaemia and hypertension, which accounts for 70–80% of deaths in type 2 diabetes.

Weight loss is achieved by decreasing total energy intake and/or increasing physical activity and thus energy expenditure. Gradual weight loss is preferred – not more than 0.5–1 kg/week. For effective weight loss and improvement in glycaemic control, the amount of energy restriction is more important than dietary composition, though compliance may be greater with high monounsaturated fat diets (Figure 11.2). Weight loss of as little as 4 kg will often ameliorate hyperglycaemia. Reduced-calorie diets result in clinically significant weight loss regardless of which macronutrients they emphasize.

Antiobesity drugs have so far played only a minor part in the management of the obese patient with diabetes.

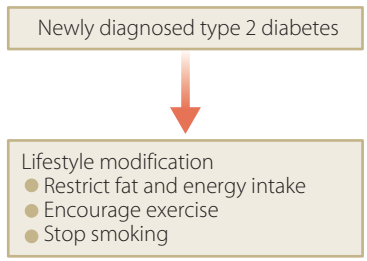

Figure 11.1 Management of type 2 diabetes: the initial measures.

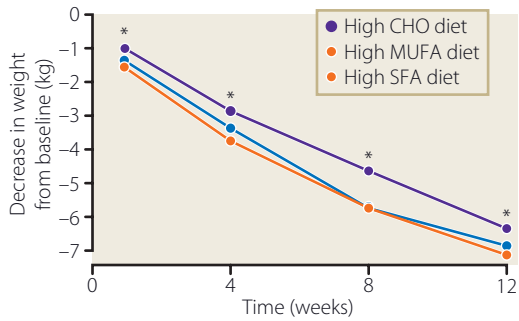

Figure 11.2 Change in weight during energy restriction is similar with high carbohydrate diet (CHO), high monounsaturated fatty acid (MUFA) diet and high saturated fatty acid (SFA) diet. From Heilbronn et al. Diabetes Care 1999; 22: 889–895.

Handbook of Diabetes, 4th edition. By © Rudy Bilous & Richard Donnelly. Published 2010 by Blackwell Publishing Ltd.

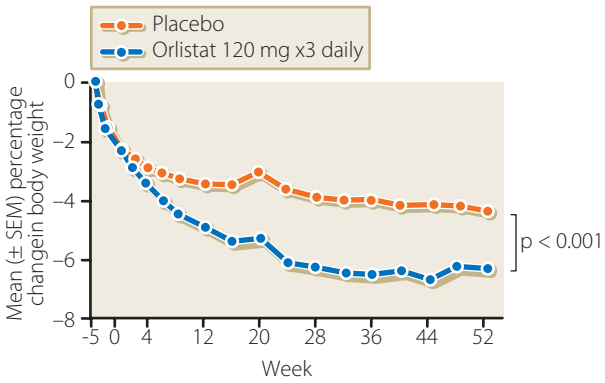

Figure 11.3 Effect of orlistat in obese patient with type 2 diabetes. From Hollander et al. Diabetes Care 1998; 21: 1288–1294.

Sibutramine is a centrally acting serotonin and norepinephrine reuptake inhibitor that acts as an appetite suppressant. It has many contraindications, potential drug interactions and stringent requirements for monitoring, and little information on long-term efficacy and safety. Orlistat acts locally in the gastrointestinal tract, where it blocks enzymatic digestion of triglyceride by inhibiting pancreatic lipase. The absorption of up to 30% of ingested fat is thus prevented. Orlistat can result in a greater weight loss in obese patients with type 2 diabetes over the course of the first year's treatment, though weight may be regained subsequently (Figure 11.3). Gastrointestinal side effects are common, including flatulence, steatorrhoea and, occasionally, faecal incontinence. A diet rich in fruit and vegetables is needed to avoid fat-soluble vitamin deficiency. Orlistat should be started only if diet alone has produced ≥2.5 kg weight loss over 1 month and should be discontinued if weight loss is <5% over 12 weeks. Orlistat may be helpful to prevent weight regain following a very-low-energy diet.

The dietary recommendations are essentially the same for type 1 and type 2 diabetes and, indeed, follow a healthy eating plan suitable for the entire population (Box 11.1). Saturated fat should be reduced and replaced with monounsaturated fat such as olive oil or polyunsaturated fats. n-6 Polyunsaturated fat, found in vegetable oils, is also beneficial for cholesterol lowering and improving glycaemic control. Dietary cholesterol may be more detrimental in diabetics than in the general population, so the consumption of foods such as eggs should be limited. Fish oils are rich in n-3 fatty acids and have lower triglyceride levels, and there is evidence that higher fish intake is associated with less CVD in diabetes; accordingly, 2–3 servings of fish per week are recommended. Simple dietary guidelines in the form of recommended foods are normally best for patients, and are better understood than measures of fat, carbohydrate or protein. 'Diabetic' foods that contain sorbitol or fructose as sweeteners are not recommended. Sucrose need not be banned from the diabetic diet, and a moderate amount for sweetening is acceptable. The focus of dietary plans should be on balancing energy intake to energy expenditure and the quality of fat and carbohydrate, rather than the quantity alone. Foods that normally improve glycaemic control and CVD risk are whole grains (brown rice, wholewheat breads, oats) and high-fibre foods (grains, cereals, fruits, vegetables and nuts).

Box 11.1 Practical food recommendations for patients with diabetes

- Quench thirst with water or other sugar-free drinks
- Eat regular meals, avoiding fried and very sugary foods
- Eat plenty of vegetables
- Have high-fibre and low glycaemic index foods, including whole grains, legumes or brown rice as the main part of each meal
- Limit consumption of high glycaemic index starchy foods, such as mashed potatoes and white bread
- Eat plenty of whole fruit
- Limit consumption of animal products with high amounts of cholesterol and saturated fat, such as red meat, eggs, liver and high-fat dairy products, and substitute them with lean meat, fish, poultry (without skin) and low-fat dairy products
- For snacks between meals, avoid convenience foods such as biscuits, cake or confectionery (which are high in saturated and trans-fats and salt); use nuts and fruits for snacks instead
- Use natural liquid vegetable oils for cooking, baking and frying instead of vegetable shortenings (solid vegetable fat, high in saturates and trans-fatty acids)
- Use trans-fat-free or soft margarine instead of stick (hardened) margarine or butter
- Be aware of the portion size of a meal, especially when eating in a restaurant. Do not overeat
- If blood glucose control is satisfactory, light to moderate drinking of alcohol (1 unit per day for women and 1–2 for men) is fine, but drink alcoholic beverages with a meal

Structured education

Several programmes have been developed in Europe and North America to educate patients about diabetes. An example in the UK for patients with type 2 diabetes is the diabetes education and self management for ongoing and newly diagnosed (DESMOND) structured education programme. Clinical studies have shown that structured education programmes focused on behaviour change can successfully engage those with newly diagnosed type 2 diabetes in starting effective lifestyle changes that are sustainable. Benefits of DESMOND include improvements in illness beliefs, weight loss, physical activity, smoking status (Figure 11.4) and depression.

Exercise should be tailored to the individual patient, according to physical condition and lifestyle, but simple

LANDMARK CLINICAL TRIALS

ACCORD Study Group. Effects of intensive glucose lowering in type 2 diabetes. N Engl J Med 2008; 358: 2545–2559.

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Alexander GC, Sehgal N, Moloney R, Stafford R. National trends in treatment of type 2 diabetes mellitus, 1994–2007. Arch Intern Med 2008; 168: 2088–2094.

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Look AHEAD Research Group. Reduction in weight and cardiovascular disease risk factors in individuals with type 2 diabetes: one year results of the Look AHEAD trial. Diabetes Care 2007; 30: 1374–1383.

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Shai I, Schwarzfuchs D, Henkin Y, et al. Weight loss with a low-carbohydrate, Mediterranean or low-fat diet. N Engl J Med 2008: 359: 229–241.

Figure 11.4 Emphasising smoking cessation is especially important. This graph shows the relative risks (RRs) of total mortality by duration of smoking cessation among women with diabetes.

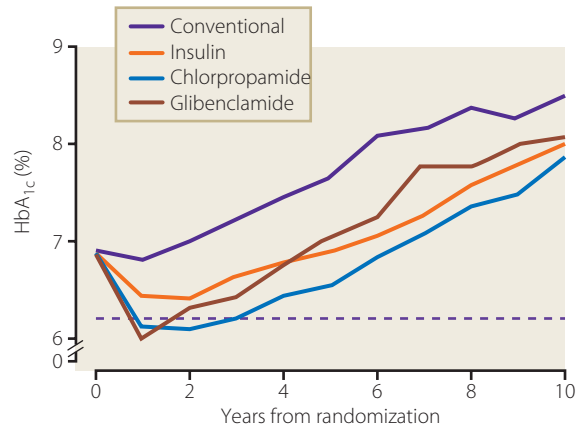


Figure 11.5 The progressive rise in median HbA_{1c} with time in the conventionally treated and intensively treated groups in the UKPDS. HbA_{1c} deteriorated in both groups, despite escalating therapy. A continued decline in β cell function, following the diagnosis of type 2 diabetes, is likely to account for this deterioration in HbA_{1c} over time, illustrating that type 2 diabetes is a progressive disorder. From Al-Delaimy et al. Diabetes Care 2001; 24: 2043–2048.

advice might include moderate exercise as part of the daily schedule, such as walking for 30–60 minutes per day (preferably an extra 30–60 minutes). Exercise does not usually cause hypoglycaemia in type 2 diabetes (in contrast to type 1 diabetes), and therefore extra carbohydrate is generally unnecessary. Resistance exercise, such as weightlifting performed 2–3 times per week, may provide extra benefits over aerobic exercise; however, it should be done with proper instruction, progressively increased over some weeks, starting with a low-intensity workload and supervised. Regular exercise can reduce long-term mortality by 50–60% in patients with type 2 diabetes compared with patients with poor cardiorespiratory fitness.

Metabolic progression: effects on treatment

There is a progressive decline in β cell function and insulin sensitivity in type 2 diabetes, which results in deteriorating glycaemic control and the constant need to revise and intensify treatment. Diet and exercise are sufficient to achieve adequate glycaemic control in <10% of type 2 patients; when control worsens, an oral hypoglycaemic agent is generally introduced.

The particular drug treatment used in an individual patient with type 2 diabetes is decided on the basis of clinical judgement about the balance of β cell impairment and insulin resistance in that particular case (Table 11.1). Overweight and obese patients are likely to be insulin resistant: here, the insulin sensitiser metformin is a logical first choice. Thin patients generally have substantial β cell failure, and sulphonylureas (which stimulate insulin secretion) are likely to be effective. β cell function declines at about 4%

Table 11.1 Major classes of drug used in the treatment of type 2 diabetes (excluding insulins)

Drugs	Action	Mechanism
Biguanides		
Metformin	Reduce insulin Resistance Reduce hepatic glucose output	Not known
Sulphonylureas		
Gliclazide Glimepiride Glipizide Glibenclamide	Increase insulin secretion	Bind to SU receptor on β cell, leading to closure of KATP channels
Meglitinide analogues		
Repaglinide Nateglinide	Increase insulin secretion	Bind to SU receptor on β cell, leading to closure of KATP channels
Thiazolidinediones ('glitazones')		
Pioglitazone Rosiglitazone	Reduce insulin resistance	PPARγ agonist
α-Glucosidase inhibitors		
Acarbose	Decreases carbohydrate absorption in gut	Inhibits α-glucosidase in intestinal brush border
GLP-1 agonists		
Exenatide Liraglutide	GLP-1-like effects on insulin secretion, satiety and gastric emptying	Bind to GLP-1 receptors on β cells and α cells
DPP-4 inhibitors		
Sitagliptin Vildagliptin Saxagliptin Alogliptin	Inhibits breakdown of endogenous GLP-1	Cleaves amino acids and inactivates DPP-4
Weight loss therapies		
Orlistat Sibutramine	Reduces fat absorption in gut Centrally acting appetite suppressant	Inhibits pancreatic lipase Serotonin and noradrenaline reuptake inhibitor

DPP-4, dipeptidyl peptidase-4, GLP-1, glucagon-like peptide-1, KATP, ATP-sensitive potassium, PPARγ, peroxisome proliferator-activated receptor γ, SU, sulphonylurea.

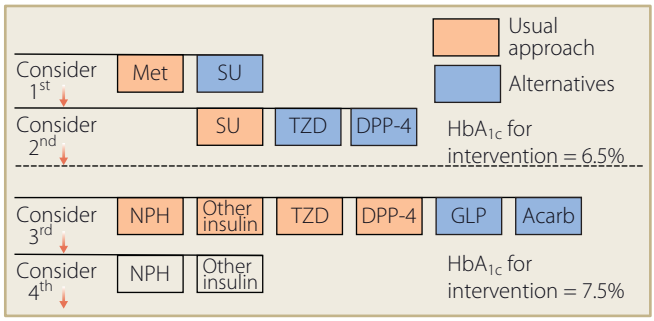


Figure 11.6 The NICE guidance on drug selection and drug sequencing for patients with type 2 diabetes. Met, metformin; SU, sulphonylurea; TZD, thiazolidinedione; DPP-4, dipeptidyl peptidase-4 inhibitor; GLP-1, GLP-1 agonist (e.g. exenatide or liraglutide); Acarb, acarbose; NPH, NPH insulin.

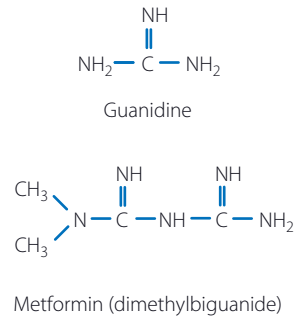


Figure 11.7 The chemical structures of guanidine and metformin. UKPDS Group. Lancet 1998; 352: 837–854.

per year, so sulphonylureas are less effective later in the disease. About 50% of type 2 diabetic patients need insulin within 6 years of diagnosis, although newer agents are providing alternative options for combination therapy.

Oral antidiabetic drugs

Metformin is a derivative of guanidine, the active ingredient of goat's rue (*Galega officianalis*), used as a treatment for diabetes in medieval Europe (Figure 11.7). Metformin

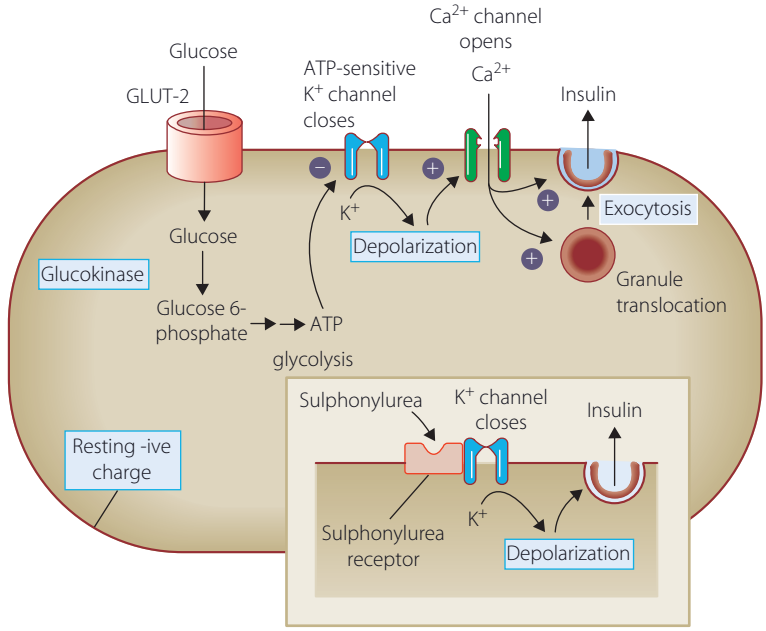


Figure 11.8 Mechanism by which glucose and sulphonylureas stimulate insulin secretion. from pancreatic β cells ATP, adenosine triphosphate; GLUT, glucose transporter.

increases insulin action (the exact mechanism is unclear), lowering glucose mainly by decreasing hepatic glucose output. Unlike sulphonylureas, it does not cause hypoglycaemia or weight gain and, indeed, has some appetite-suppressing activity that may encourage weight loss. A typical starting dose of metformin is 500 mg daily or twice daily, rising to 850 mg thrice daily. Major side effects are nausea, anorexia or diarrhoea, which affect about one-third of patients. Lactic acidosis is a rare but serious side effect that carries high mortality. It can be avoided by not giving metformin to patients with renal, hepatic, cardiac or respiratory failure or those with a history of alcohol abuse.

Sulphonylureas stimulate insulin secretion by binding to sulphonylurea (SU) receptors (SUR-1) on the β cell plasma membrane, which leads to closure of the ATP-sensitive K+ channel (Kir6.2), membrane depolarisation, opening of calcium channels, calcium influx and exocytosis of insulin granules (Figure 11.8). The most serious side effect is hypoglycaemia, which is more likely to occur with glibenclamide, especially in older patients and those with renal impairment. Modest weight gain may also accompany sulphonylurea use.

The thiazolidinediones (TZD) ('glitazones') are insulin sensitisers that enter the cell and bind to the peroxisome proliferator-activated receptor-γ (PPARγ), a nuclear receptor found predominantly in adipocytes but also in muscle and liver (Figure 11.9). PPARγ forms a complex with the retinoid X receptor (RXR), and binding of a TZD leads to enhanced expression of certain insulin-sensitive genes, such as GLUT-4, lipoprotein lipase, fatty acid transporter protein and fatty acyl CoA synthase. This increases glucose uptake and utilisation, increases adipocyte lipogenesis and decreases circulating fatty acid levels. There is also decreased production of the cytokine TNF-α and of resistin.

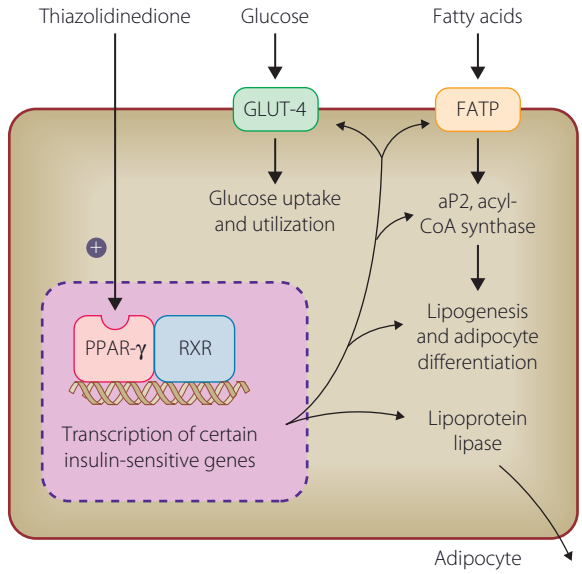


Figure 11.9 Mechanism of action of TZDs. These agents stimulate the PPARγ in the cell nucleus, mainly in the adipocyte. In conjunction with the RXR, this promotes transcription of certain genes and increased expression of GLUT-4, fatty acid transporter protein (FATP), adipocyte fatty acid-binding protein (aP2), fatty acyl coenzyme A (CoA) synthase and other enzymes involved in lipogenesis.

The first TZD, troglitazone, was associated with serious hepatotoxicity and withdrawn. Rosiglitazone and

pioglitazone do not have adverse effects on the liver – in fact, they may reverse fatty infiltration of the liver and improve liver function in some patients – but they are associated with fluid retention, weight gain and oedema. More importantly, some patients may develop features of heart failure. Because PPARγ receptors are widely expressed in the vasculature, there has been considerable interest in the cardiovascular effects of these drugs. In one trial (the PROACTIVE study), pioglitazone as add-on therapy (versus placebo) was associated with significant reductions in fatal and non-fatal myocardial infarction (MI) and stroke (secondary endpoints in the trial) (Figure 11.10). Meanwhile,

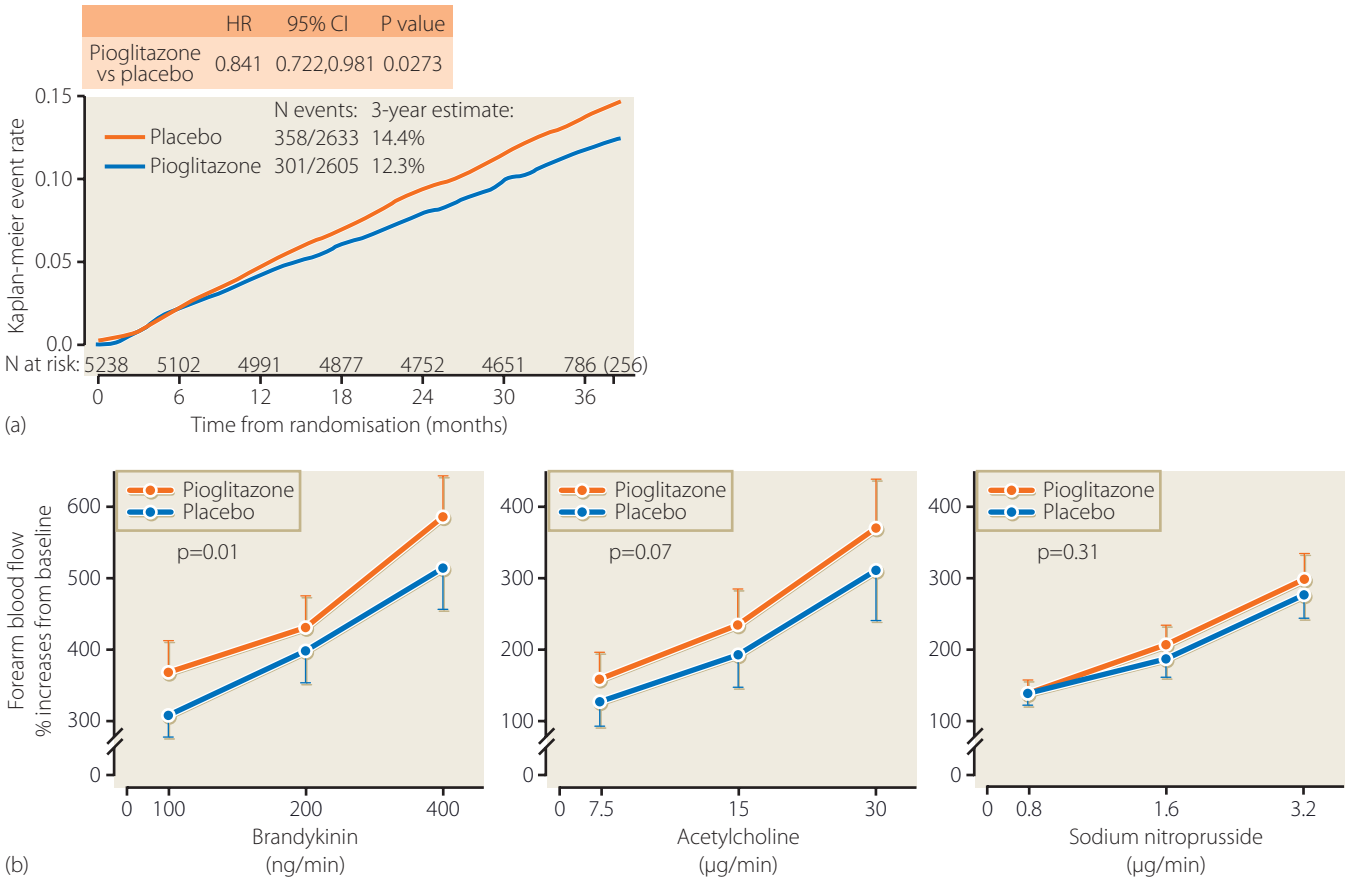


Figure 11.10 (a) The PROACTIVE Study was a prospective placebo-controlled trial of pioglitazone 45 mg od or placebo as add-on therapy in patients with type 2 diabetes and established macrovascular disease. Pioglitazone had no effect on the primary endpoint (a composite of disease and procedural outcomes), but there was a significant reduction in several prespecified secondary endpoints (Dormandy et al. Lancet 2005; 366: 1279–1289). This suggests that pioglitazone (possibly independent of glucose lowering) affects cardiovascular structure and function, e.g. (b) endothelial function is improved, as shown by the increased forearm blood flow response to intra-arterial acetylcholine but not sodium nitroprusside. Data from Campia et al. Circulation 2006; 113: 867–875.

CASE HISTORY

A 54-year-old man with a 5-year history of type 2 diabetes presents to his GP for annual review. This shows BMI 32, BP 156/94 mmHg and HbA_{1c} 7.8% using a maximum-tolerated dose of metformin 1 g bid and gliclazide 80 mg bid. He has background retinopathy and a history of previous myocardial infarction. He takes some exercise, but is limited by arthritis. There have been no significant hypos, LDL-cholesterol is 3.1 mmol/L using a statin. He has some symptoms of tiredness and nocturia.

Comment: If there is no further scope to improve his compliance with diet and exercise, this man will require additional therapy in view of his established complications. Options would include adding basal insulin, exenatide, pioglitazone or a DPP-4 inhibitor. The NICE recommendation for exenatide is at BMI >35; insulin and, to a lesser extent, pioglitazone may worsen his obesity, and a DPP-4 inhibitor is an option, either instead of the SU (if hypos were a problem) or as add-on therapy.

a meta-analysis of studies concluded that, relative to other antidiabetic agents, rosiglitazone was associated with a 2–3-fold increased risk of myocardial infarction. Differential effects on LDL-cholesterol might explain the different effects of pioglitazone and rosiglitazone on cardiovascular outcomes.

Dipeptidyl peptidase-4 (DPP-4) inhibitors are orally active and generally well tolerated. As add-on therapy to metformin, they lower HbA_{1c} to the same extent as sulphonylureas but have a lower incidence of hypoglycaemia because GLP-1 effects on pancreatic β and α cells are dependent upon glucose. DPP-4 inhibitors are weight neutral, and as yet there are no long-term studies to confirm their safety and efficacy on clinically important diabetes-related outcomes. They are licensed as add-on to metformin, SU or TZD, and as triple therapy. GLP-1 analogues, such as exenatide and liraglutide, are administered by fixed-dose subcutaneous injection, once or twice daily, and are best suited to obese patients (BMI >35) who have inadequate HbA_{1c} control despite combination oral therapy. GLP-1 agonists facilitate weight loss, but 20–30% of patients may experience nausea or sickness (Figures 11.11, 11.12). These drugs have also been associated with pancreatitis.

For very obese patients with type 2 diabetes (BMI >35), bariatric surgery is an increasingly recognised treatment option. The results with laparascopic adjustable gastric banding or gastric bypass demonstrate significant weight loss (often >20 kg) and improved glycaemic control (Figure 11.13). Patients need careful selection, and lifelong follow-up.

It is common for many patients with type 2 diabetes to progress from treatment by diet alone to monotherapy with metformin or a sulphonylurea, then to a combination of the two (and/or the introduction of a 'glitazone'), before finally

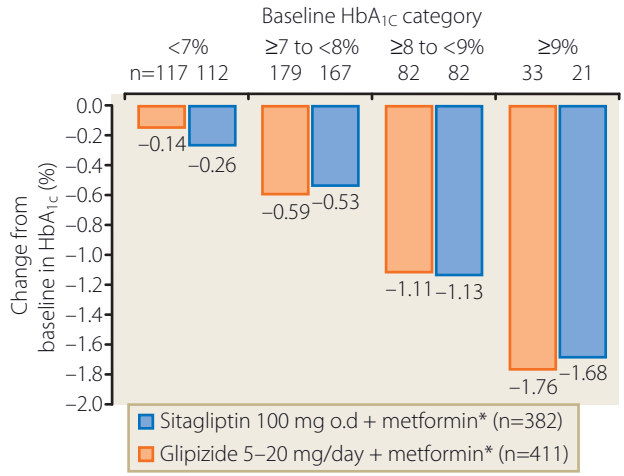


Figure 11.11 A randomised trial to compare the DPP-4 inhibitor sitagliptin with the sulphonylurea glipizide as add-on therapy to metformin showed comparable reductions in HbA_{1c}. The reductions in HbA_{1c} were dependent upon the baseline HbA_{1c} in both groups. Sitagliptin caused fewer hypoglycaemic episodes. Adapted from Nauck et al. Diab Obes Metab 2007; 9: 194–205.

KEY WEBSITES

- www.nice.org.uk/CG66
- www.diabetes.org/sitemap.jsp
- www.idf.org/home/index.cfm?unode=B7462CCB-3A4C-472C-80E4-710074D74AD3
- SIGN Guidelines: www.SIGN.ac.uk

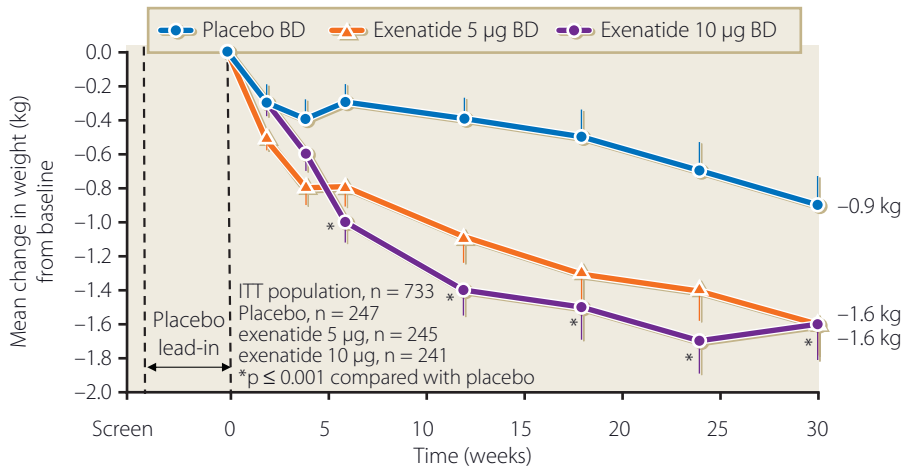
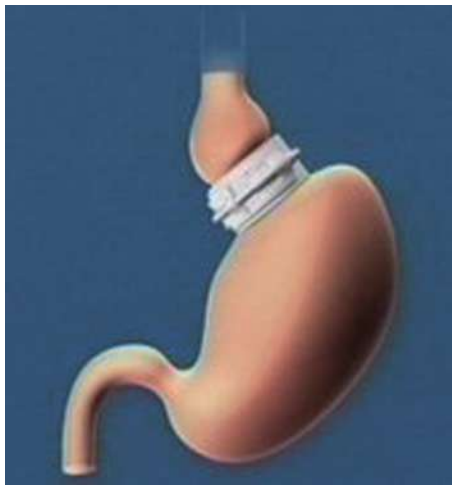
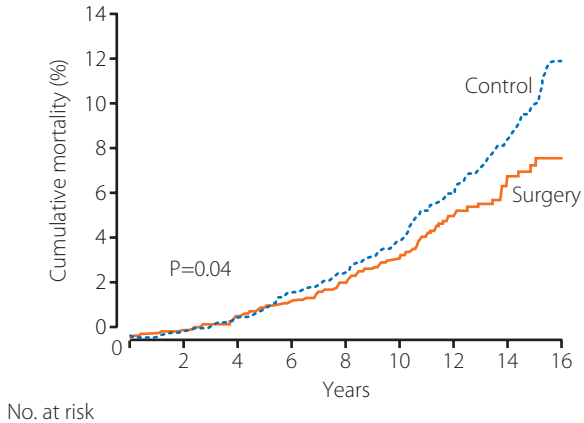


Figure 11.12 When used as add-on therapy to metformin or sulphonylurea (or both), exenatide 5–10 µg bid is associated with significant weight loss. Adapted from Kendall et al. Diabetes Care 2005; 28: 1083–1091.



(a)



No. at risk

Surgery	2010	2001	1987	1821	1590	1260	760	422	169
Control	2037	2027	2016	1842	1455	1174	749	422	156

(b)

Figure 11.13 (a) Laparascopic adjustable gastric banding. The band can be adjusted postoperatively by percutaneous injection of saline into the reservoir. (b) There is evidence that obese patients undergoing bariatric surgery survive longer. Sjostrom et al. N Engl J Med 2004; 351: 2683–2693.

starting insulin. Insulin can be given alone or in combination with oral agents, either metformin or pioglitazone (or both). A single daily injection of basal insulin can be given as add-on to oral therapy (e.g. at bedtime), and twice-daily injections of premixed insulin (e.g. 30% short-acting/70% isophane) via a 'pen' are also convenient and effective in many patients. When obesity and insulin resistance predominate, the doses may range up to 2–3 U/kg.

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Chapter

12 Diabetic ketoacidosis, hyperglycaemic hyperosmolar state and lactic acidosis

KEY POINTS

- Diabetic ketoacidosis is a state of severe uncontrolled diabetes characterized by hyperglycaemia, hyperketonaemia and metabolic acidosis in the face of absolute insulin deficiency.
- Frequency may be increasing and it accounts for 50% of deaths in people with type 1 diabetes under 24 years of age.
- Treatment requires fluid and electrolyte infusions with careful potassium replacement, and insulin by intravenous infusion, intramuscular or subcutaneous injection (in milder cases).
- Hyperosmolar hyperglycaemic state used to be called HONK. It is characterized by extreme hyperglycaemia and dehydration without acidosis. Treatment is similar to that for diabetic ketoacidosis but mortality is higher.
- Lactic acidosis is a rare serious metabolic crisis that may be more frequent in people with diabetes. Treatment requires intravenous bicarbonate infusion in addition to rehydration, and mortality is high.

Diabetic ketoacidosis (DKA) is a state of severe uncontrolled diabetes caused by insulin deficiency. It is characterised by hyperglycaemia, hyperketonaemia and metabolic acidosis, and has been somewhat arbitrarily divided into mild, moderate and severe based upon biochemical and clinical features (Table 12.1).

The frequency of DKA increased by 35% in the USA in the decade 1996–2006, with an estimated 135,000 hospital admissions per year costing around 2.4 billion US dollars. Incidence rates of 1–5% have been reported worldwide and are higher in younger type 1 patients and females. In the UK there were 12,326 emergency admissions coded as DKA in the 12 months to March 2007. Admission rates for children <15 years of age in the UK range between 0.05 and 0.38 per patient-year. Overall mortality in developed countries is reportedly low (<1–5%) but much higher in older

Table 12.1 Diagnostic criteria for DKA and HHS

	DKA (plasma glucose >13.9 mmol/L)			HHS (plasma glucose >33 mmol/L)
	Mild	**Moderate**	**Severe**	
Arterial pH	7.25–7.30	7.00–7.24	<7.00	≥7.30
Serum bicarbonate mmol/L	15–18	10–15	<10	≥18
Urine ketones	Positive (2+)	Positive (>2+)	Positive (>2+)	Small (<1+)
Serum osmolality mOsm/kg	Variable	Variable	Variable	>320
Anion gap	≥10	≥12	≥12	≤12

Osmolality = 2 [serum Na^+] + plasma glucose (mmol/L) In this situation serum urea is ignored.
Anion gap = [serum Na^+] – [serum Cl^- + HCO_3^-] (mmol/L) [normal ≤9].
NB: plasma glucose levels can be near normal in pregnant women with DKA. Mental state varies with severity but coma is an ominous development in DKA. Adapted from Kitabchi et al. Diabetes Care 2009; 32: 1335–1343.

Handbook of Diabetes, 4th edition. By © Rudy Bilous & Richard Donnelly. Published 2010 by Blackwell Publishing Ltd.

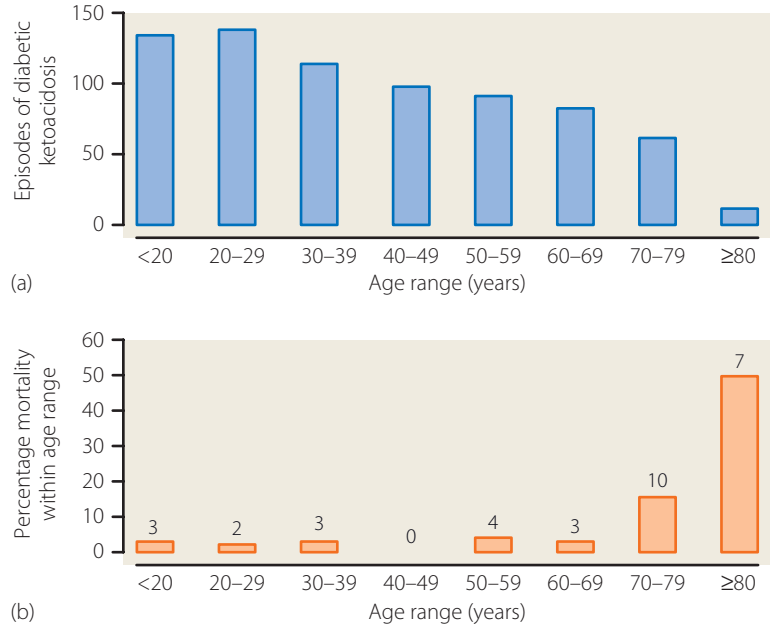

Figure 12.1 (a) Age distribution of 746 episodes of diabetic ketacidosis (excluding paediatric cases). (b) Age distribution of deaths related to diabetic ketacidosis (n = 32). Numbers of deaths in each age range are also shown. Data based upon 746 consecutive cases of DKA from Birmingham General Hospital 1971 – 85. Courtesy of Dr M Nattrass.

Box 12.1 Features of ketosis-prone type 2 diabetes mellitus

- Acute presentation
- Mean age >40 years
- Male preponderance
- BMI ≥28 (for African American, less for Hispanic and Taiwanese)
- Mostly newly diagnosed with diabetes
- Strong family history of type 2 diabetes
- HbA_{1c} at presentation >12%
- Autoimmune markers for type 1 diabetes negative
- Fasting C-peptide detectable
- Most do not require long-term insulin therapy

patients, probably as a result of the underlying cause (often cardiovascular disease). However, DKA accounts for more than 50% of all deaths in people with type 1 diabetes <24 years of age in the USA (Figure 12.1).

Although DKA mainly occurs in type 1 patients, it can occur in African American and Hispanic people who subsequently can be managed without insulin and thus behave as type 2 diabetes. This phenomenon is now termed 'ketosis-prone type 2 diabetes'; it can account for 25–50% of African American or Hispanic cases of DKA. Their clinical characteristics are shown in Box 12.1.

Table 12.2 Precipitating causes of DKA

Cause	Reported frequency
Infection	19–56%
Insulin error/omission	15–41%
Newly diagnosed	10–22%
Cardiovascular (myocardial infarction,stroke)	<10%
Pancreatitis	
Pulmonary embolism	
Alcohol excess	
Steroid use	

Precipitating factors for diabetic ketoacidosis

The most common precipitating factor is intercurrent infection (19–56%) but it is important to remember that a polymorphonucleocytosis is common in DKA, probably secondary to physiological stress, and does not necessarily imply sepsis. Other causes of DKA and their range of frequency from reported series are shown in Table 12.2. The frequency of cause will vary according to age and ethnicity. Not infrequently, no obvious cause is found.

Recurrent DKA is a feature particularly in young girls and can account for up to 15% of all admissions in some series.

Pathophysiology

Relative or absolute insulin deficiency in the presence of catabolic counter-regulatory stress hormones (particularly

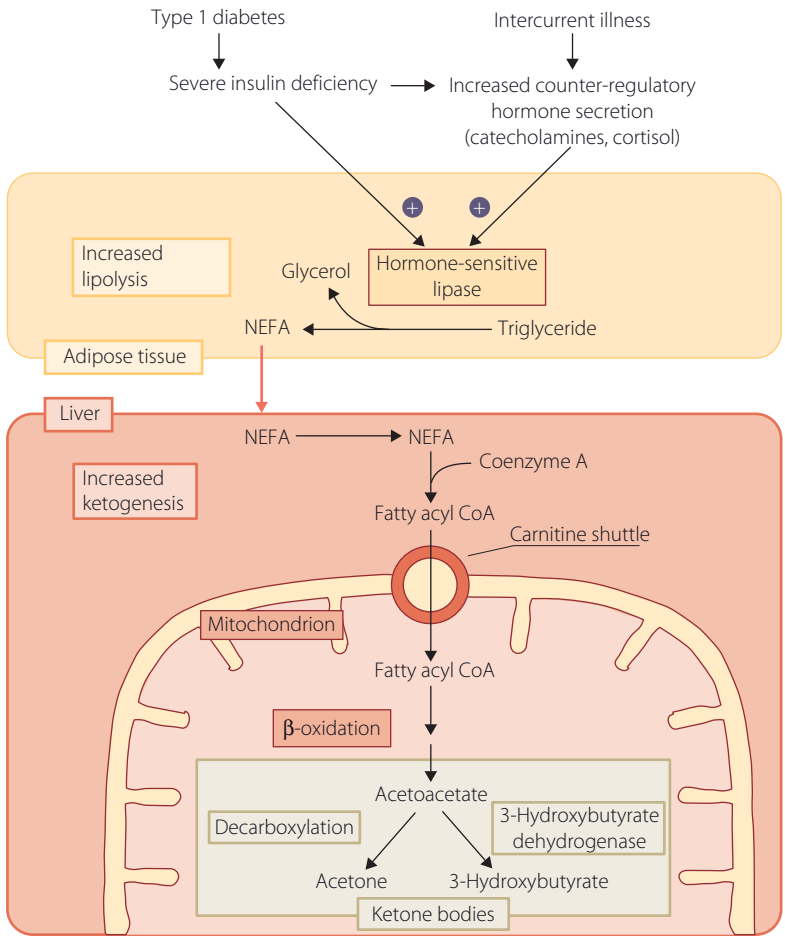

Figure 12.2 Mechanisms of ketacidosis. NEFA, non-esterified fatty acids.

glucagon and catecholamines, but also growth hormone and cortisol) leads to hepatic overproduction of glucose and ketones. Lack of insulin combined with excess stress hormones promotes lipolysis, with the release of NEFAs from adipose tissue into the circulation. In the liver, fatty acids are partially oxidised to the ketone bodies acetoacetic acid and 3-hydroxybutyric acid, which contribute to the acidosis, and acetone (formed by the non-enzymatic decarboxylation of acetoacetate). The latter is volatile and excreted via the lungs.

Hyperglycaemia results from increased glycogenolysis secondary to glucagon excess; gluoconeogenesis as a result of increased lipolysis and proteolysis; diminished peripheral uptake of glucose due to absent insulin stimulated uptake; and utilisation of alternative fuels such as NEFA and ketone bodies in preference to glucose.

Hyperglycaemia causes an osmotic diuresis that leads to dehydration and loss of electrolytes. Sodium depletion is worsened because of diminished renal sodium reabsorption due to insulin deficiency. Metabolic acidosis leads to the loss of intracellular potassium in exchange for hydrogen ions, and insulin deficiency also results in potassium loss from cells. These processes can result in high circulating plasma potassium.

The symptoms of DKA include increasing polyuria and thirst, weight loss, weakness, drowsiness and eventually coma (in about 10% of cases) (Box 12.2). Abdominal pain

Box 12.2 Clinical features of diabetic ketacidosis

- Polyuria and nocturia; thirst
- Weight loss
- Weakness
- Blurred vision
- Acidotic (Kussmaul) respiration
- Abdominal pain, especially in children
- Leg cramps
- Nausea and vomiting
- Confusion and drowsiness
- Coma (10% of cases)

can occur, particularly in the young, and should resolve within 24 hours. If not, alternative causes should be looked for. Physical signs include dehydration, hypotension, tachycardia and hypothermia. Acidosis stimulates the respiratory centre, which results in deep and rapid (Kussmaul) respirations. The smell of acetone on the patient's breath (similar to nail-varnish remover) may be obvious to some, but many people are unable to detect it.

The mechanism by which DKA induces coma is obscure, but impaired consciousness generally correlates with plasma glucose concentration and osmolality; coma at presentation is associated with a worse prognosis. This is because the unconscious brain stops utilising circulating ketone bodies which therefore accumulate more rapidly and result in a worsening metabolic acidosis. Co-existing causes of coma, such as stroke, head injury, meningitis and drug overdose, should always be considered and excluded if clinical signs suggest one of these diagnoses. Cerebral oedema should be suspected when the conscious level declines during treatment (see below).

Treatment

Diabetic ketoacidosis is a medical emergency. A rapid history, physical examination and bedside blood and urine tests should allow a provisional diagnosis in the emergency department and avoid treatment delays (Figure 12.3). Immediate bedside investigations should include blood glucose concentration and a test for the presence of urine or blood ketones with reagent strips, followed by laboratory measurements of blood glucose, urea, Na^+, K^+, Cl^-, bicarbonate (for calculation of the anion gap), arterial blood pH and gas tensions, blood count, and blood and urine cultures. Venous pH could suffice if an arterial sample is difficult to obtain.

Initial treatment involves rehydration, usually with isotonic saline (0.9%) with appropriate supplements. Although initial serum potassium levels may be normal or even high, there will be an overall deficiency, and replacement should commence more or less immediately at 20 mmol/L unless there is significant renal failure or hyperkalaemia >5.2 mmol/L. Serum potassium will fall with treatment as a

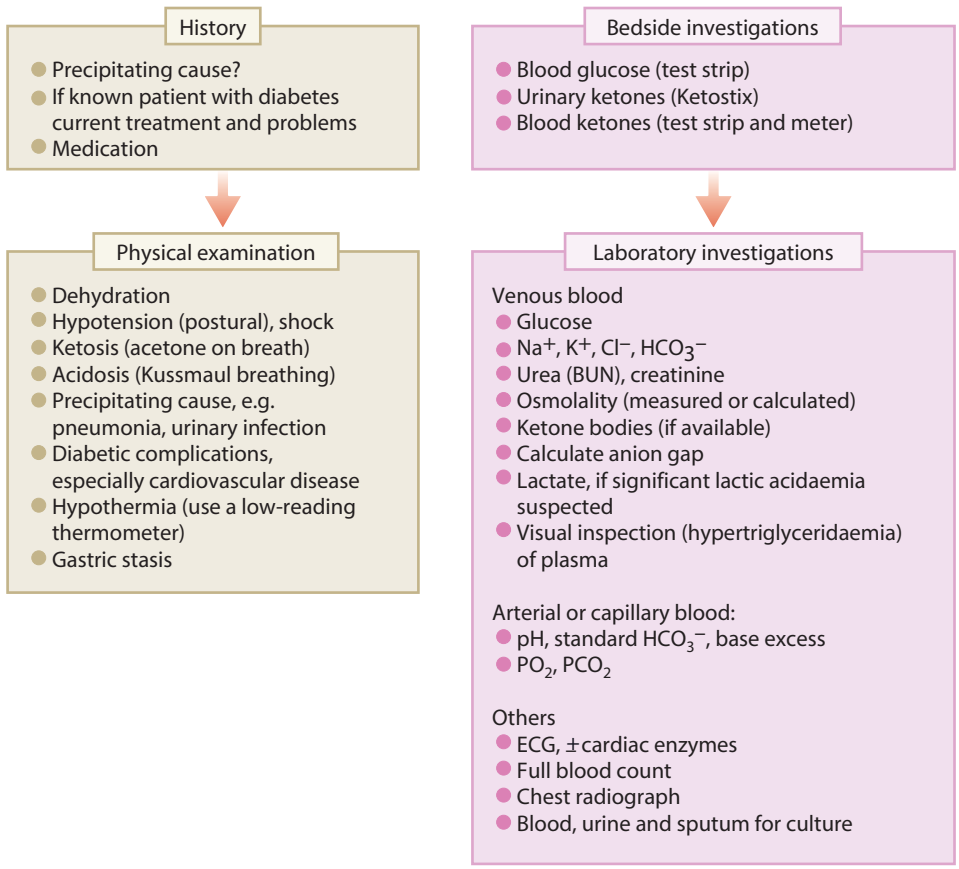

Figure 12.3 Flowchart for the investigation of diabetic ketacidosis.

result of correction of acidosis and insulin administration, both of which increase cellular uptake. Careful and regular monitoring of serum potassium is essential as treatment-induced hypokalaemia is a significant cause of cardiac dysrhythmia and even death (Table 12.3).

Regular/soluble insulin is usually given by continuous infusion, US guidelines suggest a dose of 0.1 unit/kg bodyweight/hour. They also suggest a priming IV bolus of a similar amount but there is no evidence to suggest that this influences outcome or recovery. Alternatively, insulin can be given by hourly IM injection if there is no infusion pump available. Recently, regular SC injection of short-acting

CASE HISTORY

A 32-year-old woman with type 1 diabetes was 30 weeks pregnant. She had been unwell with dysuria and vague abdominal pain, and felt nauseous. She presented to the obstetric day unit where she was found to be slightly breathless and mildly febrile (37.9°C), and urinalysis showed 3+ ketones, trace proteinuria and glycosuria 55 mmol/L (990 mg/dL). Her capillary blood glucose was 11.9 mmol/L (214 mg/dL). A diagnosis of urinary tract infection was made, she was commenced on oral cefalexin and discharged.

Twelve hours later she was brought to the accident and emergency department severely breathless and vomiting with severe abdominal pain. She was tachycardic (pulse 120/min, regular), hypotensive (BP 90/50 mmHg lying, 70/40 mmHg sitting), dehydrated and unwell. Laboratory plasma glucose was 35.6 mmol/L (641 mg/dL), blood 3-hydroxybutyrate was 8.1 mmol/L. Arterial pH was 7.0.

She was commenced on IV saline and insulin. She made a rapid recovery over the next 24 hours. Her abdominal pain settled, fetal ultrasound was normal. She was delivered by elective caesarean section at 36 weeks gestation.

Comment: Pregnancy is considered to be a proketotic state. Serum bicarbonate routinely falls in normal pregnancy; the normal range is 16–19 mmol/L. This means that DKA can occur at a relatively low blood glucose; cases of normoglycaemic DKA have been described.The clues were the heavy ketonuria and her breathlessness. After this case, new guidelines were drawn up that mandated serum electrolyte samples and whole-blood ketone tests in all diabetic women presenting with ketonuria to the obstetric unit irrespective of the blood glucose result.

Urinary tract infection rarely occurs without either positive urinary nitrite or leucocytes; proteinuria alone is not diagnostic.

Table 12.3 Water and electrolyte deficiencies in DKA and HHS

	DKA	HHS
Water mL/kg bodyweight	Approximately 100	100–200
Sodium mmol/kg bodyweight	7–10	5–13
Potassium mmol/kg bodyweight	3–5	5–15
Phosphate mmol/kg bodyweight	1–1.5	1–2
Magnesium mmol/kg bodyweight	1–2	1–2

Table 12.4 Guide to the initial treatment of diabetic ketacidosis in adults

Fluids and electrolytes

Volumes

- 1L first hour; 2L next 4 hours; 1L 4–6 hourly; thereafter adjusted according to response

Fluids

- Isotonic ('normal') saline (150 mmol/L) generally
- Hypotonic ('half-normal') saline (75 mmol/L) if serum sodium exceeds 150 mmol/L (no more than 1–2 L – consider 5% dextrose with increased insulin instead)
- Consider 5% dextrose 1 L 4–6 hourly when blood glucose has fallen to 15 mmol/L (severely dehydrated patients may require simultaneous or alternate saline infusion)

Potassium

- Give 20 mmol potassium in first litre of fluid unless initial plasma potassium >5.5 mmol/L
- Thereafter, add dosages below to each 1 L of fluid. If plasma K+:
  <3.5 mmol/L, add 40 mmol KCl (severe hypokalaemia may require more aggressive KCl replacement)
  3.5–5.5 mmol/L, add 20 mmol KCl
  >5.5 mmol/L, add no KCl.

Insulin

Continuous intravenous infusion:

- 5–10 units/h (average 6 units/h) initially until blood glucose has fallen to 15 mmol/L. Thereafter, adjust rate (1–4 units/h usually) during dextrose infusion to maintain blood glucose 5–10 mmol/L until patient is eating again
- Intramuscular injections: 20 units immediately, then 5–10 units/h until blood glucose has fallen to 15 mmol/L. Then change to 10 units 6 hourly subcutaneously until patient is eating again

Other measures

- Search for and treat precipitating cause (e.g. infection, myocardial infarction)
- Hypotension usually responds to adequate fluid replacement but may need colloid infusion
- Central venous pressure monitoring in elderly patients or if cardiac disease present
- Pass nasogastric tube if conscious level impaired, to avoid aspiration of gastric contents
- Urinary catheter if conscious level impaired or no urine passed within 4 h of start of therapy
- Continuous ECG monitoring may warn of hyper- or hypokalaemia (potassium should be measured at 0, 2 and 6 h, and more often if indicated)
- Adult respiratory distress syndrome – mechanical ventilation (100% O_2, IPPV), avoid fluid overload
- Mannitol (up to 1 g/kg IV) if cerebral oedema suspected. Dexametasone as alternative (induces insulin resistance). Consider cranial CT to exclude other pathology (e.g. cerebral haemorrhage, venous sinus thrombosis)
- Treat specific thromboembolic complications if they occur
- Keep a meticulous clinical and biochemical record using a purpose-designed flowchart

insulin analogues in a dose of 0.2 unit/kg bodyweight every 2 hours has been shown to be as effective as IV infusion in mild to moderate DKA.

The overall treatment goal is a reduction in blood glucose of no more than 3–5 mmol/L/h and osmolality by 3 mOsm/kg/h.

The role of intravenous bicarbonate is controversial. There is no proven benefit in patients with an arterial pH ≥6.9. There are good theoretical reasons why IV bicarbonate should not be given and its use has been associated with the development of cerebral oedema. The American Diabetes Association guidelines suggest 100 mmol diluted and given over 2 hours in patients with a pH <6.9 or in whom the acidosis is felt to be contributing to their clinical status.

Although phosphate and magnesium depletion are also present, there is no evidence that routine replacement is of benefit. However, serum phosphate levels <0.35 mmol/L can cause muscle weakness and myocardial dysfunction and need correction. Similarly, serum magnesium levels <0.7 mmol/L should also be treated.

LANDMARK CLINICAL TRIAL

Alberti KGMM, Hockaday TDR, Turner RC. Small doses of intramuscular insulin in the treatment of diabetic coma. Lancet 1973; 302: 515–522.

This study of 14 patients with DKA (mean plasma glucose 35.4 mmol/L (637 mg/dL) and plasma ketones 12.1 mmol/L), treated with 16 units of soluble monocomponent porcine insulin IM stat followed by 5–10 units hourly thereafter, showed conclusively that much lower doses of insulin than were currently being used could correct DKA safely. This work built upon the observation made the previous year by Sonksen et al. that low-dose IV infusion could correct hyperglycaemia safely and gradually. Prior to this large IV boluses were given with unpredictable metabolic responses. Later that year, a study using an IV bolus of 50 units followed by a 50 unit/h infusion in 11 patients with DKA was published from the USA. A long debate ensued across the Atlantic before the principle of low-dose insulin infusion was established internationally.

Complications of diabetic ketoacidosis

These include cerebral oedema which is a particular problem for children. This can cause 'coning', in which swelling of the brain within the enclosed space of the cranium forces the medulla and brainstem to herniate through the foramen magnum, leading to cardiorespiratory arrest. Cerebral oedema is often fatal, and accounts for 50% of deaths in newly presenting DKA in children. The cellular mechanisms responsible for cerebral oedema in DKA are uncertain, but clinically it is associated with rapid rehydration, a higher serum urea and lower arterial CO_2 tension at presentation and, in some cases, with IV bicarbonate replacement. It presents as a decline in conscious level, rapidly progressing to coma.

The diagnosis should be confirmed by computed tomography or magnetic resonance scanning of the brain. A reasonable treatment approach includes slowing the rate of IV fluid infusion, avoidance of hypotonic fluids, decreasing the insulin delivery rate and giving intravenous mannitol (0.2 g/kg over 30 minutes, repeated hourly if there is no improvement, or a single dose of 1 g/kg). Mechanical ventilation to remove carbon dioxide and improve acidosis has also been advocated.

Adult respiratory distress syndrome occasionally occurs in DKA, mostly in those under 50 years of age. The features include breathlessness, tachypnoea, central cyanosis and arterial hypoxia. Chest x-ray shows bilateral infiltrates which resemble pulmonary oedema. Management involves mechanical ventilation and avoidance of fluid overload.

Thromboembolism is a further potentially fatal complication usually associated with severe dehydration, increased blood viscosity and hypercoagulability. Prophylactic anticoagulation in DKA is not recommended routinely, but patients at high risk should be considered for heparin therapy.

Hyperosmolar hyperglycaemic state

Hyperosmolar hyperglycaemic state (HHS) used to be called hyperosmolar non-ketotic hyperglycaemic coma, or HONK, but is now termed HHS because mild ketosis can be present and because not all patients are comatose. The diagnostic criteria are contrasted with DKA in Table 12.1 and the fluid and electrolyte deficiencies in Table 12.3. It tends to occur gradually and is often associated with drug use (notably thiazide and loop diuretics, β-blockers, steroids and major psychotropic agents). Because of its gradual onset with thirst, many patients inadvertently compound the problem by drinking fruit juices or fluids high in glucose. Precisely why ketosis is not a feature in HHS is not known but because there is only a relative deficiency of insulin, portal venous concentrations may be enough to prevent hepatic ketogenesis, but peripheral insulin levels are insufficient to stimulate glucose uptake.

Around 25% of patients with HHS have newly diagnosed diabetes. However, HHS is unusual, accounting for <1% of hospital admissions due to diabetes in the UK. Mortality is high (5–20%), partly because of age and underlying cause – often cardiovascular disease or serious infection. In addition, thromboembolic complications may occur secondary to the marked hyperosmolality and some guidelines recommend prophylactic heparinisation.

Treatment is similar to DKA, with rehydration the key. Patients may present with significant hypernatraemia (serum sodium >150 mmol/L) in which case either 0.45% (half normal or hypotonic saline) or 5% (isotonic) dextrose

can be used. The low concentration of glucose in this solution should not exacerbate hyperglycaemia which will correct more by rehydration. Only 1–2 litres of hypotonic saline should be used as otherwise a too rapid reduction in osmolality may cause pulmonary or cerebral oedema. Many patients can be managed ultimately without insulin once they are metabolically stable.

Lactic acidosis

This is a rare but very serious and life-threatening metabolic crisis that is said to occur more frequently in people with diabetes. There are two types (type A-anaerobic and type B-aerobic) and their causes are listed in Table 12.5.

Whereas there is good evidence for a causative role of the biguanide phenformin, there is considerable debate as to whether metformin use *per se* is associated with lactic acidosis. A Cochrane systematic review of all reported trials found no episodes in 59,321 patient-years of metformin therapy or in 51,627 patient-years in diabetic patients not on metformin. Most reported cases in people with diabetes (on metformin or not) are in those with one of the serious underlying conditions listed in the table.

Table 12.5 Causes of lactic acidosis

Type A (anaerobic)		Type B (aerobic)	
Shock –	Cardiogenic	Systemic disease	Diabetes
	Endotoxic (septic)		Neoplasia
	Hypovalaemic		Hepatic failure
			Renal failure
Heart failure		Drugs	Biguanides
Asphyxia			Ethanol/methanol
Carbon monoxide poisoning			Salicylate overdose
			Inborn errors of metabolism

Most patients present with a profound metabolic acidosis with a massive anion gap. Treatment is of the underlying condition (which often determines outcome) and large volumes of IV bicarbonate are often required. Dichloroacetate can also be used to block lactate production but its use is confined to specialist centres. Most patients require ITU monitoring and care.

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Chapter
13

Hypoglycaemia

KEY POINTS

- Fear of hypoglycaemia is a major barrier to achieving optimum glycaemic control in patients with diabetes.
- Hypoglycaemic symptoms are classified as 'autonomic' (e.g. tremor, palpitation, sweating) and 'neuroglycopenic' (drowsiness, confusion and loss of consciousness). Autonomic symptoms, and their awareness, may diminish with increasing duration of diabetes.
- Hypoglycaemia is more common in patients with type 1 diabetes: 60–170 severe episodes per 100 patient-years, compared with 30–70 among insulin-treated patients with type 2 diabetes.
- The protective glucagon response to hypoglycaemia is impaired in patients with type 1 diabetes.
- The effects of GLP-1 on insulin and glucagon secretion are glucose dependent, therefore the effects of GLP-1 are attenuated if ambient plasma glucose concentrations are low. DPP-4 inhibitors, therefore, have a lower risk of hypoglycaemia.
- IM or SC glucagon can be administered in an emergency setting to treat hypoglycaemia if the patient is unable or unwilling to take glucose orally.

Aetiology and clinical presentation

Hypoglycaemia is a common side effect of treatment with insulin and oral antidiabetic drugs, especially sulphonylureas, and is a major factor preventing patients with type 1 and 2 diabetes from achieving near normoglycaemia. The brain is dependent on a continuous supply of glucose, and its interruption for more than a few minutes leads to central nervous system dysfunction, impaired cognition and eventually coma. The brain cannot synthesise glucose or store more than 5 minutes supply as glycogen. At normal or high circulating glucose concentrations, blood-to-brain glucose transport exceeds the rate of brain glucose metabolism but as glucose levels fall, blood-to-brain glucose transport becomes limiting to brain glucose utilisation. Hypoglycaemia is more common in young children and may be responsible for the cognitive impairment and lowered academic achievement in children diagnosed with diabetes under the age of 5 years – the developing brain is especially sensitive to hypoglycaemia.

Iatrogenic hypoglycaemia often causes physical and psychosocial morbidity and sometimes causes death (the 'dead-in-bed' syndrome may be due to cardiac arrhythmias secondary to nocturnal hypoglycaemia) (Box 13.1).

Box 13.1 Some consequences of hypoglycaemia in diabetes

- Obstacle to achieving normoglycaemia
- Disabling symptoms
- Sudden death syndrome
- Cognitive impairment in children
- Major source of anxiety in patients

In the person without diabetes, hypoglycaemia is limited in part by inhibition of insulin release from the pancreatic β cells and stimulation of glucagon from the α cells. The major physiological responses to hypoglycaemia occur as a result of activation of neurones in the ventromedial region of the hypothalamus and elsewhere in the brain; these neurones sense the lowered plasma glucose levels, activate the autonomic nervous system and stimulate pituitary counter-regulatory hormone release (Figure 13.1). Glucagon and epinephrine (adrenaline) release are probably the main

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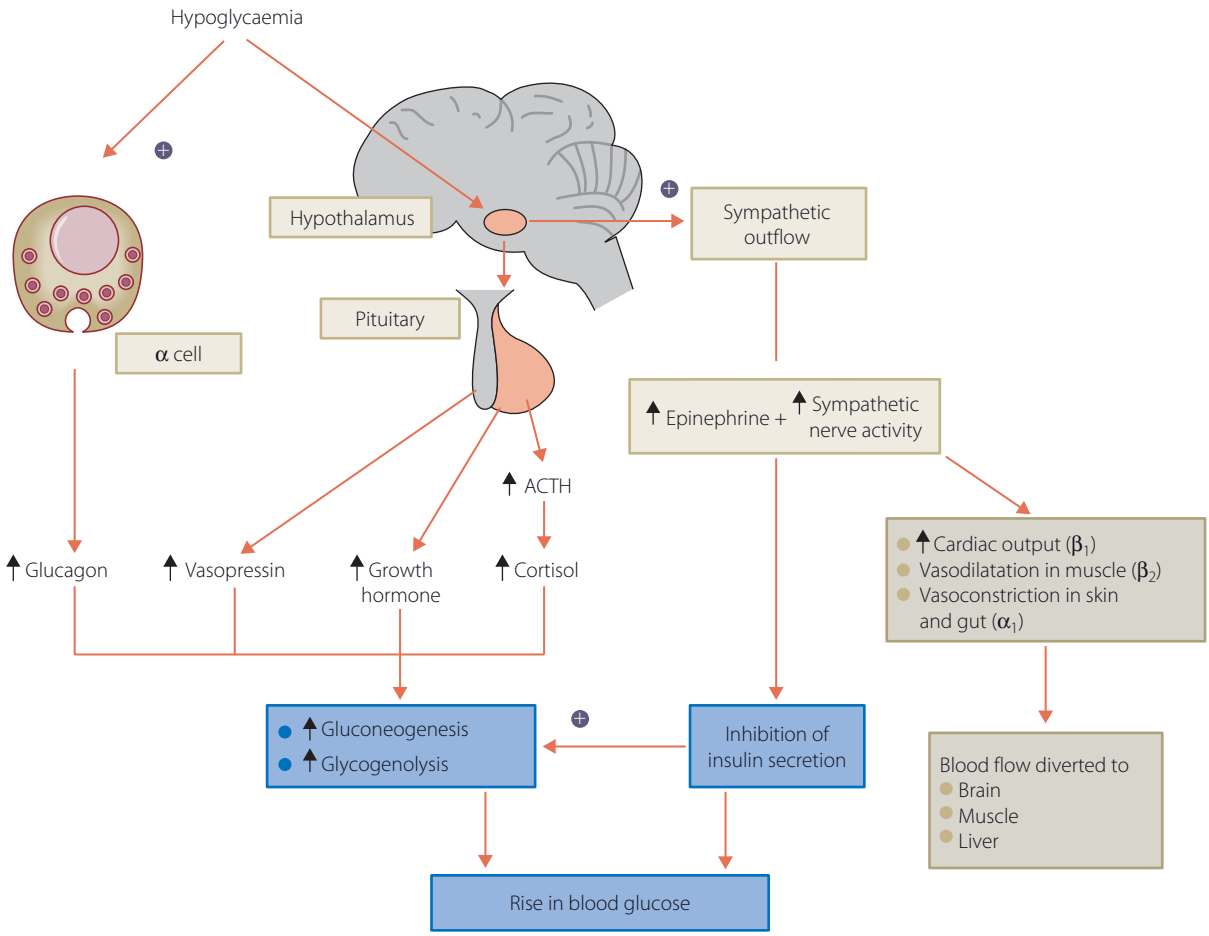

Figure 13.1 Major components of the counter-regulatory and sympathetic nervous system responses to hypoglycaemia. Vasopressin has weak counter-regulatory effects on its own, but acts synergistically with the other hormones.

factors that limit hypoglycaemia and ensure glucose recovery in normal subjects.

The physiological responses to a falling plasma glucose level produce a range of symptoms that help individuals to recognise hypoglycaemia and take corrective action. Hypoglycaemic symptoms can be classified as 'autonomic', caused by activation of the sympathetic or parasympathetic nervous system (e.g. tremor, palpitations or sweating), or 'neuroglycopenic', caused by the effects of glucose deprivation on the brain (e.g. drowsiness, confusion and loss of consciousness) (Table 13.1). Headache and nausea are probably non-specific symptoms of malaise. Autonomic symptoms are prominent in subjects with a short duration of diabetes, but diminish with increasing duration of diabetes.

In patients with type 1 diabetes, episodes of asymptomatic hypoglycaemia are common: plasma glucose levels may be in the region of 2.8–3.3 mmol/L (50–60 mg/dL) 10% of the time. Patients experience an average of two episodes of symptomatic hypoglycaemia per week, and one episode of severe disabling hypoglycaemia per year; 2–4% of deaths among people with type 1 diabetes are attributed to hypoglycaemia. Hypoglycaemia causes unpleasant symptoms, e.g. anxiety, palpitations, sweating, and the neurological consequences include behavioural changes, cognitive dysfunction, seizures and coma.

Table 13.1 Common symptoms of acute hypoglycaemia in patients with diabetes

Autonomic	Neuroglycopenic	Malaise
Sweating	Confusion	Nausea
Pounding heart	Drowsiness	Headache
Shaking (tremor)	Speech difficulty	
Hunger	Inco-ordination	
	Atypical behaviour	
	Visual disturbance	
	Circumoral paraesthesiae	

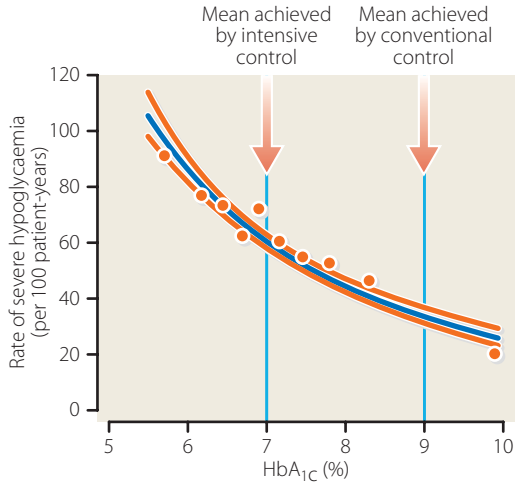

Figure 13.2 In the DCCT, a landmark trial that compared the effects of 'intensive' and 'conventional' glycaemic control on vascular complications in patients with type 1 diabetes, the risk of hypoglycaemia increased in proportion to the reduction in HbA_{1c}. At lower levels of HbA_{1c} (e.g. <7%), tighter glycaemic control may confer only small additional benefits in terms of preventing retinopathy but carry a significant increased risk of life-threatening hypoglycaemia. From Diabetes Control and Complications Trial. N Engl J Med 1993; 329: 977–986.

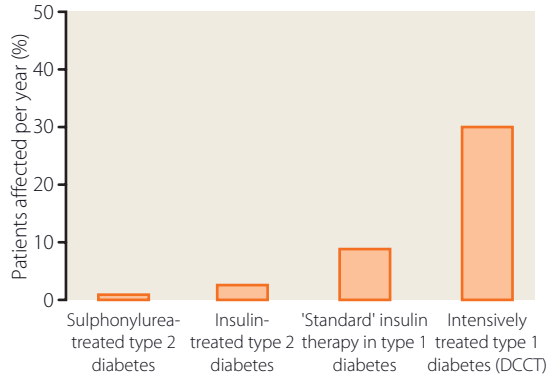

Figure 13.3 Risks of severe hypoglycaemia associated with different diabetes treatments.

CASE HISTORY

A 36-year-old woman with a 25+ year history of type 1 diabetes presents with recurrent severe hypoglycaemia, often in the early hours of the morning. She has multiple microangiopathic complications, including proliferative retinopathy (treated by laser photocoagulation), painful neuropathy, microalbuminuria and gastroparesis. HbA_{1c} is 8.4% using a basal-bolus insulin regimen. She has considerable anxiety about hypoglycaemia, having embarrassed herself at work with odd behaviour associated with a hypo. She has mostly lost her awareness of hypoglycaemic symptoms, and is reluctant to modify her insulin doses (in order to improve HbA_{1c}) because of the risk of hypos. On admission to hospital, she reports at least six severe hypos in the past year requiring third-party assistance.

Comment: Hypoglycaemia unawareness is common among patients with long-duration type 1 diabetes, especially when autonomic dysfunction is present. Fear of severe hypoglycaemia, associated with behavioural disturbance and altered cognition, is an understandable barrier to improving glycaemic control, yet because of advanced microvascular complications, this woman would benefit from lower HbA_{1c} levels in the long term. This is a complex management problem. She would be a candidate for continuous subcutaneous insulin infusion using a pump.

The frequency of iatrogenic hypoglycaemia is much lower in patients with type 2 diabetes. For example, published rates of severe hypoglycaemia among type 1 diabetic patients treated aggressively with insulin range from 60 to 170 episodes per 100 patient-years. Corresponding rates for insulin-treated type 2 diabetic patients range from 3 to 70 episodes per 100 patient-years. Severe hypoglycaemia rates in type 2 diabetes are only 10% of those in type 1 diabetes, even during aggressive insulin therapy. During 6 years of follow-up in the UKPDS, only 2.4% of metformin-treated patients, 3.3% of sulphonylurea-treated patients and 11.2% of those on insulin reported a major hypoglycaemia episode (requiring third-party assistance). Modern therapies, including long-acting insulin analogues, third-generation sulphonylureas, and DPP-4 inhibitors are associated with less hypoglycaemia (Figure 13.3).

Hypoglycaemia in diabetes is caused by absolute or relative insulin excess, but the integrity of glucose counter-regulatory mechanisms has an important effect on the clinical outcomes. Thus, compromised glucose counter-regulation is well recognised in type 1 diabetes and probably also occurs in advanced type 2 diabetes. Risk factors for compromised glucose counter-regulation include: (1) insulin deficiency states; (2) history of severe hypoglycaemia, hypoglycaemia unawareness or both; and (3) aggressive antidiabetic therapy, as shown by lower HbA_{1c} (Table 13.2).

The initial response to hypoglycaemia is the acute release of counter-regulatory hormones (in particular, glucagon and epinephrine) which occurs at a plasma glucose concentration of about 3.6–3.8 mmol/L (65–68 mg/dL). Autonomic symptoms develop at about 3.2 mmol/L (58 mg/dL), before cognitive function starts to deteriorate at around 3 mmol/L (54 mg/dL) (Figure 13.4). Those patients who retain awareness of hypoglycaemia are thus alerted before significant cerebral dysfunction occurs. However, the inability to recognise symptoms of impending hypoglycaemia, known as 'hypoglycaemia unawareness', is a major clinical problem in those with insulin-treated diabetes. Hypoglycaemic unawareness affects about 25% of patients with type 1 dia-

Table 13.2 Factors that precipitate or predispose to hypoglycaemia in patients with diabetes

Excessive insulin levels		**Enhanced insulin effect**		
Excessive dosage	Increased insulin bio-availability	Increased insulin sensitivity	Inadequate carbohydrate intake	Other factors
Error by patient, doctor or pharmacist	Accelerated absorption • Exercise • Injection into abdomen • Change to human insulin	Counter-regulatory hormone deficiencies • Addison's disease • Hypopituitarism	Missed, small or delayed meals	Exercise • Acute: accelerated absorption • Late: repletion of muscle glycogen
Poor matching to patient's needs or lifestyle needs	Insulin antibodies (release of bound insulin)	Weight loss	Slimming diets	Alcohol (inhibits hepatic glucose production)
Deliberate overdose (fictitious hypoglycaemia)	Renal failure (reduced insulin clearance)	Physical training	Anorexia nervosa	Drugs • Enhance sulphonylurea action (salicylates, sulphonamides) • Block counter-regulation (non-selective β-blockers)
	'Honeymoon period' (partial β cell recovery) in type 1 diabetes	Postpartum	Vomiting, including gastroparesis	
		Menstrual cycle variation	Breastfeeding Failure to cover exercise (early or delayed hypoglycaemia)	

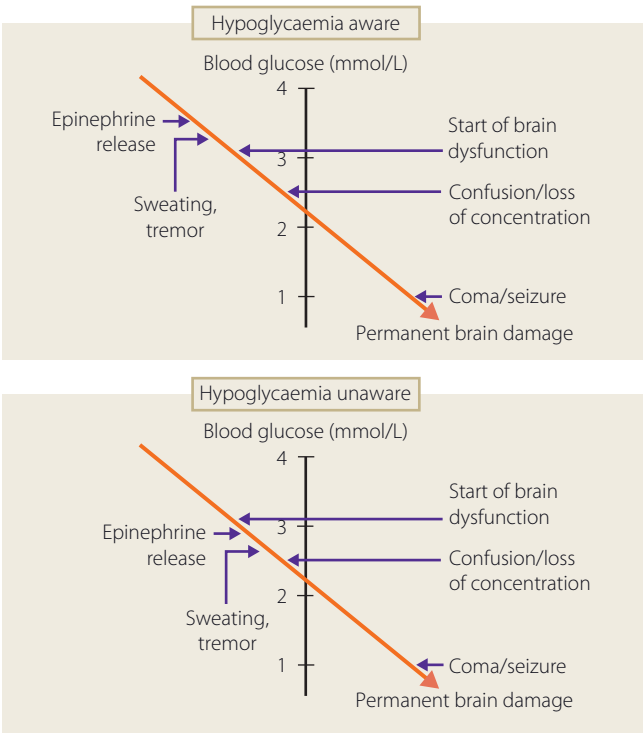

Figure 13.4 Glycaemic thresholds for the release of epinephrine and activation of autonomic symptoms and for neuroglycopenic effects in subjects with diabetes who are aware or unaware of hypoglycaemia. Note that in those who are unaware of hypoglycaemia, activation of autonomic symptoms occurs at a glycaemic threshold below that for cognitive impairment.

betes. In these patients, sympathoadrenal activation occurs at a lower plasma glucose level than for cognitive impairment. The risk of a severe episode of hypoglycaemia increases 6–7-fold in patients with hypoglycaemia unawareness.

Nearly all people with insulin-treated diabetes have some defect in the mechanisms that protect them against hypoglycaemia, although the impairment is mild in type 2 diabetes. The glucagon response to hypoglycaemia begins to fail within 1–2 years of type 1 diabetes onset, probably because of disruption to paracrine mechanisms of cross-talk within the islet, as endogenous insulin production declines. A reduced sympathoadrenal response is common in type 1 diabetes of long duration; those who exhibit both glucagon and epinephrine impairment are particularly susceptible to hypoglycaemia, because of both impaired glucose counter-regulation and impaired hypoglycaemia awareness (Figure 13.5). Autonomic neuropathy is a major cause of hypoglycaemia unawareness.

Glucose-dependent actions of GLP-1

The incretin hormone GLP-1, released by the gut in response to food intake, acts on β and α cells in the pancreatic islets to increase insulin secretion and decrease glucagon secretion, respectively. But the glucose-lowering effects of GLP-1 are glucose dependent. This means that GLP-1 effects are attenuated at low plasma glucose concentrations. Thus, GLP-1 analogues, such as exenatide and liraglutide, and the

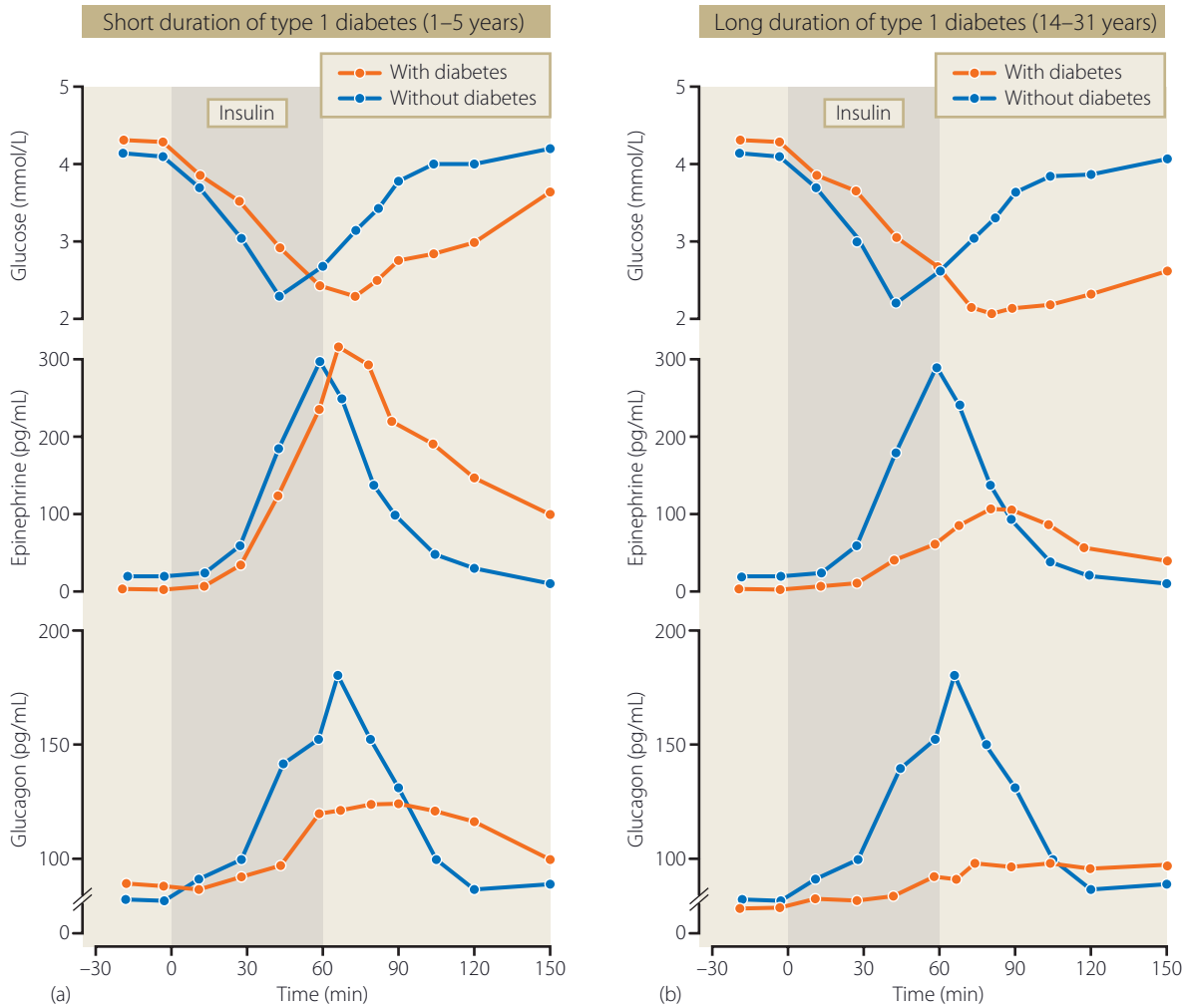

Figure 13.5 Impairment of counter-regulatory responses in type 1 diabetes. (a) After 1–5 years of type 1 diabetes, the mean glucagon response (*lower panel*) is blunted, but the rise in epinephrine secretion is preserved (*middle panel*) and glycaemic recovery is delayed (*upper panel*). (b) With long-standing type 2 diabetes, both glucagon and epinephrine responses are impaired severely and glycaemic recovery is markedly delayed and slowed. From Boli et al. Diabetes 1983; 32: 134–141.

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DPP-4 inhibitors which lower glucose levels by GLP-1 mediated effects, appear to have a very low incidence of hypoglycaemia in clinical trials (Figure 13.6). Avoidance of hypoglycaemia, especially in comparison with sulphonylureas and insulin, is likely to be the major advantage of these newer treatments for type 2 diabetes.

Hypoglycaemia awareness

Tight glycaemic control is a risk factor for impaired glucose counter-regulation and hypoglycaemia unawareness – lower levels of HbA_{1c} result in a resetting of thresholds for the counter-regulatory and symptomatic responses to hypoglycaemia at lower glucose concentrations. In addition, recurrent hypoglycaemia exacerbates the defective responses to subsequent hypoglycaemia, thus leading to a vicious circle of reduced awareness, increased vulnerability and further episodes of hypoglycaemia (Figure 13.7). It is likely that the neurones that initiate the autonomic response adapt to chronic hypoglycaemia by increasing glucose transporter expression and glucose uptake. Subsequent hypoglycaemia then fails to produce sufficient intracellular glycopenia and therefore no longer elicits a response. There is also evidence that cortisol (released during the counter-regulatory response to hypoglycaemia) dampens the hypothalamic sensing of glucose.

Most episodes of hypoglycaemia can be self-treated by ingestion of glucose tablets or 20 g of carbohydrate in the form of juice, biscuits or a meal. Parenteral therapy is needed when a hypoglycaemic patient is unable or unwilling (because of neuroglycopenia) to take carbohydrate orally. Intramuscular glucagon is used by family members of patients with type 1 diabetes, but glucagon is less useful in type 2 diabetes because it stimulates insulin secretion as well as glycogenolysis. Continuous subcutaneous insulin infusion (CSII, see Chapter 10) is associated with a lower frequency of hypoglycaemia than multiple insulin injection therapy and should be considered as a therapeutic option in those patients with type 1 diabetes with frequent, unpredictable hypoglycaemia. Newer insulin analogues may also decrease the risk of hypoglycaemia.

Suspected severe hypoglycaemia (e.g. in a diabetic patient with impaired consciousness or coma) should be confirmed

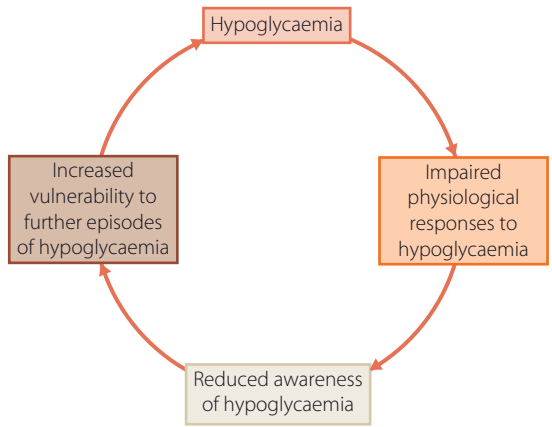

Figure 13.7 The vicious circle of repeated hypoglycaemia.

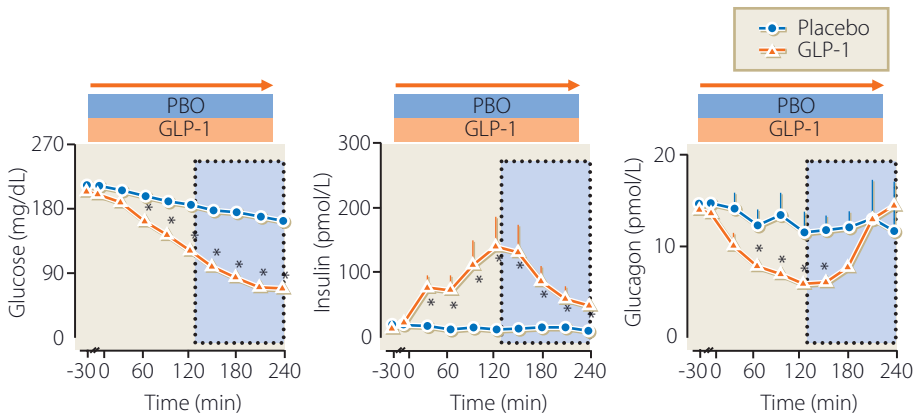

Figure 13.6 On two separate occasions, volunteers received an IV infusion of GLP-1 or placebo for 4 hours. The effects of placebo and GLP-1 on plasma glucose (*left panel*), insulin (*middle*) and glucagon (*right panel*) concentrations are shown. GLP-1 lowered glucose levels progressively, but the effects on insulin and glucagon reached a peak at 120 min. After 120 min, in the relative absence of glucose, insulin concentrations declined and glucagon suppression decreased. The effects of GLP-1 on β and α cells are glucose dependent. Adapted from Nauck et al. Diabetologia 1993; 36: 741–744.

by blood glucose testing. It should be treated immediately with oral glucose or, if the patient is unconscious or unable to swallow safely, with intravenous glucose or intramuscular or subcutaneous glucagon injection (Figure 13.8). Patients usually recover within minutes.

Box 13.2 General principles for optimising glycaemic control and minimising the risk of hypoglycaemia

- Patient education and empowerment
- Flexible insulin and treatment regimens
- Frequent self-monitoring of blood glucose levels
- Individualised glycaemic targets
- Ongoing professional advice and support

KEY WEBSITES

- www.diabetes.co.uk/Diabetes-and-Hypoglycaemia.html
- www.gpnotebook.co.uk/simplepage.cfm?ID=-19922936
- www.library.nhs.uk/guidelinesFinder/ViewResource.aspx?resID=59817
- www.diabetes.org/type-1-diabetes/hypoglycemia.jsp
- SIGN Guidelines: www.SIGN.ac.uk

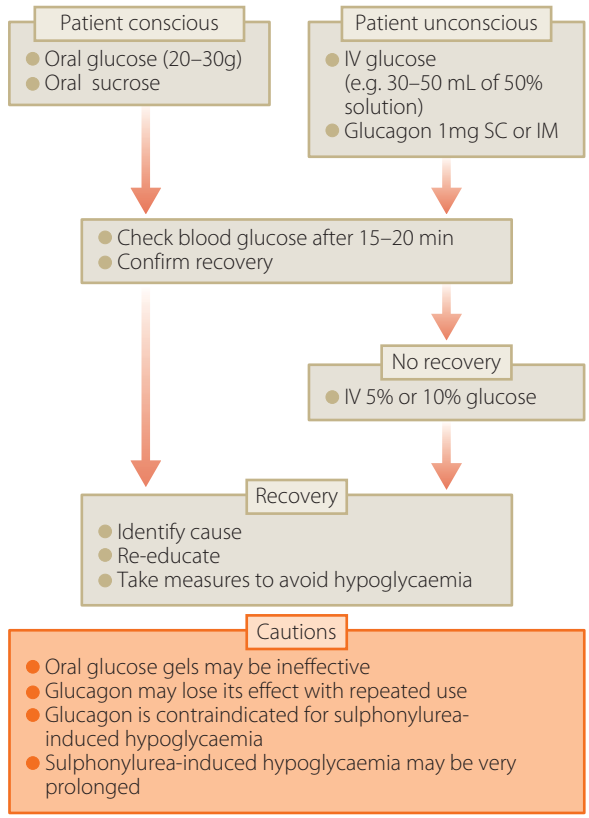

Figure 13.8 Algorithm for treating acute hypoglycaemia in patients with diabetes. Some important cautions are also indicated.

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Chapter

14

Control and complications

KEY POINTS

- Tissue complications of diabetes can be specific, microvascular damage to the eye, kidney or peripheral nerve (retinopathy, nephropathy or neuropathy), or non-specific macrovascular accelerated atherosclerosis.
- Conclusive evidence now links the level of hyperglycaemia to development of microvascular complications and glycaemic correction can prevent or slow their progression.
- The evidence for macrovascular disease is much less secure. Hyperglycaemia causes complications by several potential mechanisms including activation of the polyol and hexosamine pathways, and production of advanced glycation end-products. Each of these processes results in the generation of reactive oxygen species, so oxidative stress may represent the final common path towards complications.

Much of the impact of chronic diabetes results from the development of tissue complications, mainly microvascular (retinopathy, nephropathy and neuropathy) and macrovascular disease (atherosclerosis). Microangiopathy is characterised by progressive occlusion of the capillary lumen with subsequent impaired tissue perfusion, increased vascular permeability and increased production of extracellular material by perivascular cells, resulting in basement membrane thickening. There is strong evidence that microvascular disease is related to the duration and severity of hyperglycaemia in both type 1 and type 2 diabetes. A classic observational study by Pirart demonstrated this link in 4400 type 1 and 2 patients followed for up to 25 years (Figure 14.1). As diabetes duration increased, the prevalence of retinopathy, nephropathy and neuropathy was greatest in those with the worst glycaemic control and least in those with the best control.

Many other epidemiological studies have supported this relationship. In the Wisconsin Epidemiologic Study of Diabetic Retinopathy (WESDR), the incidence and progression of retinopathy in subjects with type 1 ('younger onset') and type 2 ('older onset') diabetes were clearly related to glycaemic status (Figure 14.2).

Convincing proof that good glycaemic control could prevent complications in type 1 diabetes came with the Diabetes Control and Complications Trial (DCCT), which reported in 1993. This study is often regarded as a landmark in diabetes research: 1441 patients in 29 centres in North America were allocated randomly to either 'conventional' therapy (one or two daily insulin injections, 3-monthly clinic visits, no insulin dosage adjustments according to self-

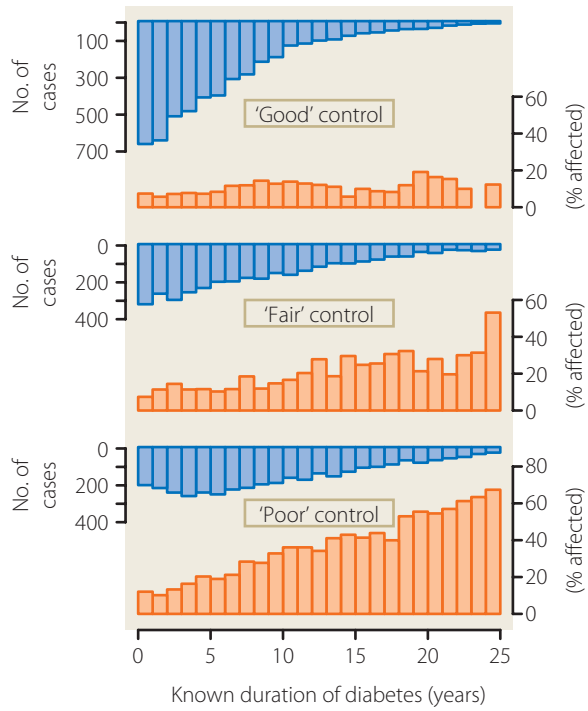

Figure 14.1 Prevalence of diabetic neuropathy as a function of duration of diabetes in patients with 'good', 'fair' and 'poor' control. From Pirart. Diabetes Care 1978; 1: 168–188, 262–261.

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monitored glucose data) or to 'intensive' therapy (three or more daily insulin injections or insulin pump therapy, monthly clinic visits and weekly telephone calls, frequent blood glucose self-monitoring with insulin dosage adjustment, and a diet and exercise programme). Throughout the 9-year study, there was markedly better glycaemic control in the intensively treated group. After a mean of 6.5 years follow-up, the intensive treatment arm had an HbA_{1c} of 7.4% versus 9.1% (56 versus 76 mmol/mol) in the conventionally treated patients (Figure 14.3). However, less than 5% in the intensive arm had an average HbA_{1c} consistently within the normal range.

Patients were divided into those who had no evidence of retinopathy at baseline (primary prevention) and those with mild to moderate retinopathy (secondary prevention). The study was powered for retinal and not renal or neurological endpoints.

However, the study showed clinically important reductions in retinopathy, nephropathy (as defined by urinary albumin excretion) and neuropathy in the intensively treated patients. Retinopathy was assessed by seven field fundus stereophotographs and classified according to the Early Treatment Diabetic Retinopathy Study (ETDRS) scale. A three-step change was regarded as significant (see Chapter 15).

In the primary prevention arm there was a 76% risk reduction (Figure 14.4), and a 54% risk reduction in the secondary prevention arm (63% risk reduction for both arms combined).

In type 2 diabetes similar evidence came from the UKPDS which reported in 1998. This was a 20-year study recruiting over 5000 patients with type 2 diabetes in 23 centres throughout the UK. In the main study, 3867 patients with newly diagnosed type 2 diabetes were allocated randomly to 'intensive' therapy (sulphonylureas, [chlorpropamide or glibenclamide/glyburide] or to insulin) or to 'conventional' therapy, which was diet initially although tablets or insulin could be added later if patients became symptomatic or developed a fasting blood glucose above 15 mmol/L.

Over 10 years those in the intensive arm had an HbA_{1c} of 7.0% versus 7.9% (53 versus 63 mmol/mol) in the conventionally treated patients. Intensive therapy was associated with a significant 25% reduction in microvascular disease endpoints (an aggregate of vitreous haemorrhage, laser photocoagulation, renal failure, defined as a serum creatinine >250 µmol/L, or death from renal failure). At 12 years using the ETDRS scale, there was a 21% reduction in a two-step change in retinopathy level in the intensively treated patients (Figure 14.5).

Blood pressure

In the DCCT, patients were normotensive at entry. In the UKPDS, however, nearly one-third of patients were hypertensive at entry. Embedded within the trial was a blood pressure-lowering study in which 1148 hypertensive patients

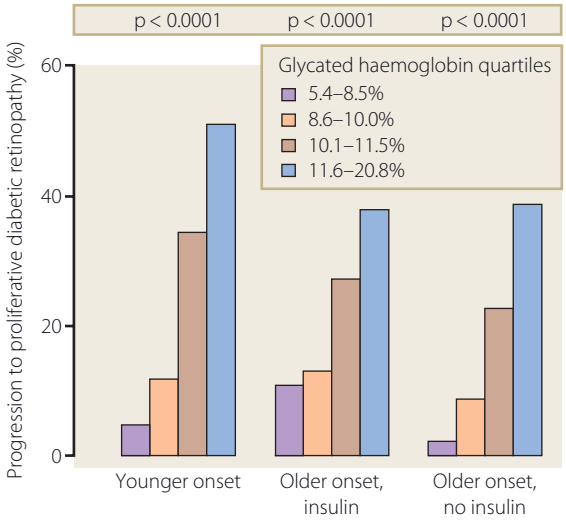

Figure 14.2 Progression of proliferative retinopathy is related to glycated haemoglobin percentage in the Wisconsin Eye Study. From Klein et al. Ann Intern Med 1996; 124: 90–96.

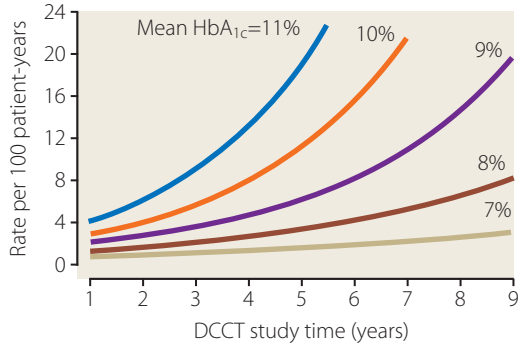

Figure 14.3 Risk of retinopathy progression and mean glycated haemoglobin in the conventional arm of the DCCT.

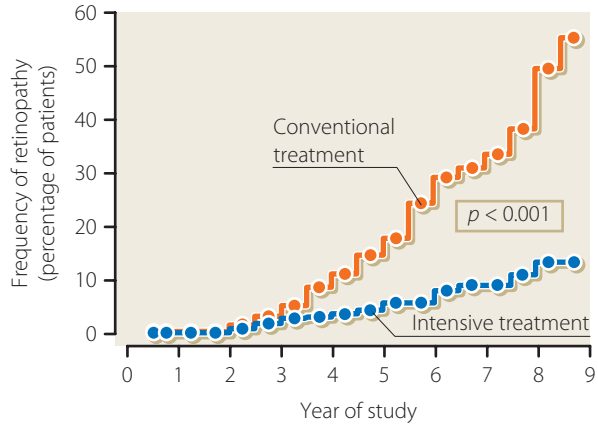

Figure 14.4 Effect of intensive treatment on the onset of retinopathy. Cumulative incidence of background retinopathy in patients with type 1 diabetes who entered the DCCT without retinopathy (primary prevention). From DCCT. N Engl J Med 1993; 329: 977–986.

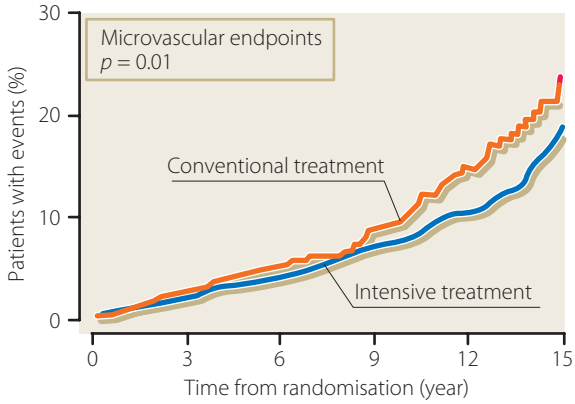

Figure 14.5 Effect of intensive blood glucose control on microvascular complications in type 2 diabetes (UKPDS). From UKPDS Group. Lancet 1998; 352: 837–854.

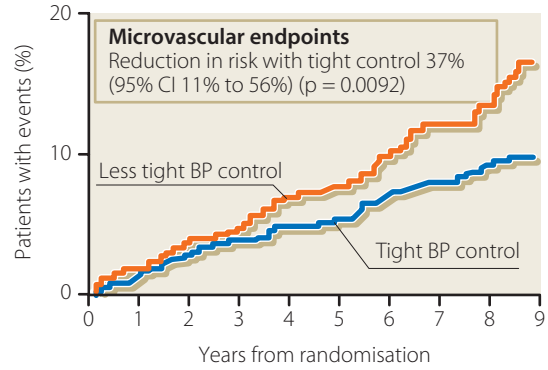

Figure 14.6 Kaplan–Meier plots of proportions of patients who developed microvascular endpoints (mostly retinal photocoagulation) during tight or less tight BP control (UKPDS). From UKPDS Group. BMJ 1998; 317: 703–713.

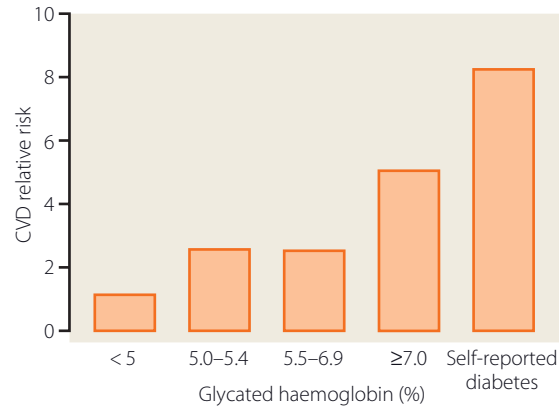

Figure 14.7 The relationship between glycated haemoglobin percentage and cardiovascular disease (CVD) in the EPIC Norfolk Study of 4662 men. From Khaw et al. BMJ 2001; 322:15–18.

were allocated to either tight (target <150/<85 mmHg) or less tight (target <180/<105 mmHg) control (Figure 14.6). Moreover, the tight control group were further randomised to a regimen based upon either captopril or atenolol.

Using the same aggregate microvascular endpoint as for the glycaemic control study, there was a reduction of 37% in the tight control group. No difference was seen in those treated with atenolol or captopril. Blood pressure and hyperglycaemia have an undoubtedly additive effect on the development of diabetic complications (see Chapter 19).

Macrovascular disease

Epidemiological studies show a clear positive relationship between glycaemia and macrovascular disease in the general population. For example, in the European Prospective Investigation of Cancer and Nutrition (EPIC) study of 4600 men in the UK, HbA_{1c} was continuously related to cardiovascular mortality from low normal levels (<5%; <31 mmol/mol) to values >7% (>53 mmol/mol) and in people with self-reported diabetes (Figure 14.7).

In the UKPDS, however, there was no significant impact of intensive glycaemic control on macrovascular complications although at 10 years there was a 16% reduction in relative risk for myocardial infarction which just failed to reach statistical significance (p = 0.052).

In 2008 the results from three large randomised controlled trials were reported, involving over 23,000 patients with type 2 diabetes who were allocated to a strategy of intensive versus less intensive glycaemic control and for whom the main outcome variable was macrovascular disease. These trials showed no benefit of glycaemic control on the standard combined cardiovascular endpoint of fatal and non-fatal myocardial infarction and stroke. Moreover, there was a slight increase in cardiac mortality in the intensively treated arm of the ACCORD trial although the total number of myocardial infarctions was almost identical in the intensive and less intensive arms (Table 14.1).

The reason for this discrepancy with the findings from intensive control on microvascular disease probably relates to their pathogenesis. Retinopathy, nephropathy and neuropathy are virtually diabetes specific and therefore hyperglycaemia is the main driving force for them. On the other hand, atherosclerosis is more multifactorial and although blood glucose is important, it is only one of many factors which contribute.

Metabolic memory

The DCCT and UKPDS have published follow-up of the patients who took part in the original studies. At the end of the respective trials, patients were followed but no longer randomised to differing standards of glycaemic control.

Most of the DCCT patients took part in the Epidemiology of Diabetes Interventions and Complications (EDIC) Study. Eight years after the end of the DCCT, the relative risk for development of new microalbuminuria was 49% (95% CI 32–62%) for intensive control and for clinical or overt nephropathy 85% (68–92%). This was despite the fact that the HbA_{1c} levels in the original intensive and conventional

Table 14.1 Main features of the ACCORD (Action to Control CardiOvascular Risk in Diabetes), ADVANCE (Action in Diabetes and Vascular Disease – Preterax and Diamicron Modified Release Controlled Evaluation) and VADT (Veterans Affairs Diabetes Trials) studies

	ACCORD	ADVANCE	VADT
Patient characteristics *n* (male %)	10,251 (39%)	11,140 (42%)	1791 (97%)
Mean age (years)	62	66	60
Known duration of diabetes years	10	8	11.5
History of cardiovascular disease (%)	35%	32%	40%
BMI kg/m^2	32	28	31
Median baseline HbA_{1c} (%)	8.1	7.2	9.4
Target HbA_{1c} (%)	<6.0 vs 7.0–7.9	<6.5	<6.0 vs planned separation of 1.5
Study characteristics			
Median duration of follow-up (years)	3.5	5.0	5.6
Achieved median HbA_{1c} (%)*	6.4 vs 7.5	6.3 vs 7.0	6.9 vs 8.5
Weight change (kg)*	+3.5 vs +0.4	–0.1 vs –1.0	+7.8 vs +3.4
Participants with one or more severe hypoglycaemic reactions (%)*	16.2 vs 5.1	2.7 vs 1.5	21.2 vs 9.9
Hazard ratio for primary macrovascular outcome (95% CI)	0.90 (0.78–1.04)	0.94 (0.84–1.06)	0.88 (0.74–1.05)

*Intensive versus less intensive arms.
Adapted from Skyler et al. Diabetes Care 2009; 32: 187–192.

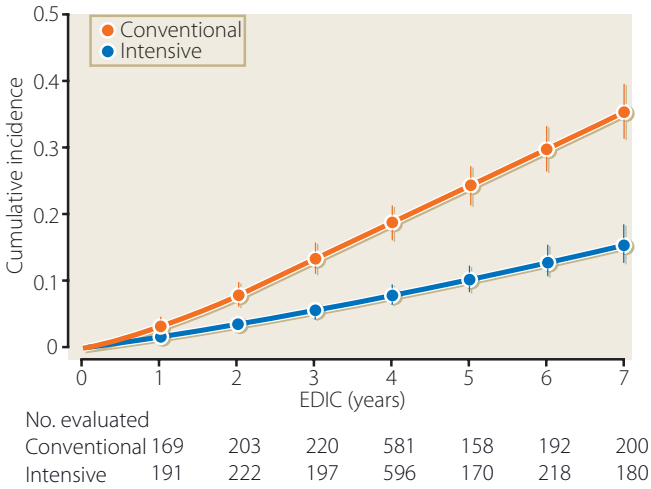

Figure 14.8 Metabolic memory in the DCCT/EDIC trial. Significant reduction in the development of new retinopathy was maintained in the original intensive therapy arm of the DCCT 8 years after the conclusion of the study despite similar HbA_{1c} levels to the conventional arm. From DCCT/EDIC. JAMA 2002;287:2563–2569.

groups had almost merged at 8.0 versus 8.2% (64 versus 67 mmol/mol) respectively (p = 0.002).

Similarly, in the UKPDS, a 10-year follow-up at the end of the trial revealed that glycaemia was almost identical in the intensive and conventional groups (HbA_{1c} approximately 7.8%; 62 mmol/mol) but there was a remaining relative risk of 0.76 (95% CI 0.64–0.89) for the combined microvascular disease endpoint in the intensive arm.

Interestingly, for myocardial infarction there was a significantly lower relative risk of 0.85 (0.74–0.97) for the intensively treated group. Moreover, the DCCT/EDIC study also showed a benefit in terms of cardiovascular events in the intensively treated group 8 years after the close of the original study (risk reduction 42%; 9–68%) although numbers of events were very small (46 versus 98).

The long-term benefit of intensive control despite the fact that there is no long-term glycaemic separation remains unexplained. It is not clear whether there is merely a delay in the intensively treated patients and that ultimately they will catch up or whether this is of long-term clinical benefit. As the DCCT participants were relatively short duration and the UKPDS involved patients with newly diagnosed type 2 diabetes, the message is that the better the glycaemic control in the early stages of diabetes, the better the long-term outlook in terms of both micro- and macrovascular complications.

CASE HISTORY

A 65-year-old man with type 1 diabetes for over 50 years attended for annual review. He had few tissue complications apart from minor cheiroarthropathy, minimal background retinopathy and mild angina, well-controlled medically. His control had always been excellent with HbA_{1c} levels never above 7.5% (58 mmol/mol). He had noticed hypoglycaemic unawareness, however, and because of this he was commenced on CSII 2 years previously.

He is remarkable in other ways. He and his wife had their own family but they have also fostered over 20 children and have a consequently very large and globally dispersed extended family. He says he was always too active and busy not to look after his diet and diabetes.

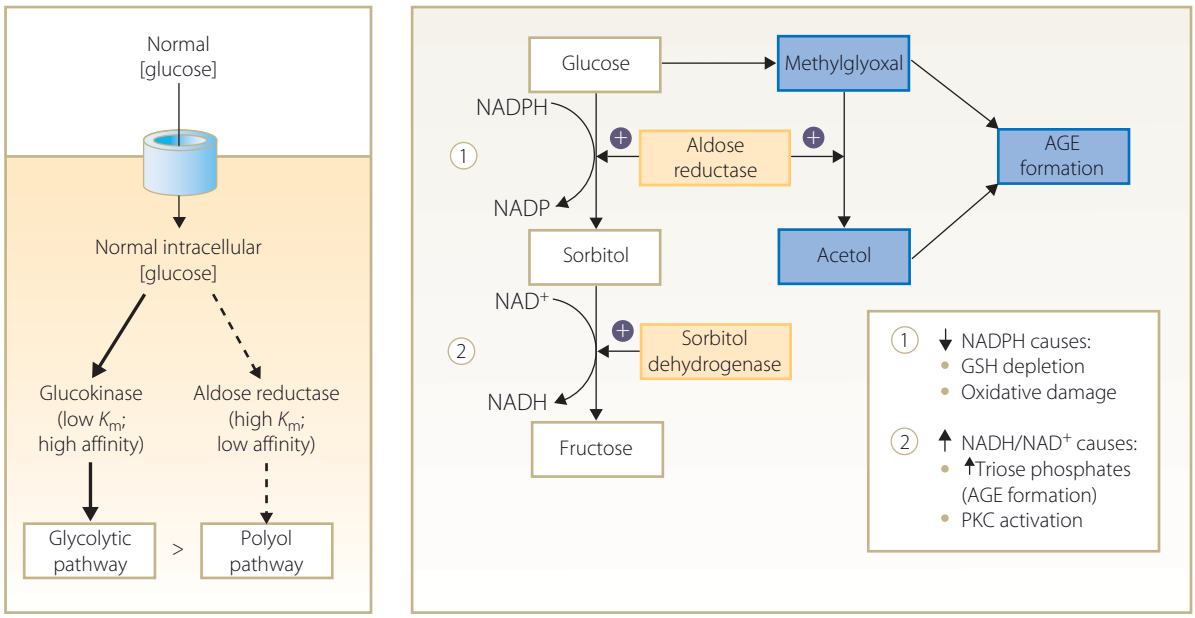

Figure 14.9 The polyol pathway. (*Left*) The pathway is normally inactive, but becomes active when intracellular glucose levels rise. (*Right*) Consequences of increased glucose flux through the polyol pathway include the generation of powerful glycating sugars (methylglyoxal, acetol and triose phosphates), enhanced oxidative damage and protein kinase C (PKC) activation. AGE, advanced glycation end-products; GSH, reduced glutathione; NAD, nicotinamide adenine dinucleotide.

How does hyperglycaemia cause complications?

Microvascular complications occur in cells and tissues which are unable to limit glucose transport in the face of hyperglycaemia (particularly the retina, the mesangium in the kidney and Schwann cells). Several metabolic pathways and secondary messengers have been implicated in these tissues and the main ones are dealt with here.

Polyol pathway (Figure 14.9)

In this pathway, the rate-limiting enzyme, aldose reductase, reduces glucose to its sugar alcohol, sorbitol. This is then oxidised by sorbitol dehydrogenase into fructose. Aldose reductase is a ubiquitous enzyme found in many tissues but specifically nerve cells, retinal cells, the glomerulus and kidney tubule, and blood vessel walls. The pathway is normally inactive but in the presence of hyperglycaemia there is increased flux leading to accumulation of intracellular glucose and glucose-derived substances, such as methylglyoxal and acetol, which can rapidly glycate proteins (see below). Sorbitol does not diffuse easily across cell membranes and damage may occur because of osmotic stress (currently thought to be less likely although may be operative in the lens of the eye in the formation of cataract). Alternative mechanisms involve decreased levels of nicotinamide adenine dinucleotide phosphate hydrogen (NADPH), and increases in nicotinamide adenine dinucleotide plus hydrogen (NADH). The result of these changes is activation of protein kinase C and the promotion of advanced glycation endproduct formation (see below). Moreover, these changes result in increased oxidative stress (see below).

Advanced glycation endproducts

Advanced glycation endproducts (AGEs) are formed by the reaction of glucose and other glycating compounds, such as methylglyoxal, with proteins (an analagous process to the formation of glycated haemoglobin), and other long-lived molecules, such as nucleic acids. Early glycation products are reversible, but eventually they undergo irreversible change through cross-linking (Figure 14.10).

Advanced glycation endproducts can cause damage and ultimately complications of diabetes in two ways; firstly, as a result of cross-linkage of matrix proteins, such as collagen and laminin, leading to thickening and stiffening of blood vessels which can affect permeability and elasticity. Secondly, AGE-modified circulating proteins bind to specific receptors (RAGEs – three subtypes have now been described) on several types of cell, including monocyte/macrophages, glomerular mesangial cells and endothelial cells. This binding leads to the generation of reactive oxygen species, activation of secondary messengers such as protein kinase C (PKC), release of transcription factor NFκB and stimulation of cytokine and growth factor production, which can result in inflammatory cell adhesion (via increased VCAM-1), procoagulant protein expression and increased vascular permeability (via VEGF) (Figure 14.11).

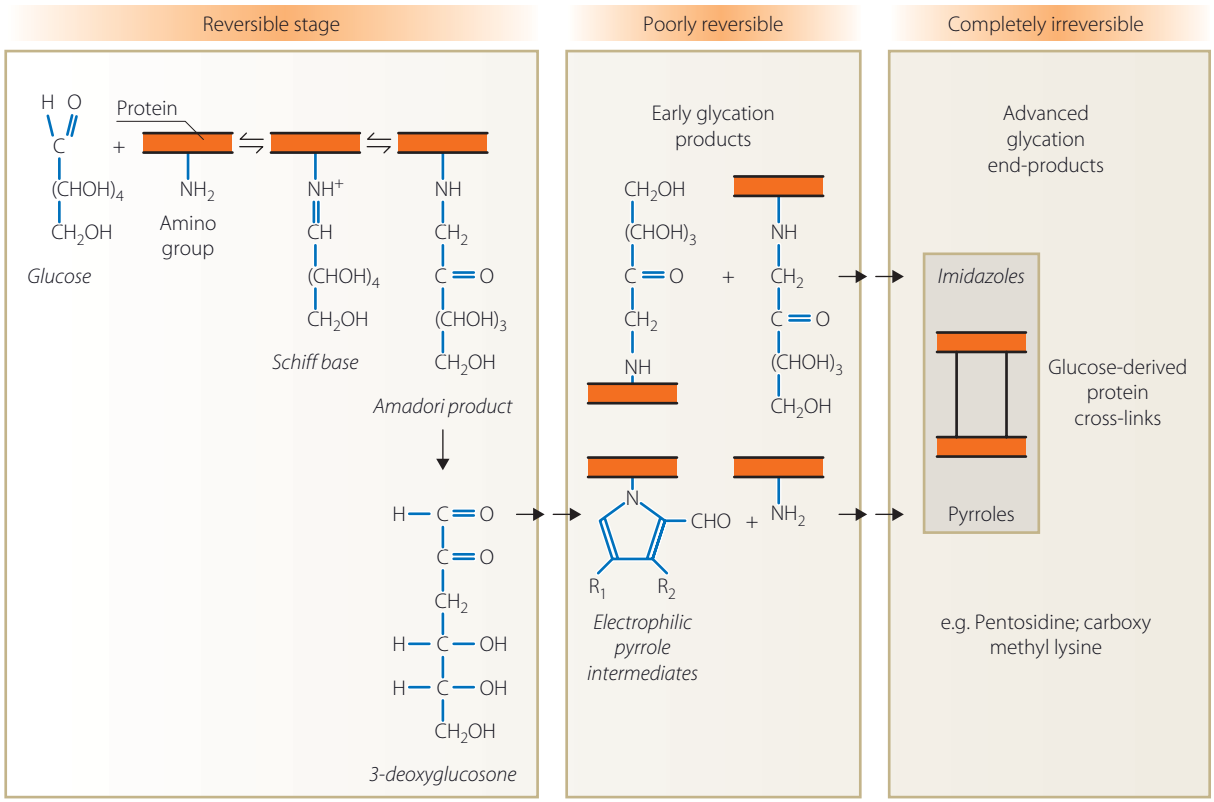

Figure 14.10 Formation of reversible, early, non-enzymatic glycation products, and of irreversible advanced glycation end-products (AGEs). Through a complex series of chemical reactions, Amadori products can form families of imidazole-based and pyrrole-based glucose-derived cross-links.

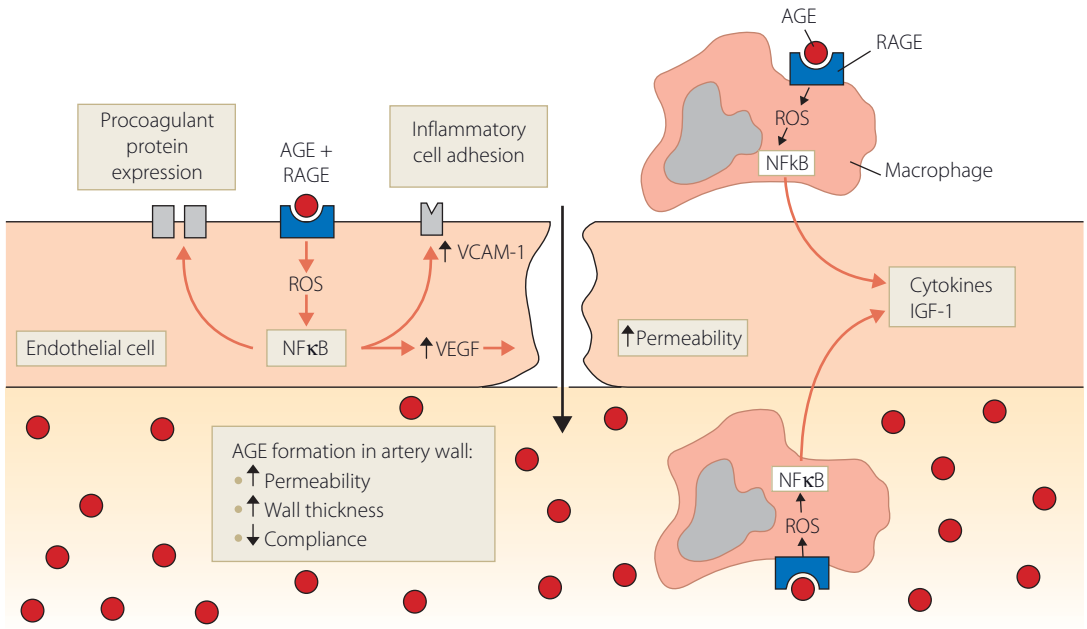

Figure 14.11 Possible mechanisms of cell damage by interactions of advanced glycation end-products (AGEs) with their receptor (RAGE) in endothelial cells and macrophages. IGF, insulin-like growth factor; NFκB, nuclear factor kappa B; ROS, reactive oxygen species; VCAM-1, vascular cell adhesion molecule-1; VEGF, vascular endothelium-derived growth factor.

Recently a circulating soluble RAGE has been identified which appears to mop up AGEs; reduced levels of this scavenger have been linked with increased atherosclerosis.

Several experimental agents that either reduce AGE formation or break cross-links have been tested in animals and humans. The first of these, aminoguanidine, has proven to be too toxic but others are in phase II trials.

Extrinsic AGEs are found in tobacco smoke and processed foods (notably roasted meats and some soft drinks). High levels of dietary AGEs have been associated with accelerated atherosclerosis in animals but their role in human disease is uncertain.

Secondary messengers

Protein kinase C is an enzyme that phosphorylates several target proteins. It exists in many isoforms and is activated by diacylglycerol which is a direct product of increased glucose flux and increased glycolysis. Overactivity of PKC has been implicated in increased vascular permeability and blood flow, particularly in the retina (Figure 14.12).

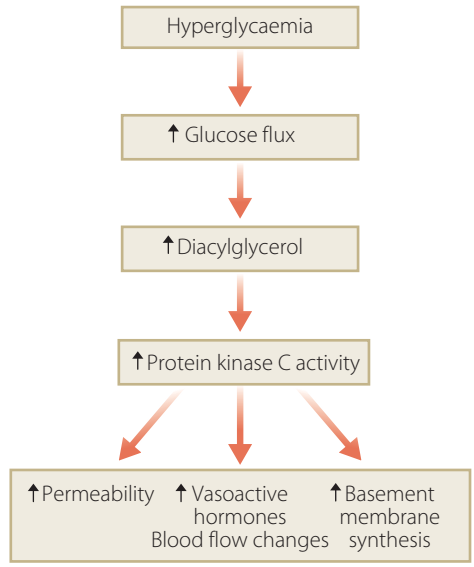

Figure 14.12 Activation of protein kinase C by *de novo* synthesis of diacylglycerol, following increased glucose utilisation.

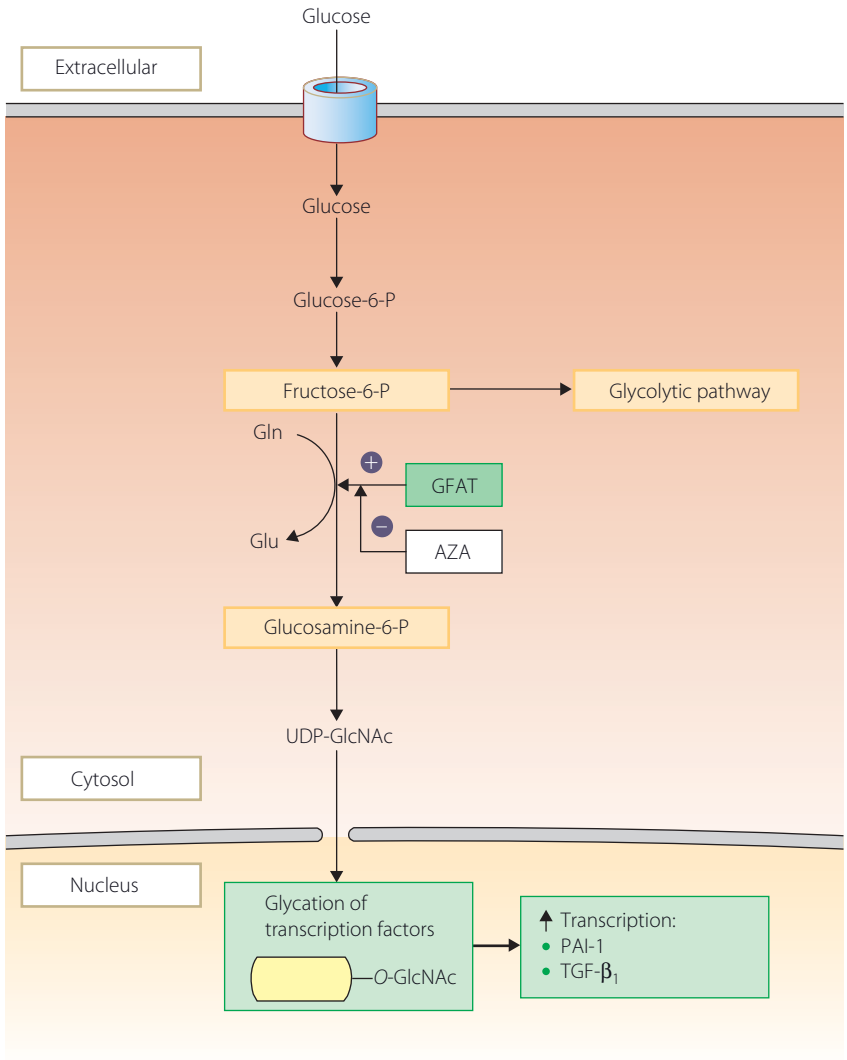

Figure 14.13 The glucosamine pathway. Glucosamine-6-phosphate, generated from fructose-6-phosphate and glutamine (Gln), is converted into UDP-N-acetylglucosamine (UDP-GlcNAc), which can glycate transcription factors and thus enhance transcription of genes including plasminogen activator inhibitor (PAI)-1 and transforming growth factor-β1 (TGF-β1). Glutamine:fructose-6-phosphate amidotransferase (GFAT), the rate-limiting enzyme, is inhibited by azaserine (AZA). Glu, glutamic acid.

LANDMARK CLINICAL TRIAL

Pirart J. Diabetes mellitus and its degenerative complications: a prospective study of 4,400 patients observed between 1947 and 1973. Diabetes Care 1978; 1: 168–188.

This report was initially published in French in *Diabete et Metabolisme* in three parts in 1977 but was felt to be so important that the editor of the new journal *Diabetes Care* had it translated into English to reach a wider audience. It is a remarkable analysis of 4398 patients (2795 since diagnosis) cared for by one physician and his small team since 1947. About 21,000 annual examinations for microvascular complications were correlated with a long-term estimate of glycaemic control (remember, this was before computer spreadsheets and databases). Patients were categorised as having good, fair or poor control based upon home urinalysis, clinic fasting and postprandial blood glucose levels and episodes of DKA. As shown in Figure 14.1, a clear relationship was found between numbers developing microvascular complications in the eye, kidney and nerve and level of control. This study is an exceptional example of how meticulous observation and record keeping can establish a crucial clinical concept.

Interest in this pathway has been stimulated by the development of a PKC β inhibitor, ruboxistaurin, which was shown in experimental animals to reduce the development of retinopathy. Trials in humans have shown benefit in advanced eye disease but confirmatory studies are awaited (see Chapter 15).

Hexosamine pathway

An increased flux of glucose can result in activation of the hexosamine pathway. Fructose-6-phosphate is diverted from glycolysis to form UDP-*N*-acetylglucosamine, which is used in the synthesis of glycoproteins. The rate-limiting step in the conversion of glucose to glucosamine is regulated by glutamine:fructose-6-phosphate amidotransferase (GFAT). It is thought that glycation of transcription factors by *N*-acetylglucosamine increases the activity of many genes. Amongst these are TGF-β (a key profibrogenic cytokine), acetyl CoA carboxylase (the rate-limiting enzyme for fatty acid synthesis and which might increase insulin resistance) and plasminogen activator inhibitor-1 (PAI-1) which promotes thrombosis (Figure 14.13).

All the mechanisms listed above have a common effect of increasing reactive oxygen species and thus increasing oxidative stress (Figure 14.14). Some workers feel that this is the final common path which underpins the development of all diabetes complications.

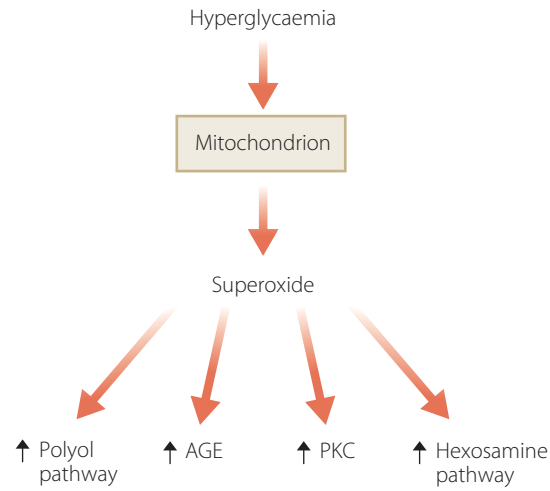

Figure 14.14 Superoxide links glucose and diabetic complications.

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Chapter
15

Diabetic eye disease

KEY POINTS

- Diabetic eye disease primarily affects the retina, but other structures can also be involved.
- Pathological damage to the microvasculature leads to retinal ischaemia and proliferative retinopathy, but macular oedema and maculopathy are the main causes of visual loss.
- Prevention of retinopathy development is critical; glycaemic control, blood pressure lowering and renin angiotensin system blockade are of proven benefit.
- Medical therapies for prevention of progression of retinopathy have shown promise but photocoagulation remains the cornerstone of treatment.
- Screening for diabetic retinopathy using digital fundus photography is now recommended by many national guidelines.

Diabetic eye disease primarily affects the retinal vasculature, but the iris and lens can also be involved. Most people with diabetes will show signs of retinopathy after 25 years duration but only a minority progress to the severest form. Photocoagulation has revolutionised the treatment of retinopathy but even so, diabetes remains a significant cause of visual loss in the working-age population in the UK, and adults with diabetes compared to those without in the USA have 1.85 times the risk of having a non-correctable reduction in visual acuity.

Pathology and clinical appearances

Retinopathy

Essentially, diabetic retinopathy can be classified as non-proliferative (now often split into background and pre-proliferative) and proliferative.

The earliest pathological features are thickening of the retinal capillary basement membrane, loss of tight junctions in the retinal endothelium, and loss of pericytes which are the contractile cells enveloping the capillaries and which control vessel calibre and thus perfusion (Figure 15.1). Physiologically, an increase in retinal blood flow is an early feature of diabetes and it is possible that this creates mechanical stress that leads to endothelial separation and pericyte loss.

The first noticeable lesions on ophthalmoscopy are microaneurysms which appear as small red dots varying in size from 20 to 200 μm in diameter (Figures 15.2, 15.3). They are blind pouches arising from capillaries, probably from weakened endothelial cell junctions adjacent to an area of pericyte loss. Microaneurysms are rarely sight threatening (unless occurring in the macula) and can seem to disappear although this is probably a result of thrombosis within the aneurysm or closure of the feeding capillary. Capillary closure is a feature of advancing retinopathy and the resultant ischaemia is a driver for subsequent proliferation.

Haemorrhages can occur superficially when they tend to be flame shaped (limited by nerve fibres) or deep (blot or round shaped and indicative of underlying ischaemia) (Figure 15.4).

Hard exudates are the result of leakage of lipid rich proteins into the retina (Figure 15.5). They appear as discrete yellow-creamy white patches which are often ring-shaped or circinate around a central area of ischaemia and capillary leakage.

Capillary closure causes microinfarcts in the nerve fibre layer and these appear as indistinct white patches and are termed cotton wool spots (previously known as soft exudates) (Figure 15.6). More advanced ischaemia results with the development of intraretinal microvascular abnormalities

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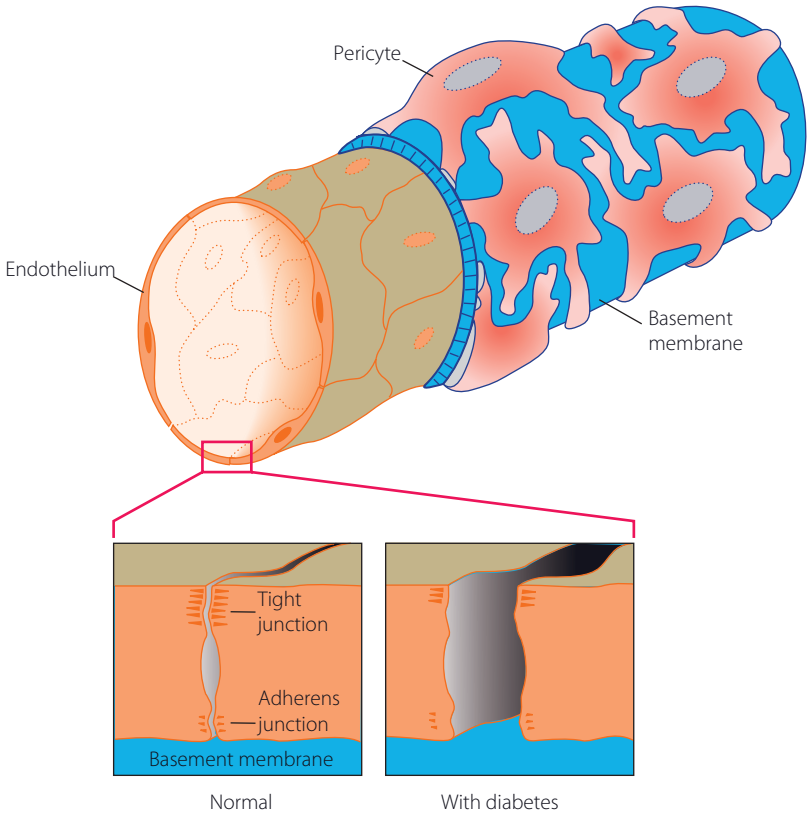


Figure 15.1 Structure of the retinal microvasculature. The endothelial cells are normally joined by tight junctions, which constitute much of the blood–retinal barrier; these separate in diabetes, causing increased vascular permeability. Other abnormalities in diabetes include thickening of the basement membrane and fall-out of both the endothelial cells and the contractile pericytes.

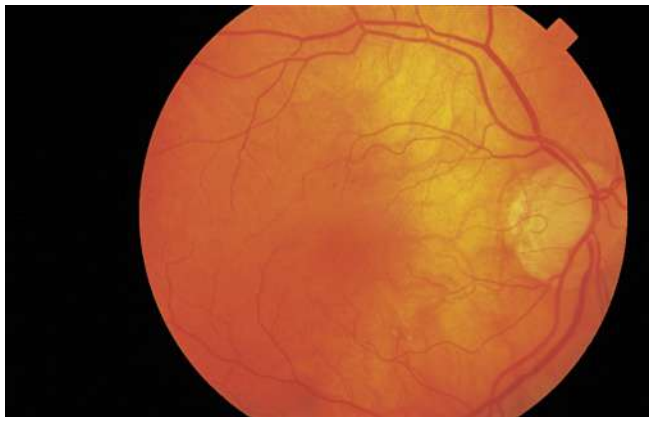


Figure 15.2 Microaneurysms, the earliest sign of diabetic retinopathy. This is a myopic eye with a pale fundus.

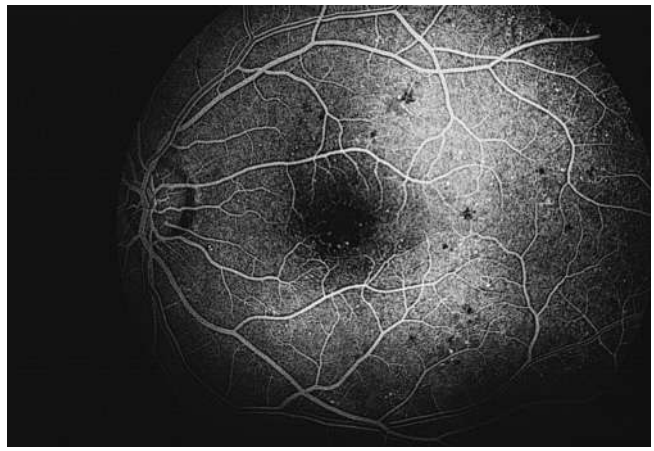


Figure 15.3 Fluorescein angiogram, showing microaneurysms as small white dots and haemorrhages as larger black spots.

(IRMAs) (Figure 15.7), which are clumps of small irregularly branching vessels within the retina, and venous dilatation, beading (segmental dilatation resembling a string of sausages) (Figure 15.8), loops and reduplication, sometimes into multiple loops resembling a four-leafed clover.

New vessel growth or neovascularisation is the hallmark of proliferative retinopathy and results from the local release of growth factors (such as vascular endothelium-derived growth factor; VEGF) in response to ischaemia (Figures 15.9, 15.10). These vessels are fragile, fine outgrowths from retinal veins and grow forward into the vitreous. Because of this, they are prone to shear stress and rupture, resulting in preretinal or vitreous haemorrhage and sudden visual loss (Figure 15.11).

New vessels are associated with fibrous bands that can cause traction retinal detachment or tearing of vessels, leading to further haemorrhage (Figure 15.12). Sometimes

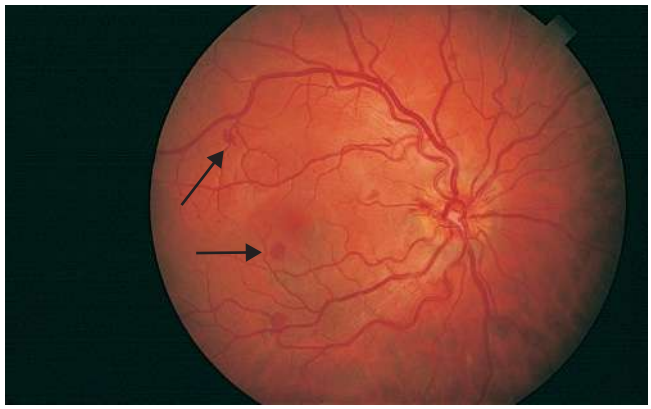


Figure 15.4 Retinal haemorrhages: red 'blots'.

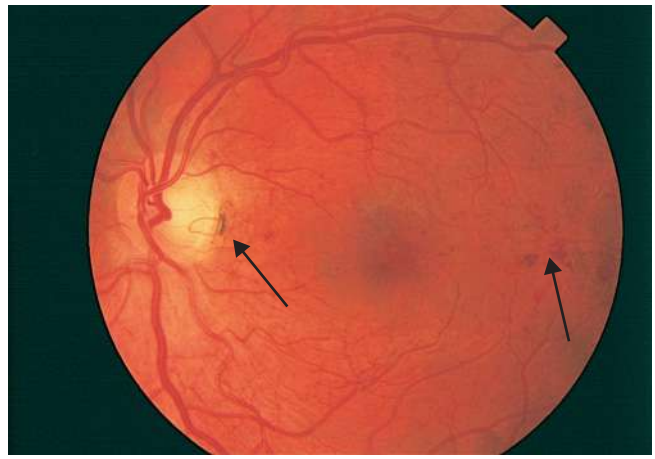


Figure 15.7 Intraretinal microvascular abnormalities (IRMAs).

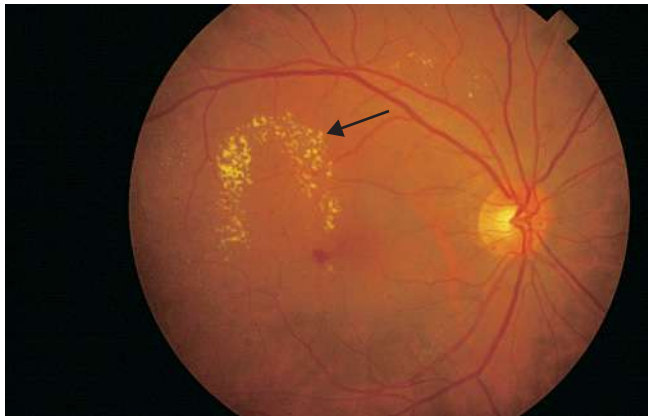


Figure 15.5 Focal diabetic maculopathy with circinate (ring-shaped) exudate. Laser treatment is applied to the leaking microaneurysms at the centre of the circinate exudates.

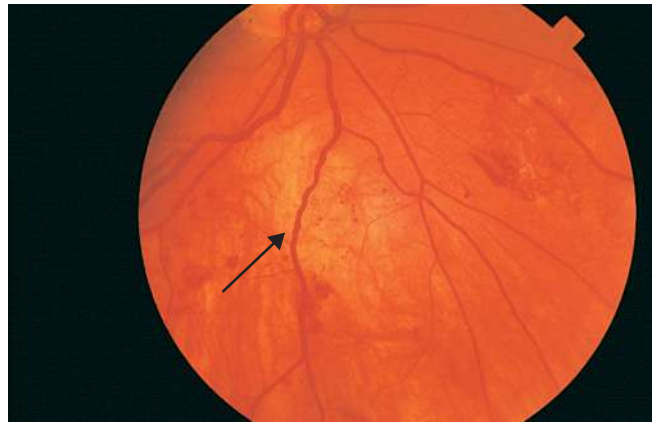


Figure 15.8 Venous irregularity or 'beading' (centre of field) and new vessels elsewhere (NVE, top right of field).

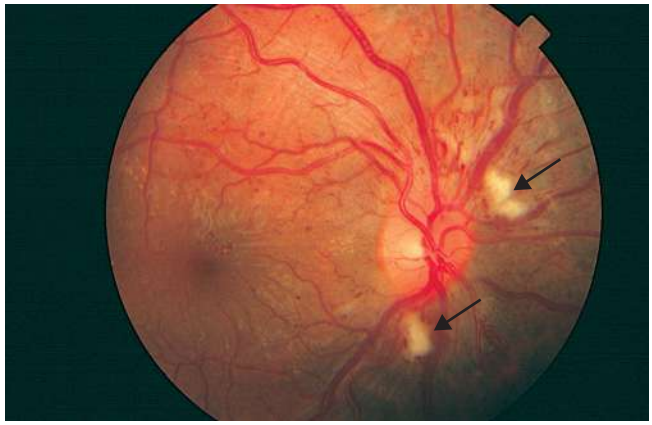


Figure 15.6 Cotton wool spots around the optic disc.

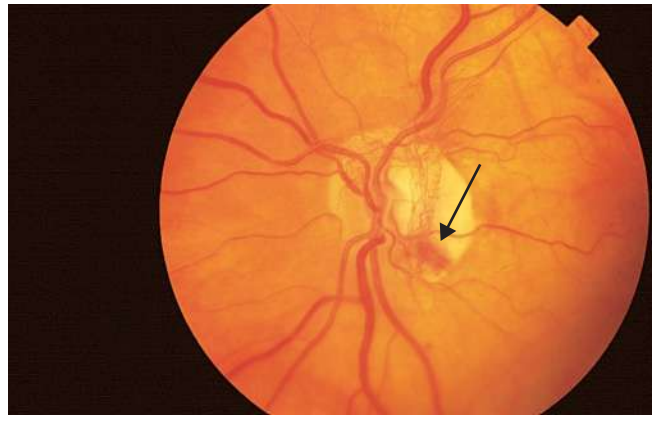


Figure 15.9 More extensive new vessels on the disc (NVD), occupying more than half the disc diameter.

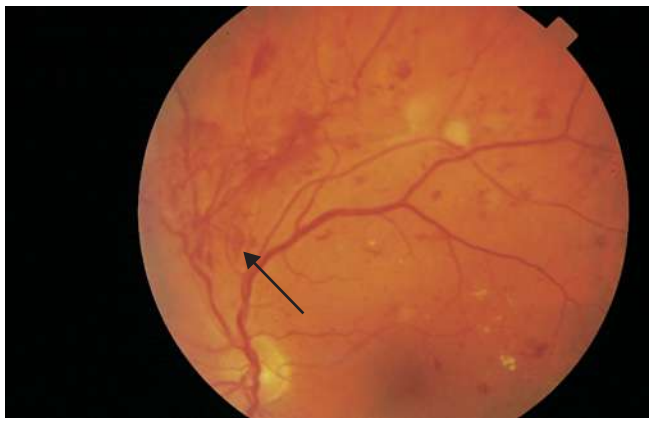


Figure 15.10 Extensive new vessels elsewhere (NVE) above the disc, with widespread signs of retinal ischaemia.

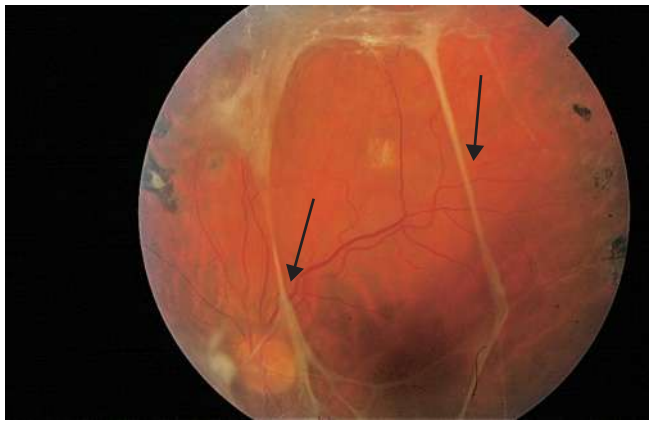


Figure 15.12 Fibrous bands that are exerting traction on the retina. The retinal scars are from previous xenon laser treatment.

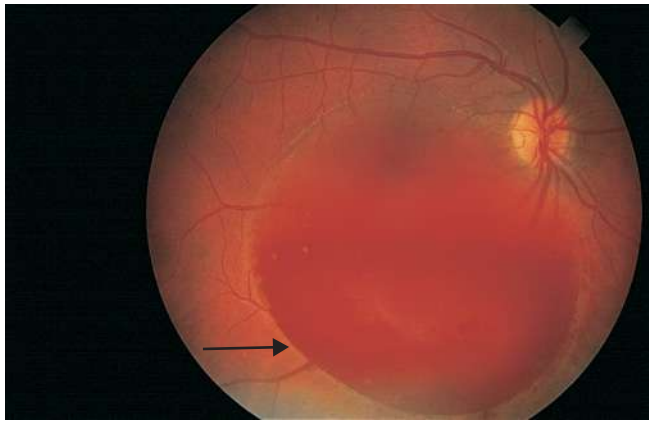


Figure 15.11 Preretinal haemorrhage. Note the settling of the uncoagulated blood. Courtesy of Dr PJ Barry, Royal Victoria Eye and Ear Hospital, Belfast, UK.

the haemorrhage remains encapsulated between these fibrous bands, the retina and the vitreous, leading to a fluid level and a flat-topped (boat-shaped) appearance.

Tractional detachment results in 'tenting' or folding of the retina with grey-white bands and occasional tears (Figure 15.13). Ophthalmic ultrasound is often helpful at detecting detachment, particularly if the retina is obscured by haemorrhage (Figure 15.14).

The most common cause of visual loss, however, is maculopathy which results from ischaemia and subsequent oedema of the central retina. Focal maculopathy is usually associated with areas of circinate or star-shaped exudate within one optic disc diameter of the macula (Figure 15.15. Diffuse macular oedema results from ischaemia and causes thickening of the retina. It is harder to detect clinically and needs either stereo ophthalmoscopy or optical coherence

LANDMARK CLINICAL TRIAL

Kroc Collaborative Study Group. Blood glucose control and the evolution of diabetic retinopathy and albuminuria. A preliminary multicentre trial. N Engl J Med 1984; 311: 365–372.

This was an international, multicentre trial of improved versus conventional glycaemic control on microvascular complications in the eye and kidney. Seventy patients were randomised to either CSII or conventional insulin (CIT) for 8 months. All had non-prolifeative retinopathy at baseline. Twenty-four hour average blood glucose from a seven-point profile collected at home using plastic fluoridated tubes was 11 mmol/L (198 mg/dL) and 10.4 mmol/L (187 mg/dL) at baseline in the CSII and CIT groups respectively. Baseline total HbA_{1c} (normal range 6.5–7.8%) was 10.3% and 10.1% respectively. During the 8-month trial glycaemia did not change in those on CIT but mean 24-hour glucose was 6.4 mmol/L (115 mg/dL) and HbA_{1c} 8.1% in those on CSII. Retinopathy worsened with the appearance of IRMAs and cotton wool spots suggestive of ischaemia. Albuminuria, however, was significantly reduced in the 10 patients with baseline values >12 µg/min on CSII with no change in the 10 on CIT. The authors concluded that medium-term maintenance of glycaemic separation was possible (previously this had been extremely difficult to achieve) but that the worsening of retinopathy was a concern. They concluded: 'These preliminary observations indicate the need for longer trials (particularly of primary prevention)'.

This study set the stage for the much bigger DCCT – it could almost be considered as the pilot. The finding of acute worsening of retinopathy was confirmed by the Stockholm and Oslo studies and was seen in the secondary prevention arm of the DCCT. Later analysis of the Kroc patients showed that in the long term, eye complications were less severe in the CSII group, thus providing reassurance for the DCCT.

The study also showed that CSII was an effective, safe and practicable research tool.

The study name derived from the Kroc Family Foundation which funded the trial. Dr Robert Kroc was one of the founders of the MacDonalds hamburger chain.

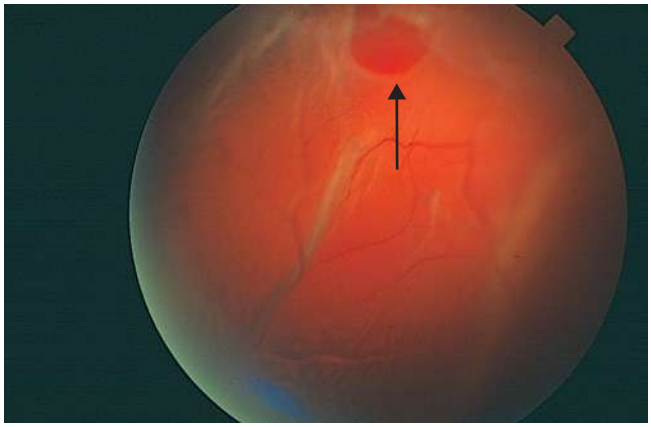


Figure 15.13 Rhegmatogenous retinal detachment: a large retinal tear (red lesion; arrow) is present at 12 o'clock, and the detached retina appears grey and folded.

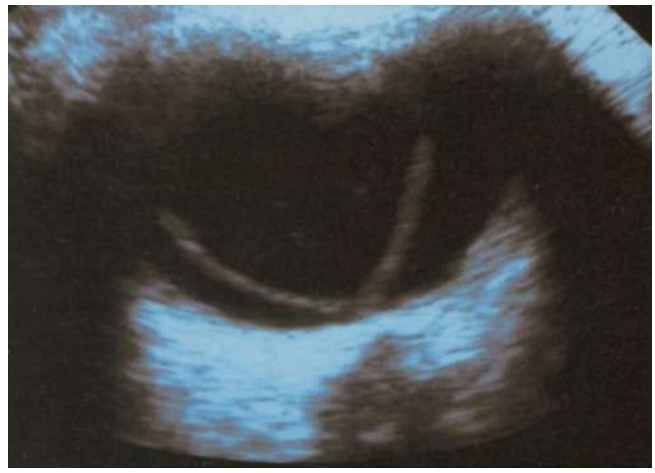
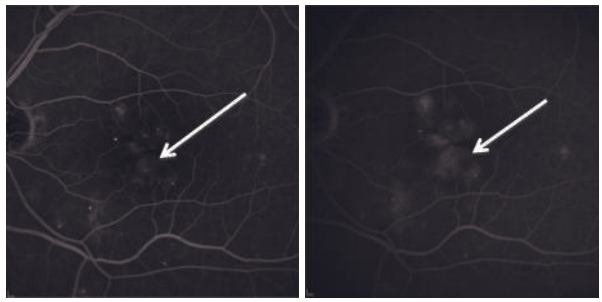
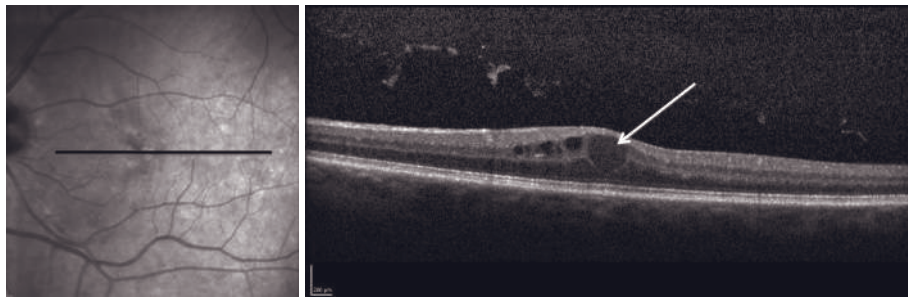


Figure 15.14 B-scan ultrasound image of the eye, showing a retinal detachment that was invisible behind a dense vitreous haemorrhage.



(a)



(b)

Figure 15.15 Left eye of a patient with diffuse diabetic macular oedema. (a) Mid (*left*) and late (*right*) phase fluorescein angiogram image showing leaking microaneurysms and pooling of dye in intraretinal spaces (*arrows*). (b) Red free image (*left*) showing location of single line scan on Spectralis OCT (optical coherence tomography). OCT (*right*) shows mixed reflectivity intraretinal cysts with thickening of the retina and a detached hyaloid face (*arrow*). Courtesy of Professor Simon Harding, Liverpool.

tomography (OCT) which can generate clear images of the retina and accurate estimates of thickness (Figure 15.16).

Iris

New vessel growth on the iris (rubeosis iridis – also in response to ischaemia) (Figure 15.17) can close the drainage angle and cause acute glaucoma. This condition is called rubeotic glaucoma, it is acutely painful and can occasionally occur following cataract surgery or vitrectomy if there is active proliferative retinopathy. Treatment is unsatisfactory and the end result is often a painful blind eye.

Lens

Cataract is common and can occur acutely and diffusely with newly diagnosed diabetes (so-called snowstorm cataract) or, more commonly, posterior subcapsular and cortical cataracts

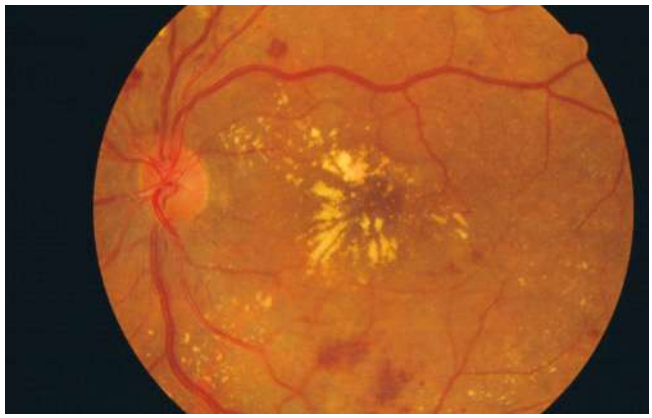


Figure 15.16 Diffuse macular oedema, with a macular 'star'. This requires laser photocoagulation.

Box 15.1 Associated ocular conditions

Definite
- Primary open angle glaucoma: 1.6–4.7 times more likely in diabetes
- Primary angle closure glaucoma
- Ocular ischaemic syndrome

Possible
- Retinal vein occlusion: may mimic retinopathy but asymmetrical
- Retinal arteriolar emboli
- Retinal artery occlusion
- Corneal disease

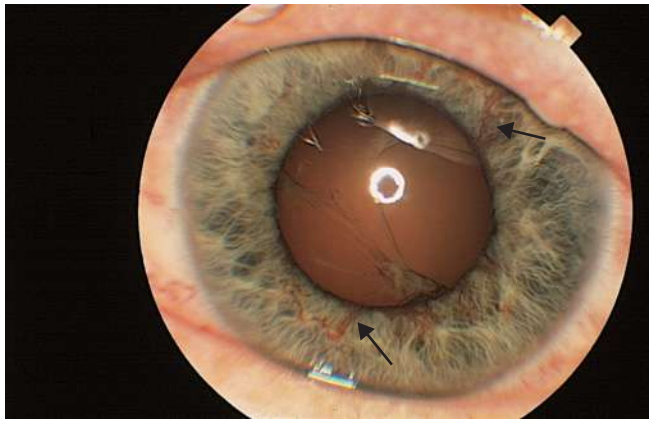


Figure 15.17 New vessels (arrows) on the iris (rubeosis iridis). There is also a vitreous haemorrhage.

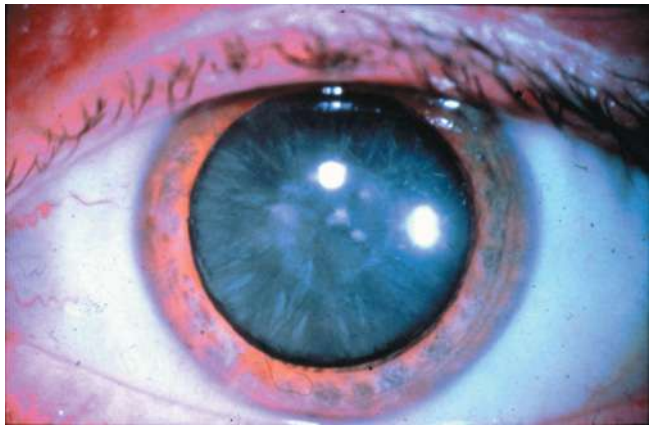


Figure 15.18 Diabetic cataract.

which occur after several years duration (Figure 15.18). The 10-year cumulative incidence of cataract surgery in the WESDR study was 8% and 25% for patients with type 1 and type 2 diabetes respectively. The underlying cause for snow-storm cataract is probably acute fluid shift due to hyperglycaemia and hyperosmolality. Linear or central cataract probably results from non-enzymatic glycation and subsequent cross-linkage of lens crystallins. Sorbitol accumulation secondary to activation of the polyol pathway may also contribute. Extraction and replacement with a plastic implant is the treatment of choice. The results are generally good but active proliferative retinopathy should be treated first.

Optic disc

Anterior ischaemic optic neuropathy is caused by microvascular disease of the anterior optic nerve. Patients present with painless loss of vision upon wakening. The condition usually remains stable but there is no known effective treatment.

A related problem of acute disc oedema and moderate visual loss can occur and is termed diabetic papillopathy. This usually improves spontaneously but it may take up to 12 months. It can be confused with papilloedema.

Other associated ocular conditions are listed in Box 15.1.

Factors associated with the development of retinopathy

Many of these have been identified from epidemiological studies and are therefore associations (Box 15.2), but most have been confirmed from intervention trials such as the DCCT and UKPDS.

Many of these factors are co-related, for example hyperglycaemia (as estimated from HbA_{1c} levels and thus severity of protein glycation) and duration of diabetes (being a measure of exposure to the hyperglycaemic insult). Other

Box 15.2 Associated risk factors for development of retinopathy

Hyperglycaemic exposure
- High glycated haemoglobin concentrations
- Duration of diabetes

Associated microvascular disease
- Diabetic nephropathy

Capillary leakage/endothelial damage
- Hypertension
- Hyperlipidaemia

Rapid correction of glycaemia
- Pregnancy
- Insulin pump therapy (CSII)

Hypoxia
- Smoking

Others
- Obesity
- Alcohol excess
- Physical inactivity

factors are less intuitive; in pregnancy, many women rapidly improve glycaemic control in order to minimise fetal risk of malformation. This can precipitate rapid worsening of retinopathy, perhaps by reducing blood flow through an already ischaemic retina and causing a sudden release of growth factors. This phenomenon can also occur with too rapid correction of glycaemia in non-pregnant patients (e.g. commencing CSII). Careful retinal surveillance is needed in these situations (see below).

Classification of retinopathy

The clinical categories of non-proliferative and proliferative, although useful, have proven too broad for research purposes. Moreover, the nomenclature 'background' implies a somewhat benign condition which nonetheless represents pathological damage and can progress.

The Early Treatment Diabetic Retinopathy Study (ETDRS) devised a modified scale based upon the Airlie House classification and this has become the gold standard for all intervention trials such as the DCCT and UKPDS (Box 15.3). A two- or three-step change in combined eye score is positively associated with progression to proliferative retinopathy and visual loss. Moreover, in the UKPDS, 30% of patients with a level of ≥35 in both eyes required photocoagulation after 9 years.

Box 15.3 Modified Airlie House classification (ETDRS scale)

Level	10	Nil
	20	1 or more microaneurysms only
	35	Microaneurysms and haemorrhages and/or hard exudates and/or cotton wool spots
	43	As above plus severe haemorrhages or IRMA
	47	As 35 plus severe haemorrhages and IRMA and/or venous beading
	53	Severe haemorrhages and IRMA and venous beading and cotton wool spots
	61+	Proliferative diabetic retinopathy

IRMA, intraretinal microvascular abnormalities

Box 15.4 UK Retinal Screening Committee classification

Retinopathy

R_0	No retinopathy
R_1	Any retinopathy but not R_2 or R_3
R_2	IRMAs, venous beading or loops, multiple deep round haemorrhages and/or cotton wool spots
R_3	Proliferative retinopathy (new vessels, preretinal or vitreous haemorrhage, preretinal fibrosis with or without detachment)

Maculopathy

M_0	No referable maculopathy
M_1	Referable maculopathy – hard exudate within 1 disc diameter of fovea Circinate exudate in macula Thickening within 1 disc diameter of fovea Microaneurysms or haemorrhages within 1 disc diameter of fovea (if associated with visual acuity ≤6/12)

Photocoagulation

P_0	No photocoagulation scars
P_1	Photocoagulation scars

However, this grading is complex and was based upon seven-field stereo fundus photographs which are both time consuming and expensive as well as being uncomfortable for the patient. Moreover, the classification is hard to apply without expert training and experience. The UK National Screening Committee has proposed a simpler classification that feeds into a treatment algorithm with referral targets and forms the basis of the Diabetic Retinopathy Screening Programme (Box 15.4).

Treatment of retinopathy

Glycaemic control

Both the DCCT in type 1 and the UKPDS in type 2 diabetes demonstrated the benefit of glycaemic control for the primary prevention of new retinopathy, and secondary prevention of progression of existing retinopathy. Moreover, there are long-term benefits of glycaemic control (see Chapter 14).

However, as previously mentioned, rapid improvement in glycaemia can result in an early worsening of retinopathy. Most of the trials in which this was noticed (DCCT, KROC, Stockholm and Oslo Studies) found that in the long term, patients on intensive insulin regimens still had better retinal outcomes than their conventionally treated controls.

Blood pressure control

Embedded within the UKPDS was a trial of tight (target <150/<85 mmHg) or less tight (target <180/<105 mmHg) blood pressure control in 1148 hypertensive newly diagnosed type 2 diabetic patients. There was a 34% (99% CI 11–50%) risk reduction in progression (two-step ETDRS change), and 35% risk reduction in the need for laser photocoagulation. *Post hoc* analysis suggested a 13% decrease in the aggregate microvascular endpoint (combination of retinopathy requiring photocoagulation, vitreous haemorrhage and/or fatal or non-fatal renal failure) for every 10 mmHg reduction in blood pressure.

Similar results were found in the normotensive (but not hypertensive) patients in the Appropriate Blood Pressure Control in Diabetes (ABCD) trial. The ADVANCE study also found no benefit of a mean reduction in blood pressure of 5.6/2.2 mmHg on retinopathy progression in 11,140 mainly hypertensive type 2 patients. The reasons for these disparities between normo- and hypertensive patients are not clear. The magnitude of the blood pressure reduction was greater in the two positive studies, and the ascertainment of effect was most precise in the UKPDS.

There are no data on the effect of blood pressure lowering on retinopathy in type 1 diabetes.

Renin angiotensin system (RAS) blockade

The EURODIAB Controlled Trial of Lisinopril in Insulin-Dependent Diabetes Mellitus (EUCLID) found a benefit of lisinopril on retinopathy progression over 2 years but statistical significance was lost when results were corrected for HbA_{1c}.

The much larger and longer DIRECT study (DIabetic REtinopathy Candesartan Trial) looked at the effect of a median 4.7 years of candesartan 32 mg per day on development and progression of retinopathy in 3326 normotensive type 1 and 1905 normotensive or well-controlled hypertensive patients with type 2 diabetes. There was a 35% relative risk reduction in a three-step ETDRS change in incidence of retinopathy in type 1 diabetes, and a 34% increase in the chance of regression (three steps for 1 year or two steps for 2 or more years) in type 2 diabetes. No significant effect was seen on three-step progression of existing retinopathy in patients with type 1 or type 2 diabetes, although candesartan use was uniformly and statistically significantly associated with less retinopathy progression (one-step change).

PKCβ inhibition

Ruboxistaurin has been shown to reduce visual loss in patients with moderately severe non-proliferative retinopathy and macular oedema. Further trials are ongoing to better establish its place in retinopathy management.

Lipid-lowering agents

The Fenofibrate Intervention and Event Lowering in Diabetes (FIELD) study found a significant reduction in the need for laser therapy (5.2% versus 3.6%: p = 0.0003) in 9795 patients with type 2 diabetes treated for 5 years. This effect was independent of blood lipid levels and is unexplained. Absolute numbers of patients were small and the indications for laser therapy were not specified so interpretation of these data is difficult. No consistent effect of statin therapy on retinopathy has been reported.

Growth hormone inhibitors

The observation of a regression in proliferative retinopathy in a woman with Sheehan's syndrome (postpartum hypopituitarism) and the subsequent clinical trials (in the days before photocoagulation) of hypophysectomy in patients with advanced eye disease established a potential link between growth hormone and neovascularisation. Octreotide (a somatostatin analogue that blocks growth hormone release) has been shown to decrease progression of severe non-proliferative or early proliferative retinopathy but had serious GI side effects.

Intravitreal steroids

Both triamcinolone (by injection) and fluocinolone (by implant) have been shown to reduce macular oedema and improve visual acuity but with the serious side effects of glaucoma and cataract formation. Many patients required multiple steroid injections and some developed infections. The long-term benefits and safety of these treatments need to be established.

VEGF inhibitors

These agents have been shown to benefit patients with 'wet' age-related macular degeneration which shows some similarities with diabetes-related macular oedema (DME). One hundred and seventy two patients with DME were randomised to pegaptanib or sham injections and after 36 weeks those on active treatment had visual improvement of 10 letters or more and less need for photocoagulation. Larger

trials in diabetic patients of this and other similar agents are under way.

Laser photocoagulation

Meta-analysis shows that panretinal laser photocoagulation (PRP) (Figure 15.19) reduces the risk of blindness in eyes with proliferative retinopathy by 61%, and this has now become the cornerstone of treatment of advanced disease. Focal laser photocoagulation can be effective for more discrete neovascularisation or ischaemia. There is no evidence that PRP confers benefit until sight-threatening proliferative retinopathy is present.

Similarly, in the ETDRS, focal grid laser photocoagulation to the macula decreased the risk of moderate visual loss due to DME by 50% (95% CI 47–53%) over 3 years in 2244 patients with bilateral disease (Figure 15.20).

Photocoagulation is generally well tolerated but some patients can experience discomfort and need local anaesthetic. Up to 23% of patients experience transient or permanent visual loss following PRP; there can also be visual field constriction and night blindness which can affect eligibility for driving.

These problems emphasise the essentially destructive nature of PRP which is why prevention of retinopathy is so important and also why there is active research into alternative medical treatment.

CASE HISTORY

A 29-year-old woman with type 1 diabetes and coeliac disease had a profound fear of hypoglycaemia. Consequently, she maintained high blood glucose levels and her HbA_{1c} was consistently above 9% (75 mmol/mol). Because of developing retinopathy, she elected to try CSII. There was a dramatic improvement in blood glucose control without hypoglycaemia and her HbA_{1c} came down to 6.5% (48 mmol/mol) over 6 months. Regular ophthalmic assessments were scheduled but she missed two appointments. Four months later she presented with acute vitreous haemorrhage in her right eye secondary to advanced proliferative retinopathy. Extensive panretinal photocoagulation has prevented further haemorrhage and preserved vision in her left eye, but she now requires vitreoretinal surgery on the right for traction detachment.

Comment: This case demonstrates the potential for rapid worsening of retinopathy with glycaemic improvement. It is essential to arrange frequent eye examinations in this and similar situations (such as pregnancy) and also to impress upon the patient their importance. Panretinal photocoagulation is best carried out before neovascularisation and haemorrhage.

Vitrectomy

Surgical vitrectomy in advanced eye disease results in sustained benefit in terms of visual acuity, with 6/12 (20/40) or greater vision in at least 25% of eyes at 4 years. Improved operative technique with intraoperative imaging has greatly advanced the field and is likely to have improved outcomes.

Surveillance and screening

Regular retinal examination is recommended by all national guidelines. The ADA suggests expert examination within 5 years of diagnosis of all with type 1 diabetes aged >10 years and as soon as possible after diagnosis of type 2 diabetes. The best periodicity thereafter is controversial. The ADA suggests that review could be every 2 or more years if there are several annual assessments with no retinopathy. Studies from Liverpool in the UK suggest that there is a minimal likelihood of progression from no retinopathy to significant change requiring therapy in less than 2 years in patients with type 2 diabetes.

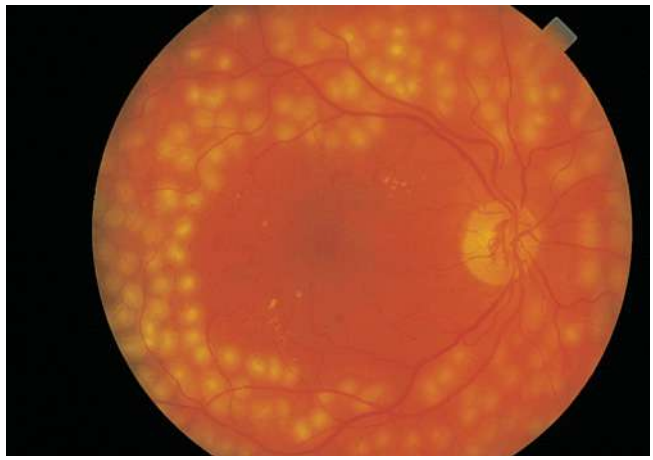


Figure 15.19 Fresh panretinal (scatter) laser photocoagulation burns for treating new vessels on the disc.

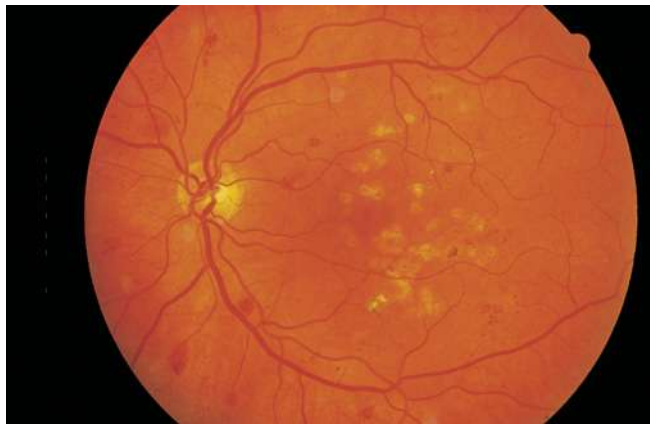


Figure 15.20 Focal laser photocoagulation scars around the macula following successful focal treatment.

The most effective mode of surveillance has been the subject of intense research and in the UK there is general agreement that digital fundus photography is superior to both optometrist-based slit lamp ophthalmoscopy as well as opportunistic direct ophthalmoscopy performed by diabetologists. The National Screening Committee and the National Service Framework for Diabetes have both recommended annual two-field digital fundus photography for everyone with diabetes and a nationally funded programme is now in place. Photographs are graded according to the scale in Box 15.4 and there are set referral targets based upon their score (Box 15.5). At the time of writing, well over 80% of patients were being offered, and most were taking up, annual fundus photography. In pregnancy, women should be screened as soon as possible after booking and at 28 weeks' gestation. An additional review should occur at 16–20 weeks if the first one reveals any retinopathy.

Box 15.5 Referral targets for ophthalmologist review for patients with detected retinopathy or maculopathy in the UK

R_3 M_0, R_3, M_1	100% in 4 weeks
R_2 M_0, R_2 M_1, R_1 M_1	70% in 13 weeks
R_2 M_0, R_2 M_1, R_1 M_1	100% in 18 weeks

KEY WEBSITES

- UKPDS: www.dtu.ox.ac.uk/ukpds/
- DCCT/EDIC: www.niddk.nih.gov/patient/edic/edic-public.htm
- UK National Screening Committee portal: www.screening.nhs.uk/
- UK National Service Framework for Diabetes: www.dh.gov.uk/en/Publicationsandstatistics/Publications/PublicationsPolicyAndGuidance/Browsable/DH_4096591
- SIGN Guidelines: www.SIGN.ac.uk

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Chapter
16

Diabetic nephropathy

KEY POINTS

- Diabetic nephropathy is a clinical diagnosis based upon the presence of albuminuria in a person with diabetes.
- Classic staging based upon albuminuria does not map clearly to the current classification of chronic kidney disease. Once patients develop clinical nephropathy (urinary albumin concentration >300 mg/L or Albustix* positive), their renal function declines toward end-stage renal failure.
- Patients with nephropathy have an increased cardiovascular mortality, which increases further as proteinuria and renal function worsen.
- The pathological features are of glomerular basement membrane thickening and diffuse glomerulosclerosis, both secondary to matrix protein accumulation. Both metabolic and haemodynamic factors play a role in pathogenesis.
- Tight glycaemic control can prevent nephropathy developing but once it is established, the cornerstone of treatment is blood pressure lowering, primarily with agents that block the renin-angiotensin system.
- Diabetes is the biggest single cause of end-stage renal failure requiring renal replacement therapy, accounting for 44% of incident cases in the USA and 22% in the UK in 2007.
- Survival on renal replacement therapy is best for kidney transplant recipients, but is improving for all modalities. Simultaneous kidney and pancreas transplantation could be considered for patients in end stage, although complication rates are higher than for kidney transplant alone.

Diabetic nephropathy is a clinical diagnosis based upon the detection of proteinuria in a patient with diabetes in the absence of another obvious cause such as infection. Many of these patients will also be hypertensive, have retinopathy and, in advanced stages, renal impairment.

The original definition was based upon relatively crude tests that detected protein concentrations of around 500 mg/L. With the development of accurate dipstick urine tests, this has fallen to 300 mg/L (largely albumin). It is now possible to detect much lower concentrations using laboratory and dipstick tests, and the concept of microalbuminuria or incipient nephropathy was developed in the 1980s. Persistent albuminuria in the microalbuminuric range is now widely accepted as a positive diagnosis for diabetic nephropathy (Table 16.1).

National Institute of Health and Clinical Excellence (NICE) guidance suggests that positive tests for microalbuminuria should be confirmed within 3–4 months before making a diagnosis of nephropathy.

Table 16.1 Definition of diabetic nephropathy by albuminuria and test

Urine specimen	Microalbuminuria	Clinical nephropathy
Timed overnight collection	20–199 µg/min	>200 µg/min
24-hour collection	30–299 mg/d	≥300 mg/d
Albumin concentration	20–300 mg/L	>300 mg/L
Albumin:creatinine ratio (Europe)	Men 2.5–30 mg/mmol	>30 mg/mmol
	Women 3.5–30 mg/mmol	>30 mg/mmol
USA	Both 30–300 mg/g	>300 mg/g

Natural history

Classically, patients were considered to progress relentlessly from normoalbuminuria through microalbuminuria to clinical nephropathy. It is now recognised that patients with microalbuminuria may spontaneously revert to normoalbuminuria, up to 50% in some series of type 1 patients. Moreover, albuminuria can increase during periods of poor glycaemic control (and then decrease with glycaemic correction), and reduce with antihypertensive therapy (notably drugs which block the renin-angiotensin system (RAS)).

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Microalbuminuria has also been found in patients with coronary artery disease and essential hypertension and who have either normal or only mildly impaired glucose tolerance. In the UKPDS, the majority of those with microalbuminuria did not progress to need renal replacement therapy and the median period spent in the microalbuminuric range was 11 years. Thus it is not inevitable that all microalbuminuric patients will progress to renal failure and it also means that the contribution from cardiovascular or renal disease or both will vary from patient to patient.

Glomerular filtration rate (GFR) is often abnormally high (>135 mL/min/1.73 m^2) in patients with newly diagnosed type 1 and, to a lesser extent, type 2 diabetes. This is called hyperfiltration and its relationship to subsequent nephropathy risk is controversial. Improving glycaemic control in hyperfiltering patients reduces GFR toward normal.

With increasing albuminuria, GFR declines and the rate of loss is greater in those with higher systemic blood pressure. Historically, patients with clinical nephropathy had a rate of loss of GFR of 10–12 mL/min/yr. More recent studies suggest rates of decline of <4 mL/min/yr in patients with well-controlled blood pressure. Ultimately, GFR declines relentlessly in patients with clinical nephropathy towards end-stage renal disease (ESRD) <15 mL/min/1.73 m^2, albeit at very different rates in individual patients.

The other clinical concomitant of nephropathy is blood pressure. In type 1 diabetes this is normal until microalbuminuria starts to develop although some studies have shown that, on average, patients who go on to develop nephropathy have higher blood pressures when normoalbuminuric (although still well within the normal range). In type 2 diabetes, many patients have hypertension when diagnosed and these individuals are at higher risk of nephropathy. Thus, hypertension is a feature of developing nephropathy in type 1, whereas it may be an initiating factor in type 2 diabetes; it is an exacerbating factor in both.

Patients with nephropathy are at much greater risk of cardiovascular disease. In the UKPDS, annual mortality was over twice and three times higher for those with microalbuminuria or clinical nephropathy respectively compared to their normoalbuminuric comparators. For those with a plasma creatinine >175 µmol/L and/or on renal replacement therapy, the mortality was 14 times greater. In type 1 diabetes, excess mortality in patients with clinical nephropathy is 10–20 times higher than for their age-matched non-proteinuric comparators (Figure 16.1).

This excess mortality explains why many patients with renal impairment do not survive to need dialysis, although with better treatment many more are now doing so.

Stages of nephropathy

An international classification of chronic kidney disease (CKD) has now been widely adopted, but unfortunately it does not map precisely to staging of diabetic nephropathy based upon albuminuria (Table 16.2). The new staging is based upon GFR as estimated (eGFR) from a plasma creatinine concentration using a formula derived from the Modification of Diet in Renal Disease (MDRD) Study.

$$\text{eGFR}\,(\text{mL/min/1.73 m}^2) = 175 \times [\text{serum creatinine}\,(\mu\text{mol/L}) \times 0.0113]^{-1.154} \times \text{age}\,(\text{years})^{-0.203}$$

If female multiply by 0.742
If African American multiply by 1.21

This formula uses a serum creatinine assay aligned to an international reference method. It has not been specifically validated in people with diabetes, in other ethnic subgroups such as South Asians or Chinese/Japanese, in children or in pregnancy. Alternative formulae for estimating creatinine clearance (not GFR) exist, such as Cockroft–Gault, and for GFR using serum cystatin C. Both have their advocates but although cystatin C has advantages, it is expensive and not widely available in the UK.

The MDRD eGFR is much less accurate above 60 mL/min/1.73 m^2 and tends to underestimate true GFR below this value. Values below 60 mL/min/1.73 m^2 are, however, associated with an increasing cardiovascular mortality in US and UK populations, and more so in those with diabetes. It is therefore now considered as an extra cardiovascular disease risk factor.

Despite its drawbacks as an accurate measure of kidney function, eGFR is useful in alerting the clinician (and patient) to renal impairment that would not be apparent from the serum creatinine concentration alone. This helps to guide therapy (therapeutic dose adjustment or drug avoidance) and also a rapidly declining eGFR should prompt referral for specialist assessment (see later).

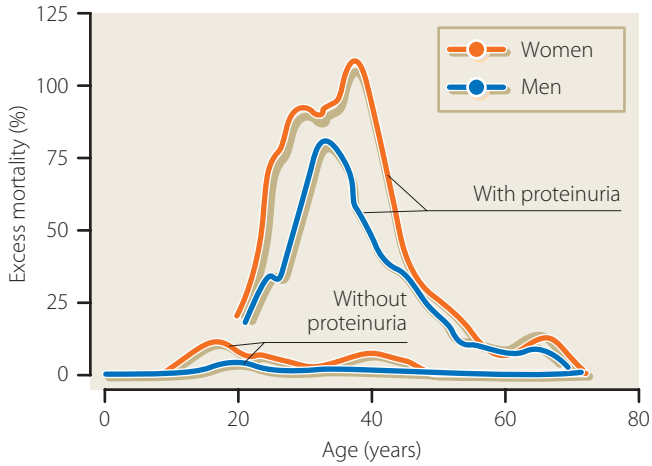

Figure 16.1 Relative mortality of patients with diabetes with and without persistent proteinuria in men and women as a function of age. Mortality is greatly increased at all ages in proteinuric patients. From Borch-Johnsen et al. Diabetologia 1989; 28: 590–596.

Table 16.2 Stages of chronic kidney disease (CKD) and their mapping to diabetic kidney disease (DKD)

Stage	Defining eGFR (mL/min/1.73 m^2)	Other required features	Patients with diabetes		
			Normoalbuminuria	Microalbuminuria	Clinical nephropathy
1	>90	Abnormal urinalysis and/or renal imaging	At risk for DKD	Likely DKD (type 1) Possible DKD (type 2)	DKD
2	60–89	Abnormal urinalysis and/or renal imaging	At risk for DKD	Likely DKD (type 1) Possible DKD (type 2)	DKD
3A 3B	45–59 30–44	None	Likely DKD (type 1) Possible DKD (type 2)	DKD (type 1) Likely DKD (type 2)	DKD
4	15–29	None	Probable DKD	DKD	DKD
5	<15 or RRT	None	DKD	DKD	DKD

RRT, renal replacement therapy.
Abnormal urinalysis = albuminuria and/or haematuria.

Epidemiology

Reported prevalence and incidence of microalbuminuria and clinical nephropathy vary according to the population under study (type 1 versus type 2; age range; population or hospital clinic base; ethnicity; year of reporting; type of test). In population-based studies the prevalence of microalbuminuria ranged from 12.3% to 27.2% for type 1 and 19.4% to 42.1% for type 2 diabetes. For clinical nephropathy, the figures were 0.3–24% and 9.2–32.9% for type 1 and type 2 diabetes population-based studies respectively.

The incidence of persistent microalbuminuria is around 2% per annum for both type 1 and type 2 diabetes with normoalbuminuria. For microalbuminuric patients, the incidence of clinical nephropathy is around 3% per annum.

Rates for ESRD are more difficult to interpret because they are not linear with time and vary according to duration of diabetes. For type 1 diabetes, the latest Finnish National Data reports rates of 2.2% at 20 years' and 7.8% at 30 years' duration; for the UKPDS the rate of renal replacement therapy or death from renal failure was 0.6% at 10.4 years.

Pathology and pathophysiology

The classic pathological lesions of nodular glomerulosclerosis were first described in 1936. The earliest pathological feature is thickening of the glomerular capillary basement membrane due to an accumulation of matrix material, which is detectable within 5 years of diabetes onset in patients with type 1 diabetes (Figures 16.2–16.4).

Increasing proteinuria is preceded and accompanied by further accumulations of matrix material (mostly type IV collagen and laminin) in the mesangium (called diffuse glomerulosclerosis), due to both overproduction and reduced breakdown and clearance. Ultimately this process obliterates the capillary and reduces filtration, leading to renal failure.

Arteriolar hyalinosis leading to glomerular ischaemia, glomerular epithelial cell (podocyte) loss and tubulointersti-

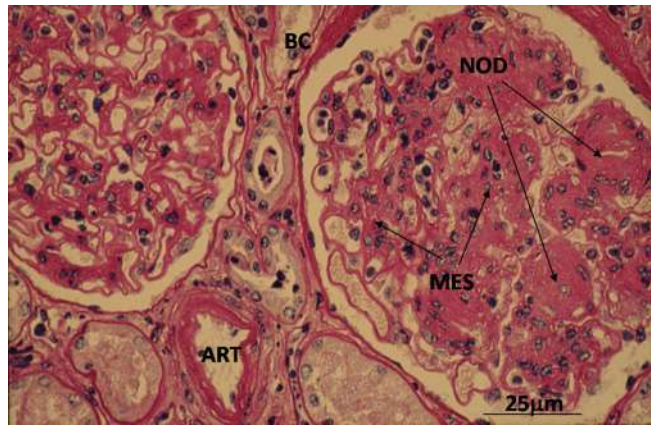

Figure 16.2 Nodular glomerulosclerosis in a patient with type 1 diabetes and clinical nephropathy. ART, arteriolar nephropathy; BC, thickened Bowman's capsule; MES, mesangial expansion; NOD, nodules.

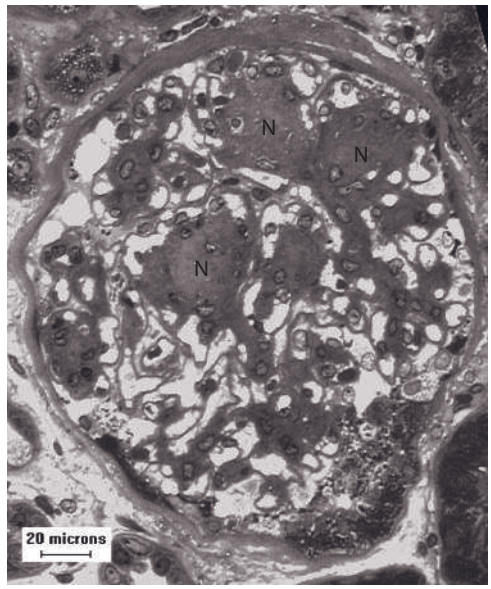

Figure 16.3 Nodular glomerulosclerosis (Kimmelstiel–Wilson kidney) in a patient with diabetic nephropathy. N, nodule.

tial inflammation and fibrosis are also features of advanced nephropathy.

The pathophysiology of these changes has been partly covered in Chapter 14. Essentially, metabolic and haemodynamic factors combine to stimulate the release of profibrogenic cytokines such as transforming growth factor β (TGF-β) and connected tissue growth factor, as well as decreasing matrix degradation by inhibition of enzymes such as metalloproteinases. In experimental and human diabetes, renal blood flow is increased and there is a relative dilatation of the afferent compared to the efferent glomerular arteriole. This leads to an increase in glomerular capillary pressure which has been closely related to the development of glomerulosclerosis in diabetic animals. Angiotensin II blockade relaxes the efferent arteriole and lowers intraglomerular capillary pressure (Figure 16.5).

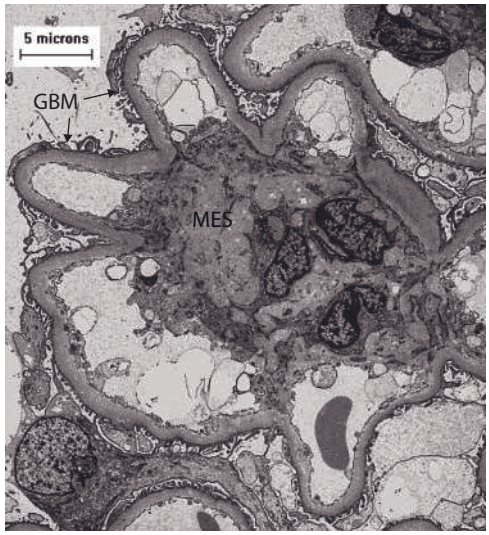

Figure 16.4 Electron micrograph of the glomerulus from a patient with diabetes, showing basement membrane thickening (GBM) and mesangial expansion with extracellular matrix accumulation (MES).

These changes in structure and capillary pressure underpin the development of albuminuria. The glomerular capillary has an inherent size and molecular charge selectivity. In structural terms the endothelium lining the capillary is fenestrated and has a complex glycocalyx of proteins on its surface. The glomerular basement membrane (GBM) is a meshwork of mainly type IV collagen which is cross-linked in a lattice formation. Finally the epithelial surface comprises the podocytes which have a series of interdigitating foot processes (Figure 16.6).

The glomerular barrier normally retains most circulating proteins of the size and charge of albumin. Glycation of the glycocalyx proteins, disruption of the GBM lattice by matrix accumulation, and podocyte loss allow filtration of increas-

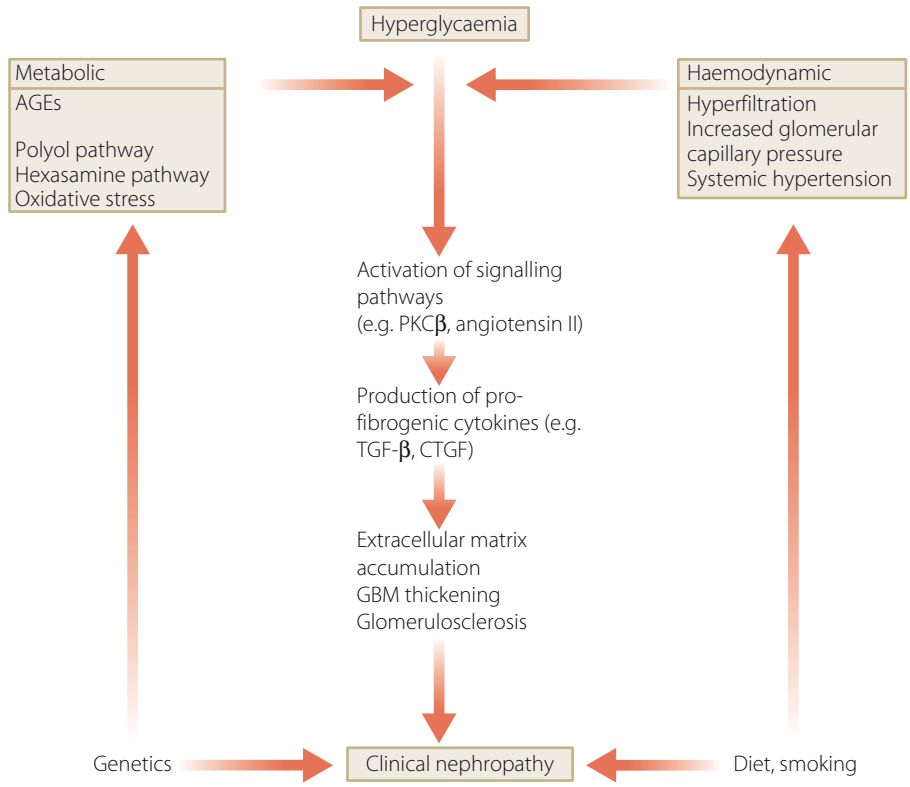

Figure 16.5 Schematic diagram illustrating how metabolic and haemodynamic factors combine to cause glomerulosclerosis. PKCβ, protein kinase C β; GBM, glomerular basement membrane; TGF-β, transforming growth factor β; CTGF, connective tissue growth factor.

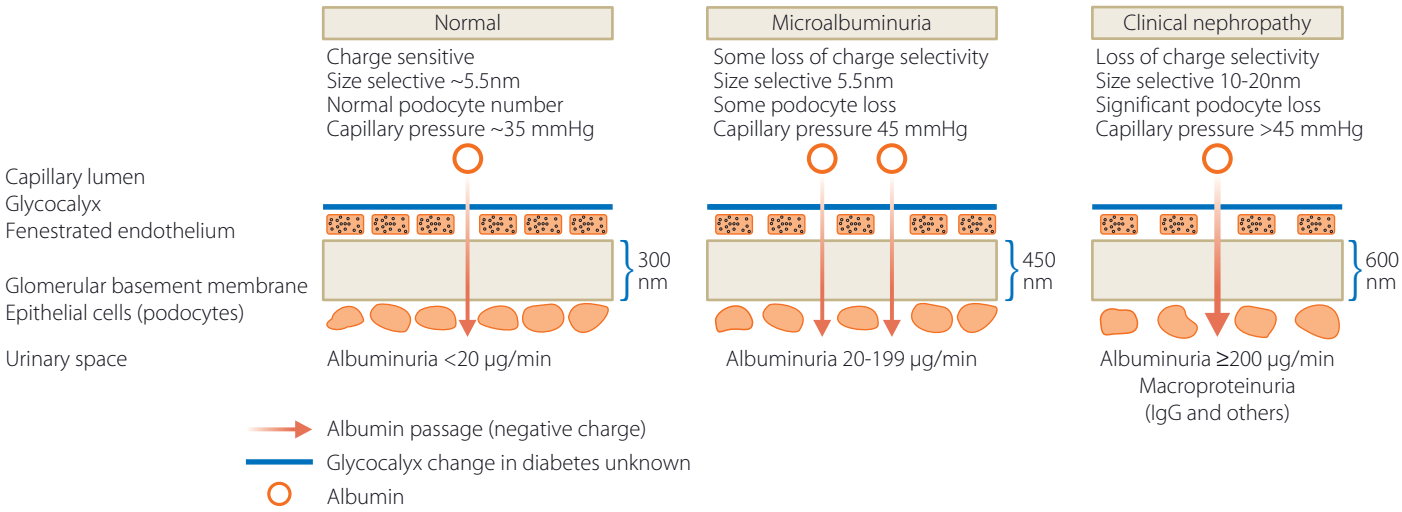

Figure 16.6 Schematic of changes in selectivity of glomerular capillary to albumin in diabetic nephropathy. A rise in capillary pressure and thickening of the glomerular basement membrane (GBM), together with loss of podocytes, result in increasing passage of circulating proteins into the urinary space. Most charge selectivity takes place at the podocyte layer, size selectivity at the GBM. The role of the glycocalyx is still unclear. IgG, immunoglobulin G.

CASE HISTORY

A 32-year-old man with type 1 diabetes, modest renal impairment (serum creatinine 212 µmol/L) and clinical nephropathy had a BP of 170/110 mmHg when he first presented in 1994. His diabetic control was poor and he would only take insulin once a day in an unusual mixture of lente and ultralente preparations. He was started on enalapril 10 mg bd with an immediate response; his BP fell to 120/80 mmHg. Although there was an initial increase in his serum creatinine, this stabilised and now 15 years later he is still independent of dialysis. His inverse creatinine chart is shown in Figure 16.12.

During this time his BP has always been <140/90 mmHg and usually much less than that. He was working until 5 years ago as a scaffolder but had to stop because of postural dizziness due to autonomic neuropathy. His HbA_{1c} has varied between 8% and 11% over this time; he is now on twice-daily premixed insulin (after ultralente was withdrawn).

Comment: The renal response to therapy in this man is striking and was achieved despite poor glycaemic control. This underscores the primacy of BP in driving progression of diabetic nephropathy once it is established. The initial increase in serum creatinine is significant but still within a 35% change that is acceptable when commencing RAS-blocking drugs. His blood pressure response was dramatic which supports the role of angiotensin II in nephropathy-related hypertension.

Although eGFR is a useful reminder of kidney function, a reciprocal serum creatinine chart like this is also helpful in monitoring progression and the impact of any interventions, especially once the level is >150 µmol/L.

ing amounts of albumin and larger macromolecules which characterise progressive nephropathy. There is evidence that the increased presentation of proteins in the filtrate to tubular cells leads to tubulointerstial inflammation and fibrosis, contributing to declining GFR.

Risk factors for nephropathy (Box 16.1)

Prospective observational studies have shown a consistent association between glycaemia and known duration of diabetes, and development of nephropathy.

The role of hypertension has been mentioned earlier; blood pressure rises as nephropathy develops in type 1 and plays a more causative role in type 2 diabetes.

Box 16.1 Factors associated with the development of diabetic nephropathy

- Glycaemia
- Diabetes duration
- Hypertension
- Hyperfiltration
- Ethnicity
- Genetics
- Diet (protein intake)

A meta-analysis of studies of directly measured GFR in type 1 diabetes found a significant link between hyperfiltration and later development of nephropathy but there was marked heterogeneity and the relationship was weakened when glycaemic control was taken into account.

Ethnicity plays an important but ill-understood role. Rates of nephropathy are much higher in Native American, South Asian, some Pacific Islander, non-Ashkenazi Jewish and Afro-Caribbean diabetic patients compared to their white Europid age- and duration-matched controls. Some of this increased risk relates to increased rates of hypertension (e.g. in Afro-Caribbean patients), and some may be related to the low birthweight (thrifty phenotype) hypothesis (see Chapter 7) which has been linked to higher blood pressures and nephropathies generally as well as to type 2 diabetes *per se*.

Sibling studies in multiplex families with type 1 diabetes have shown an increased incidence of nephropathy in siblings of a proband with the condition compared to those of a proband with normal albuminuria (Figure 16.7). These observations do not completely rule out environmental factors but the heritability of a risk for nephropathy is supported by the observation that a positive family history of hypertension and cardiovascular disease is more likely in the parents of type 1 patients with nephropathy compared to those of patients without. Extensive search for candidate genes and genome-wide screening have so far yielded some positive associations (with polymorphisms in genes related to the RAS) but on the whole, these relationships are not very strong and no major gene effect has yet been identified.

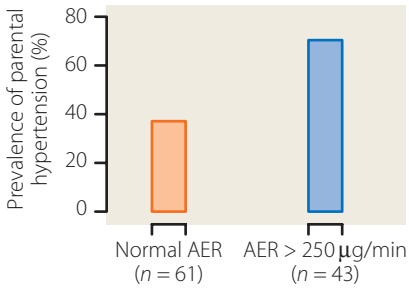

Figure 16.7 The cumulative incidence of persistent proteinuria in siblings with type 1 diabetes of probands with type 1 diabetes, with or without proteinuria. From Barzilay et al. Kidney Int 1992; 41: 723–730.

Management

Glycaemic control

The DCCT/EDIC Study and UKPDS provide incontrovertible evidence that good glycaemic control can prevent the development of microalbuminuria and this benefit was apparent for at least 8–10 years after the studies concluded (Figure 16.8). There is very little evidence to suggest that it can prevent or delay the progress of nephropathy once it is established. This is probably because after nephropathy has been initiated (by largely glucose-dependent mechanisms), it is continued by pathways that are no longer sensitive to changes in glycaemia. Intriguingly, though, in a small group of type 1 pancreas transplant recipients, renal pathology improved in their native kidneys after 10 (but not 5) years of normoglycaemia, implying that not only is complete normalisation of blood glucose required, but also the lesions take almost as long to resolve as they do to develop. Good glycaemic control, however, will continue to benefit other complications such as retinopathy.

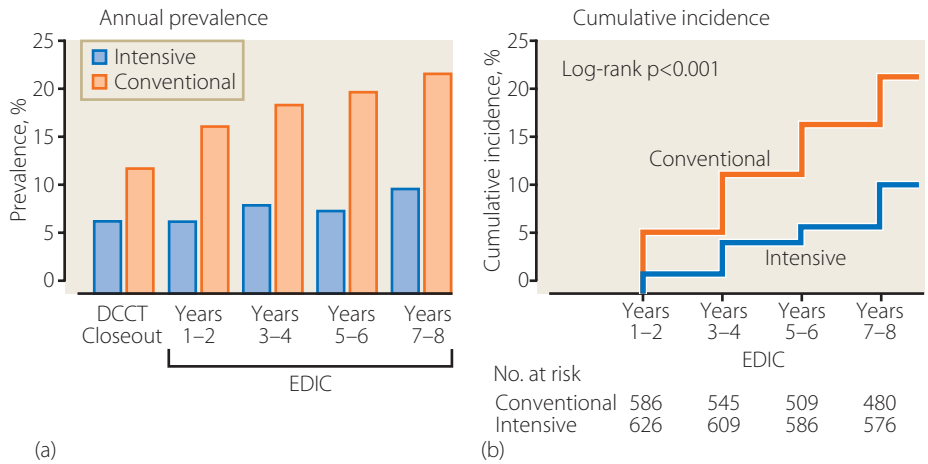

Figure 16.8 (a) Prevalence and (b) cumulative incidence of microalbuminuria in the DCCT/EDIC study showing continuing benefit of intensive diabetic control for up to 8 years after the main study concluded. Data from DCCT/EDIC Research Group. JAMA 2003; 290:2159–2167.

Blood pressure

Target blood pressure for people with diabetes has been set at <130/80 mmHg by most guidelines, with some suggesting <120/75 in those with nephropathy and proteinuria >1 g/day. Improved control of blood pressure is probably the main reason why the median duration of clinical nephropathy prior to ESRD has risen from 7 to 14 years since 1980 (Figure 16.9).

Because of the involvement of angiotensin II in the glomerular haemodynamic changes in diabetes, agents which block the RAS feature as first-line therapy in most guidelines. These drugs also reduce albuminuria which would help ameliorate any tubulointerstitial insult caused by increased protein trafficking across the tubular epithelium. Meta-analysis in normotensive patients with type 1 diabetes and microalbuminuria confirms that angiotensin-converting enzyme inhibitors (ACEI) can reduce the numbers developing clinical nephropathy by around 60%, with those having higher levels of albuminuria at baseline showing the most benefit (Figure 16.10).

However, there is little evidence that RAS blockade can prevent primary development of microalbuminuria in type 1 diabetes and may only be effective in patients with type 2 diabetes who are already hypertensive or at high cardiovascular risk.

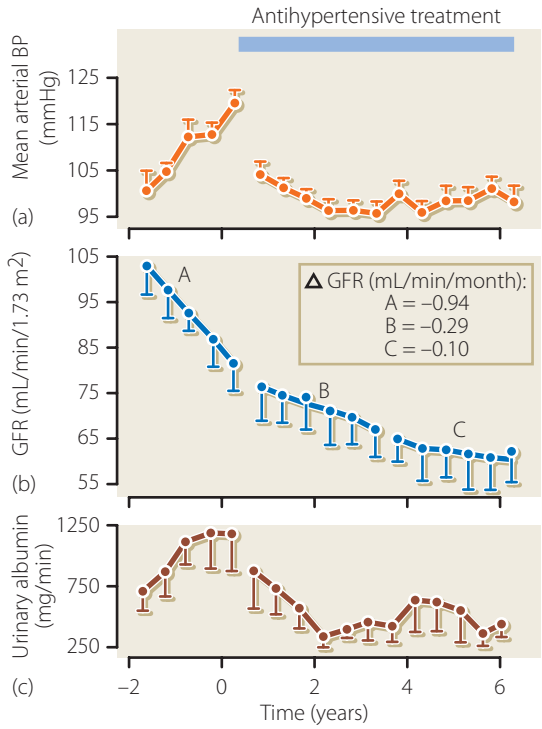

Figure 16.9 Effects of antihypertensive treatment on (a) mean arterial blood pressure, (b) GFR, and (c) urinary albumin excretion in patients with type 1 diabetes and nephropathy. Rates of decline in both GFR and albumin excretion were significantly reduced. From Parving et al. BMJ 1987; 294: 1443–1447.

Most patients with nephropathy will require two or more agents to achieve blood pressure targets. For more details of blood pressure management, please see Chapter 19.

Proteinuria

There is evidence from intervention trials that patients who have a greater reduction in proteinuria in response to treatment do better in terms of rate of decline in renal function.

LANDMARK CLINICAL TRIAL

Mogensen CE. Long-term antihypertensive treatment inhibiting progression of diabetic nephropathy. BMJ 1982; 285: 685–688.

This small observational study in six type 1 diabetic men with clinical nephropathy was published 8 months before the much more widely known study of Parving (shown in Figure 16.12). GFR was measured directly using isotopic clearance methods three or four times in the 20–31 months before commencing antihypertensive therapy, and 12–18 times over the subsequent 28–86 months.

Blood pressure treatment was first-line β blockade plus hydralazine in 4 and furosemide in 3. Mean BP readings fell from 162/103 mmHg to 144/95 (range 138–160 mmHg systolic). Rate of fall of GFR was 1.24 mL/min/1.73 m^2/month before antihypertensive therapy and 0.49 mL/min/1.73m^2/month during treatment. A statistically significant positive relationship was found between achieved BP and rate of decline in GFR. Baseline proteinuria was 3.9 (range 0.5–8.8) g/day and stabilised during treatment. Prior to this there was an average annual increase of 107%.

At the time of this study, there were still concerns that lowering blood pressure in patients with CKD would reduce kidney perfusion and exacerbate renal failure. This observational study and others that followed showed that BP lowering actually preserved renal function and slowed the otherwise rapid and relentless decline to ESRD. The principle of BP control in CKD is now firmly established but only 27 years ago this was far from the case.

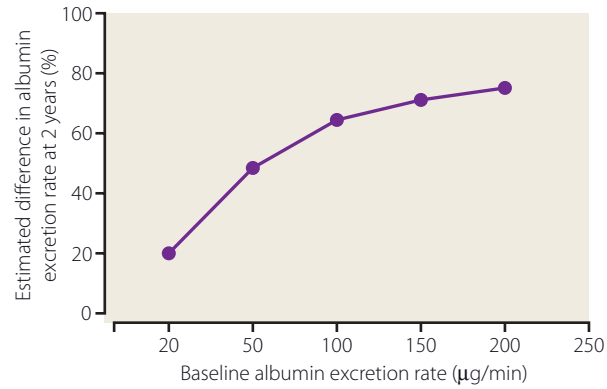

Figure 16.10 Meta-analysis of the effects of angiotensin-converting enzyme (ACE) inhibition on microalbuminuria. Estimated difference in albumin excretion rate between placebo and ACE inhibitor treatment groups at 2 years, according to albuminuric status at baseline. From ACE Inhibitors in Diabetic Nephropathy Trialist Group. Ann Intern Med 2001; 134: 370–379.

This observation has led to the proposal that reduction of proteinuria to <1 g/day should be a therapeutic target. This is not widely accepted, but studies of multiple blockade of the RAS using combinations of ACEI, angiotensin type 1 receptor blockers, aldosterone antagonists and renin inhibitors have shown greater reductions in albuminuria compared to the use of individual agents alone. However, there is a real risk of hyperkalaemia and acute deterioration in renal function (see Chapter 19).

Protein restriction

In experimental diabetes, dietary protein restriction reduces albuminuria and progression to renal failure. Studies in humans have been variable in duration and endpoint. A systematic review has shown a modest reduction in the rate of decline of GFR in type 1 diabetes with a restriction of dietary protein intake to 0.7–1.1 g/kg bodyweight/day. Only one study used mortality and ESRD as endpoints and found a relative risk of 0.23 (95% CI 0.07–0.72). For type 2 diabetes the data were not significant. The National Kidney Foundation guideline recommends a dietary protein intake of 0.8 g/kg bodyweight/day for diabetic patients and CKD stages 1–4.

Anaemia correction

Anaemia secondary to erythropoietin (EPO) deficiency is a feature of CKD generally and some studies suggest that it occurs earlier at a higher GFR in people with diabetes. Hospital clinic-based surveys suggest prevalence rates of WHO-defined anaemia (<12 g/dL women, <13 g/dL men) of 15–25%, and many cases were in patients with an eGFR >60 mL/min/1.73 m^2. Several large trials of anaemia correction using various preparations of EPO have suggested no benefit (and possibly some harm) of achieving a haemoglobin concentration >13 g/dL. Below this level, patients feel better but no conclusive impact on rate of decline in GFR or cardiovascular morbidity/mortality has been demonstrated. Current NICE guidance has set an intervention threshold of 11 g/dL and a target of 10.5–12.5 g/dL for all patients with CKD and adequate iron stores.

Cardiovascular risk factor management

There are no conclusive trial data to support aspirin or lipid-lowering therapy specifically in diabetic nephropathy. Thus targets are the same as for diabetes generally.

The Steno 2 Study of multifactorial cardiovascular risk intervention in type 2 patients with microalbuminuria at baseline showed a major impact on mortality, development of nephropathy and ESRD, as well as cardiovascular complications including myocardial infarction and amputation (Figure 16.11). The protocol for the intensive arm was for RAS-blocking drugs in all, lipid-lowering therapy with a target total cholesterol <4.5 mmol/L, intensive glycaemic

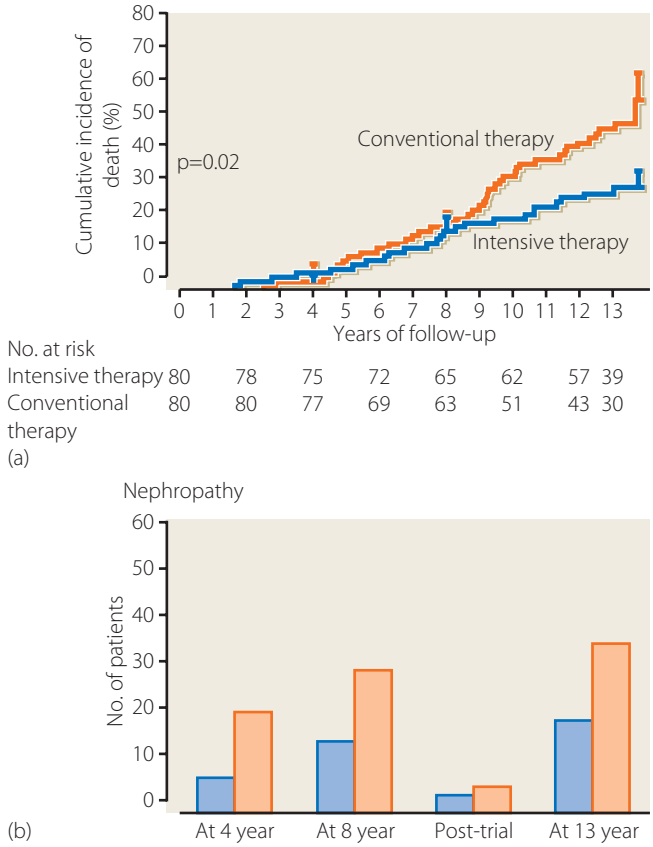

Figure 16.11 (a) Cumulative incidence of death in 160 microalbuminuric patients with type 2 diabetes randomised to intensive or conventional management of cardiovascular risk factors for 8 years in the Steno 2 trial and for 5 years afterwards. (b) Number of patients developing nephropathy on intensive or conventional treatment during and after the Steno 2 trial. Data from Gaede et al. N Engl J Med 2008; 358: 580–591.

control with a target HbA_{1c} <6.5% (48 mmol/mol), low-dose aspirin, antioxidants (vitamins C and E) and lifestyle changes including stopping smoking, weight reduction and increasing exercise. As with the DCCT/EDIC and UKPDS, these benefits continued beyond the end of the trial but it was not possible to determine which were the most effective interventions.

Thus the patient with nephropathy should have intensive management of all known cardiovascular and diabetic complication risk factors.

Renal replacement therapy (RRT) and pancreas transplantation

The incidence rates for commencement of RRT in patients with diabetes are 159/million population in the USA and 24/million population in the UK. Proportionally, these represent 44% and 22% of total incident patients starting RRT per year. There are similar differences in rates between northern (lower) and central (higher) European countries but the precise reasons are not clear.

Most patients with diabetes are managed on haemodialysis – approximately 80% of all dialysed patients with diabetes in the UK. Kidney transplantation rates tend to be lower in patients with diabetes compared to patients without diabetes in ESRD, perhaps as a result of greater co-morbidities. In the UK in 2007, 14.6% of all new transplants were in patients with diabetes (compared to a relative incidence of 22% of diabetic ESRD); only 7.7% of all established transplants in the UK at the end of 2006 were in people with diabetic nephropathy.

However, survival appears best for kidney transplant recipients compared to those remaining on dialysis, but is improving year on year for all modalities of RRT. In the UK 1-year survival for those aged <65 years on dialysis was 86.2% for patients with diabetes and 93.1% for patients without diabetes respectively. For those aged >65 years the survival was 78.4% and 79.7% respectively. Six-month mortality hazard was <20% and relatively stable over 8 years for those with diabetes <55 years of age on dialysis but there were higher rates, close to 35% and rising, for those over 65 years of age. In the US, 5-year survival for patients with diabetes on haemodialysis or peritoneal dialysis is <30%.

As patients approach ESRD, planning for RRT becomes a priority. Patients do much less well if they present in acute on chronic renal failure. All patients with CKD stage 4 (eGFR <30 mL/min/1.73 m^2) should be referred for assessment. Other indications are shown in Box 16.2.

The role of whole-organ pancreas transplantation is controversial. There are no data suggesting that simultaneous pancreas and kidney transplantation (SPK) improves outcome in terms of survival compared to kidney transplant alone. However, quality of life, particularly for patients with hypoglycaemic unawareness, is much improved. Survival rates are much better with modern immunosuppressant regimens, with reported rates of 67% at 10 years for SPK compared to 65% for living donor kidney transplants alone. In the UK, the number of SPK procedures rose from 102 in 2005 to 197 in 2007 (worldwide, the figures were approximately 1000 for both years). However, the operative procedure and acute complication rate is much greater than for kidney transplants alone and pancreas transplantation should only be carried out in specialist centres.

Is it diabetic nephropathy?

Because type 2 diabetes is a common condition, patients will also present with non-diabetes related kidney disease. However, it is likely that <10% with type 2 diabetes and albuminuria have a non-diabetic cause and few of these will have a specifically treatable disease. Interestingly, those with atypical or non-diabetic pathologies tend to have a slower rate of decline in GFR compared to patients with typical glomerulosclerosis.

In the presence of retinopathy and albuminuria >300 mg/day, it is highly likely that patients have diabetic kidney disease; in the absence of retinopathy and in the pres-

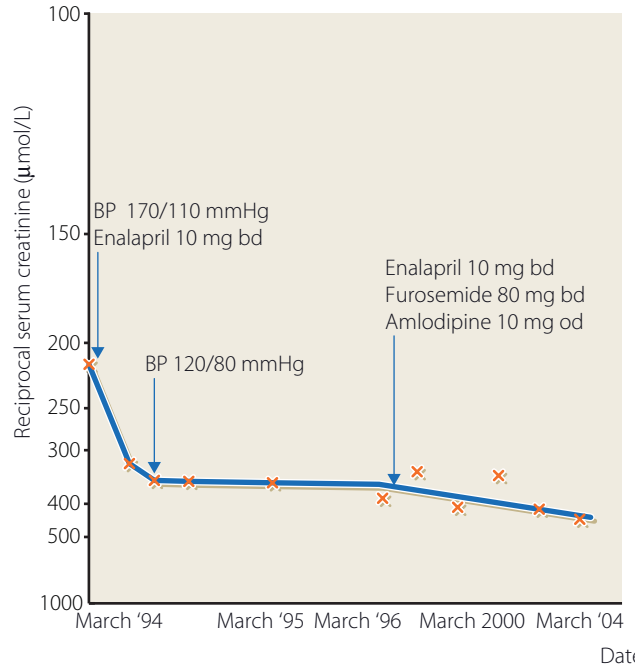

Figure 16.12 Reciprocal serum creatinine plotted against date for the case history. The patient was still not requiring dialysis in 2010.

Box 16.2 Criteria for referral for specialist review

- CKD stage 4 or 5 (eGFR <30 mL/min/1.73 m^2)
- Rapid loss of GFR (eGFR decline >5 mL/min/1.73 m^2/yr or >10 mL/min.17.3 m^2/5 yrs)
- Microscopic haematuria
- Heavy proteinuria (>1 g/day or protein:creatinine ratio >100 mg/mmol)

For further details see www.renal.org.

KEY WEBSITES

- Diabetes Atlas: www.eatlas.idf.org
- NICE guidance (all National Collaborating Centre Guidance for Chronic Conditions: CG 15; CG 66; CG 39): www.nice.org.uk
- UK Renal Registry: www.renalreg.com/report/2008.htm
- USRDS Renal Atlas: www.USRDS.org/adr/htm
- UK Renal Association: www.renal.org
- UK National Service Framework for Renal Disease: www.dh.gov.uk/en/ Healthcare/Renal/DH_4102636
- SIGN Guidelines: www.SIGN.ac.uk

ence of microalbuminuria then non-diabetic kidney disease becomes more likely. If patients have signs of systemic disease, rapidly increasing proteinuria or deteriorating renal function, or urinalysis suggesting microscopic haematuria, then they should be referred for specialist review and a non-diabetic cause of their nephropathy should be considered.

FURTHER READING

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Chapter
17

Diabetic neuropathy

KEY POINTS

- Diabetic neuropathy is a term that encompasses a heterogeneous group of disorders.
- Microvascular disease affecting the small nutrient vessels that supply peripheral nerves (vasa vasorum) results in ischaemic and metabolic neuronal injury.
- Chronic sensorimotor neuropathy is the most common form, typically affecting the stocking distribution of the lower limb, causing painful symptoms, mixed modality sensory loss, small muscle wasting and deformity (e.g. clawed toes).
- Identifying and risk-stratifying feet affected by neuropathy that are at high risk of ulceration is an important part of the annual complications assessment.
- Several drug treatments have been tried for painful diabetic neuropathy, but few have any evidence base from controlled trials. Only duloxetine and pregabalin are licensed by the US FDA.
- Excluding other causes of neuropathy is an important part of the clinical assessment, e.g. alcohol, B12 deficiency and drugs. A 10 g monofilament is useful for detecting sensory impairment, and a staging system is available to assess severity.

Symptoms, signs and classification

Diabetes is one of the most common causes of peripheral neuropathy, a term that encompasses a heterogeneous group of disorders (Figure 17.1). In population-based surveys, up to one-third of patients with diabetes have evidence of peripheral neuropathy but many are asymptomatic. Diabetic neuropathy should not be diagnosed solely on the basis of one symptom, physical sign or test; it is recommended that a minimum of two abnormalities be detected (symptoms, signs or test abnormalities – nerve conduction, quantitative sensory testing or quantitative autonomic testing) (Box 17.1).

Healthy nerves consist of myelinated and unmyelinated nerve fibres or axons. The pathophysiology of diabetic neuropathy is complex, but microvascular disease affecting small vessels (the vasa vasorum) that supply oxygen and nutrients to peripheral nerves results in ischaemic and

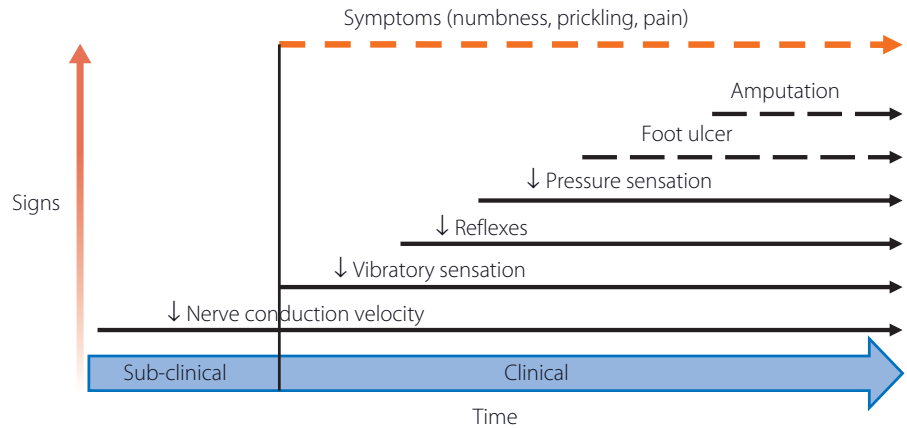

Figure 17.1 Diabetic neuropathy is common and associated with a complex mix of symptoms and signs. With increasing duration of diabetes and associated microangiopathy, diabetic neuropathy may lead to foot ulceration, deformity and/or amputation.

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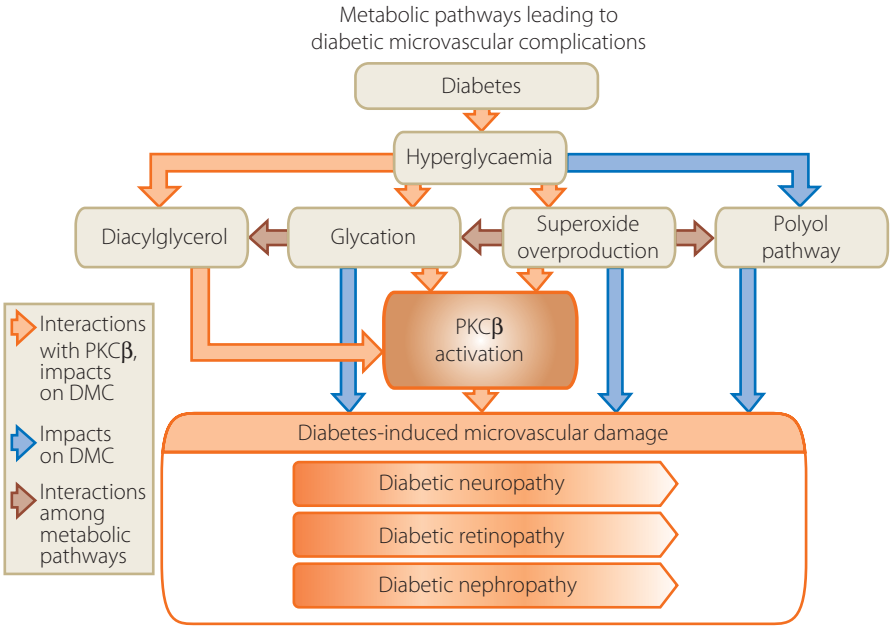

Figure 17.2 Hyperglycaemia-induced activation of key biochemical pathways in diabetic microangiopathy, affecting the vasa vasorum supplying peripheral nerves and leading to neuronal ischaemia and dysfunction.

Box 17.1 Classification of diabetic neuropathy

Generalised symmetrical polyneuropathies
- Sensorimotor (chronic)
- Acute sensory
- Hyperglycaemic neuropathy

Focal and multifocal neuropathies
- Cranial nerve
- Thoracolumbar radiculoneuropathy
- Focal limb
- Proximal motor (amyotrophy)

Superimposed chronic inflammatory demyelinating neuropathy (CIDP)

Autonomic neuropathy

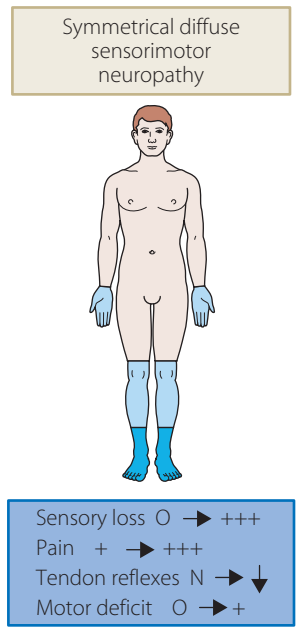

Figure 17.3 Clinical pattern of distal symmetrical neuropathies.

metabolic neuronal injury via activation of several biochemical pathways, in particular the polyol pathway, non-enzymatic glycation and formation of advanced glycation endproducts (AGEs), activation of diacylglycerol-protein kinase C-β, transcription factors (e.g. NFκB) and mitogen-activated protein kinase (MAPK), and the accumulation of reactive oxygen species (ROS) (Figure 17.2).

Chronic sensorimotor neuropathy

Chronic sensorimotor neuropathy is the most common form of diabetic neuropathy. This results from the distal dying back of axons that begins in the longest nerves; thus, the feet are affected first in a stocking distribution, and later there may be progressive involvement of the upper limbs. Sensory loss is most evident; autonomic involvement is usual, although it is mostly symptomless. Positive painful symptoms tend to be worse at night. Neurological examination shows a symmetrical sensory loss to all modalities, reduced or absent ankle or knee reflexes, and small muscle wasting of the feet and hands (Figure 17.3). The foot at high

Box 17.2 Staging the severity of diabetic neuropathy

Stage 0:	No signs or symptoms
Stage 1:	Asymptomatic neuropathy
1a:	No symptoms or signs but nerve conduction velocity abnormalities or autonomic test abnormalities
1b:	N1a criteria + neurological examination abnormality. Vibration detection threshold abnormality
Stage 2:	Symptomatic neuropathy
2a:	Symptoms, signs and tests abnormality*
2b:	N2a criteria + significant weakness of ankle dorsiflexion
Stage 3:	Disabling polyneuropathy

* Tests include nerve conduction, quantitative sensory testing and quantitative autonomic testing

Box 17.3 Positive sensory symptoms; painful neuropathy

Non-painful
- Thick
- Stiff
- Asleep
- Prickling
- Tingling

Painful
- Prickling
- Tingling
- Squeezing
- Constricting
- Freezing
- Knife-like
- Hurting
- Electric shock-like
- Allodynia
- Hyperalgesia
- Burning
- Aching
- Lancinating

risk of neuropathic ulceration might have a high arch (pes cavus deformity) and clawing of the toes.

A simple staging system has been developed for diabetic neuropathy (Box 17.2).

Positive sensory symptoms can arise spontaneously or as a response to stimulation, and they are often classified into painful and non-painful descriptors (Box 17.3). Numbness and prickling are the most common symptoms, and they usually occur earlier. Allodynia is the perception of pain from a non-noxious stimulus. The prevalence of painful symptoms varies from 3% to 20%. The natural history of painful neuropathy is unclear, but there is some suggestion that the intensity of symptoms may subside with worsening

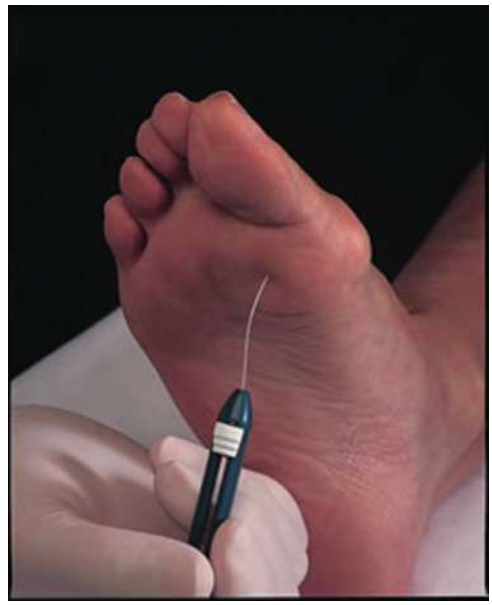

Figure 17.4 A 10 g monofilament is easy to use in the clinic and is much better than clinical assessment for identifying patients at risk of foot ulceration.

quantitative measures of nerve function. Similarly, the risk factors for painful neuropathy are ill defined. Hypoaesthetic neuropathy is associated with minimal or negative sensory symptoms, and therefore is best detected by quantitative sensory testing

In identifying feet at risk of ulceration, the 10 g monofilament has a sensitivity of 86–100%. These are patients who are unable to feel the monofilament when applied with sufficient pressure at the handle to buckle the filament (Figure 17.4). The monofilament should be applied to the sole of each foot in four places (over the hallux and metatarsal heads 1, 3, 5). More sophisticated instruments for measuring vibration detection threshold (VDT) and quantitative sensory testing (three modalities – vibration, thermal and pain thresholds) are also useful for predicting patients with neuropathy who are at high risk of ulceration and amputation.

Positive symptoms of neuropathy are distressing, often occur at night, are disabling and difficult to treat. Patients with painful peripheral neuropathy often have warm, dry feet because of autonomic involvement, which results in dilated arteriovenous shunts and absent sweating. The most important complications are:

- foot ulceration
- neuropathic oedema, caused by increased blood flow in the foot, which has reduced sympathetic innervation
- Charcot arthropathy, with chronic destruction, deformity and inflammation of the joints and bones of the mid-foot. There is reduced bone density, possibly because of increased blood flow (Figure 17.5) (see Chapter 21).

Treatment of diabetic neuropathy

Various topical and systemic therapies have been tried for painful diabetic peripheral neuropathy, but few have been subjected to well-designed randomised controlled trials (RCTs). In addition to those listed in Box 17.4, acupuncture may be helpful and the antioxidant α-lipoic acid is used in some countries. The US Food and Drug Administration (FDA) has only licensed duloxetine and pregabalin for painful diabetic neuropathy.

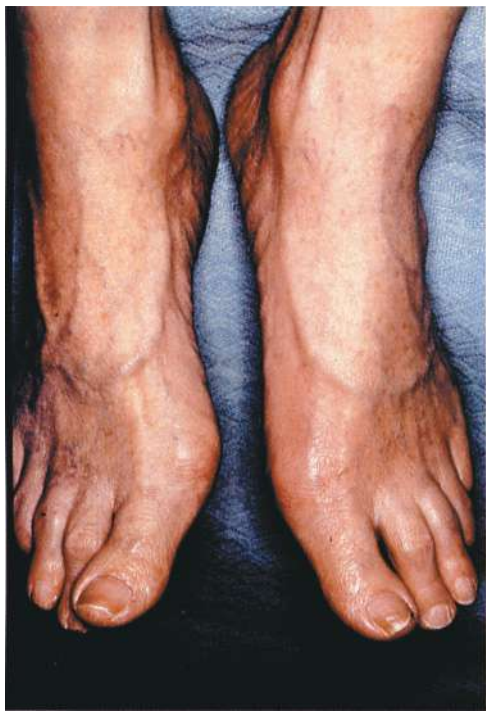

Figure 17.5 Increased blood flow (distended veins) on the dorsum of the foot of a diabetic patient with painful peripheral neuropathy. Courtesy of Dr G Gill, University of Liverpool, Liverpool, UK.

Compression neuropathies

Pressure palsies comprise focal lesions of peripheral nerves that occur at sites of entrapment or compression (Figure 17.6). Diabetic nerves are thought to be more susceptible to mechanical injury. The most common is the carpal tunnel syndrome (median nerve compression), in which paraesthesiae and sometimes numbness occur in the fingers and hands. Discomfort can radiate into the forearm. Examination can show wasting and weakness of the thenar muscles, with loss of sensation over the lateral three-and-a-half fingers. The diagnosis can be confirmed by nerve conduction studies. Most patients respond to surgical decompression.

Box 17.4 Pharmacological options with evidence of efficacy from RCTs for use in patients with painful diabetic peripheral neuropathy

Treatments with positive results from two or more RCTs

- Duloxetine (serotonin-norepinephrine reuptake inhibitor)
- Pregabalin (α-2-δ Ca^{2+} channel modulator)
- Oxycodone (opioid)
- Tricyclic antidepressants (e.g. amitriptyline)

Treatments with evidence of efficacy from a single trial in patients with diabetic neuropathies

- Gabapentin (α-2-δ Ca^{2+} channel modulator)
- Venlafaxine (SNRI)
- Tramadol

Carbamazepine and lamotrigine may also be considered

Topical therapies

- Capsaicin cream
- Lignocaine patch

CASE HISTORY

A 55-year-old man with a 6-year history of type 2 diabetes presents to his family doctor with unpleasant symptoms of prickling discomfort, numbness and tingling over both lower limbs and feet. These symptoms often disturb his sleep, and he has noticed excessive discomfort when putting his feet into a warm bath. There are no symptoms in his hands, he is a non-smoker and drinks 6 units of alcohol per week. There are no symptoms to suggest autonomic dysfunction. He has background diabetic retinopathy, and his diabetes is managed with metformin 1 g bid and gliclazide MR 120 mg daily (HbA_{1c} 8.5%). Clinical examination shows some distal muscle wasting in the feet, but no ulceration. He is unable to feel the 10 g monofilament placed over the metatarsal heads. Pedal pulses are present. His height is 6′ 1″, BMI 29.

Comment: This patient presents with typical symptoms and signs of diabetic peripheral neuropathy, including allodynia when he puts his feet into warm water. Risk factors include age, duration of diabetes and HbA_{1c}, and peripheral neuropathy is more common in tall people (longer nerves are more susceptible to damage). Alcohol consumption may aggravate his symptoms. He also has evidence of microvascular complications in the eye. Improving HbA_{1c} is important, and his feet are at high risk of ulceration. Appropriate footcare education is needed. This man may also need symptomatic treatment, e.g. pregabalin, gabapentin or amitriptyline would be reasonable choices.

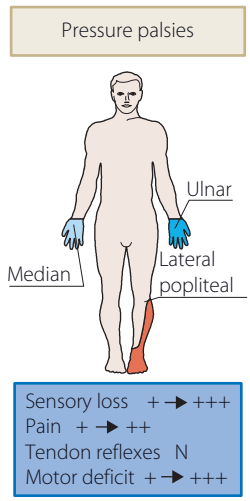

Figure 17.6 Clinical pattern of pressure palsies in patients with diabetes.

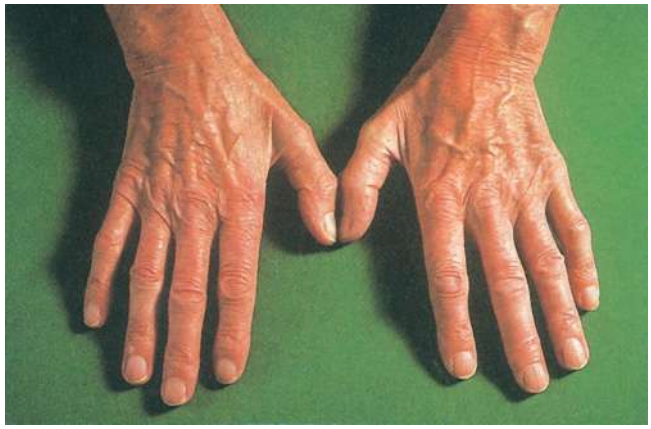

Figure 17.7 Generalised wasting of the interossei (and hypothenar eminence) caused by bilateral ulnar nerve palsies in a diabetic patient.

Ulnar nerve compression at the elbow causes numbness and weakness of the fourth and fifth fingers and wasting of the interossei muscles (Figure 17.7). Lateral popliteal nerve compression can cause foot drop.

In mononeuropathies, single nerves or their roots are affected and, in contrast to distal symmetrical neuropathy, these conditions are of rapid onset and reversible, which suggests an acute, possibly vasculitic or inflammatory origin rather than chronic metabolic disturbance. The most well known is femoral neuropathy or diabetic amyotrophy (Figures 17.8, 17.9). There is multifocal involvement of the lumbosacral roots, plexus and femoral nerve. Typically, the patient is over 50 years of age with continuous thigh pain, wasting and weakness of the quadriceps, and sometimes weight loss. The knee jerk reflex is lost.

Other mononeuropathies include cranial nerve palsies of the third or sixth nerves (causing sudden-onset diplopia). The

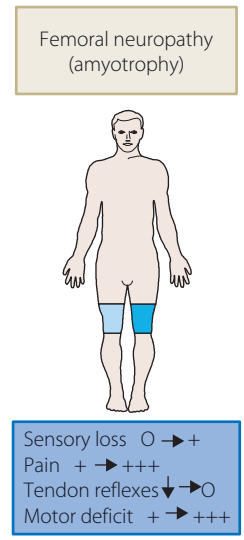

Figure 17.8 Diabetic amyotrophy, showing marked quadriceps wasting, and clinical pattern (inset).

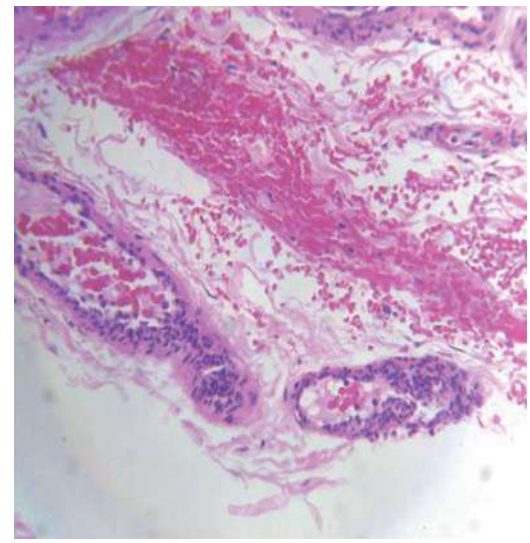

Figure 17.9 Histological changes associated with diabetic amyotrophy, in particular, an inflammatory cell infiltrate, occlusion of epineurial blood vessels and features of necrotising vasculitis. This H&E section shows inflammatory infiltrate affecting arterioles and venules. Courtesy of Dr R Malik.

cause is thought to be a localized infarct that involves brain-stem nuclei or nerve roots. Older people are affected mainly.

Autonomic neuropathy

In patients with long-standing diabetes, numerous abnormalities can be demonstrated in organs that receive an autonomic innervation (Figure 17.10). Often, autonomic abnormalities are found in those with distal sensory neuropathies. Symptoms are unusual, occurring mostly in those with poorly controlled type 1 diabetes. Common

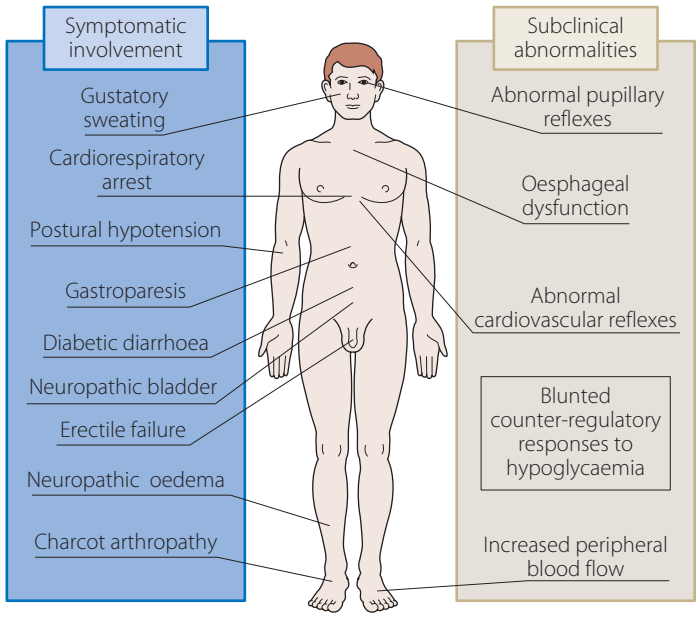

Figure 17.10 Clinical and subclinical features of diabetic autonomic neuropathy.

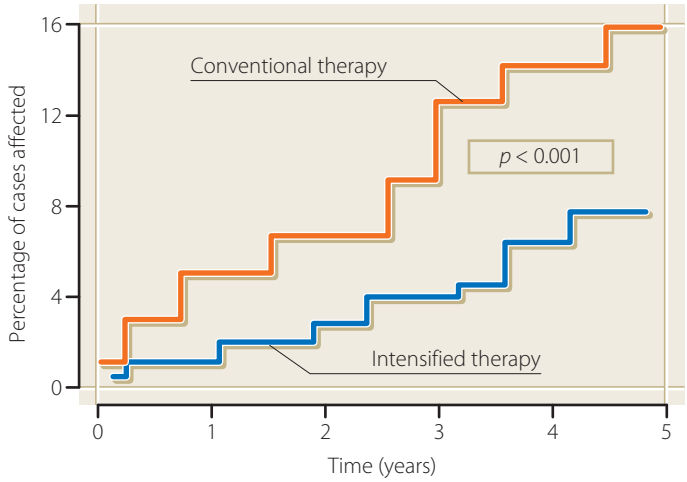

Figure 17.11 Effects of intensified insulin therapy and strict glycaemic control on the incidence of neuropathy in type 1 diabetic patients (DCCT). From Diabetes Control and Complications Trial Research Group. Ann Intern Med 1995; 122: 566–568.

LANDMARK CLINICAL TRIALS

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KEY WEBSITES

- http://diabetes.niddk.nih.gov/dm/pubs/neuropathies/
- www.ninds.nih.gov/disorders/diabetic/diabetic.htm
- www.footcareexpert.co.uk/DiabeticNeuropathy.html
- www.nice.org.uk/guidance/CG10
- SIGN Guidelines: www.SIGN.ac.uk

manifestations are gustatory sweating over the face, induced by eating cheese or other foods, postural hypotension (systolic blood pressure fall >30 mmHg on standing), blunting of physiological heart rate variations, diarrhoea and impotence. Gastroparesis (delayed gastric emptying and vomiting) and bladder dysfunction are rare.

Management of diabetic neuropathy begins with explanation and empathy, the exclusion of other causes of neuropathy (e.g. alcoholism, vitamin B12 deficiency and uraemia), and then the institution of tight glycaemic control. Both the DCCT and UKPDS trials show that strict glycaemic control can decrease the risk of developing neuropathy, as judged by objective measures such as nerve conduction velocity. However, the main complaint of patients with neuropathy is pain, and there is as yet little evidence that improving diabetic control influences the intensity of neuropathic pain (Figure 17.11).

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Chapter

18 Blood lipid abnormalities

KEY POINTS

- The characteristic dyslipidaemia of type 2 diabetes includes increased VLDL-triglyceride (TG) levels and decreased HDL-cholesterol. Total cholesterol is no different compared with non-diabetics.
- There are pathophysiological associations between dyslipidaemia, chronic low-grade inflammation, insulin resistance and diabetes-related vascular disease.
- LDL-particles are smaller, denser and more atherogenic in patients with type 2 diabetes.
- There is a strong linear relationship between total and LDL-cholesterol levels and CV mortality.
- Circulating cholesterol comes from two sources: *de novo* synthesis in the liver (involving HMG CoA reductase, the enzyme blocked by statins) and intestinal absorption of dietary and bile acid cholesterol.
- Statins are the preferred drugs of choice for lowering cholesterol and CV risk in patients with diabetes, aiming for targets of total cholesterol <4 mmol/L and LDL-cholesterol <2 mmol/L.
- There is much less evidence to support TG reduction, except when fasting TG levels are very high, but fibrates and some third-generation statins lower TG concentrations. Improving glycaemic control may indirectly lower TG levels.

Dyslipidaemia in type 2 diabetes

Abnormalities of blood lipids are common in patients with type 2 diabetes, even when there is reasonable glycaemic control. The characteristic dyslipidaemia of type 2 diabetes consists of elevated very low-density lipoprotein (VLDL) triglyceride (TG) levels, reduced high-density lipoprotein (HDL) cholesterol and minimal change in total and low-density lipoprotein (LDL) cholesterol concentrations. Overproduction of TG-rich VLDL by the liver and impaired TG clearance by endothelial lipoprotein lipase are contributory factors. Although total and LDL-cholesterol levels in patients with type 2 diabetes are no different from those in subjects without diabetes, the profile of LDL subfractions in patients with type 2 diabetes is more atherogenic due to a greater proportion of small, dense LDL particles (known as the 'type B' pattern) which are more susceptible to oxidation; oxidised LDL plays a major role in atherogenesis. Improved glycaemic control results in less VLDL-triglyceride synthesis in the liver, but these lipid abnormalities are not completely resolved by lowering HbA_{1c}.

Box 18.1 Features of dyslipidaemia in type 2 diabetes

Fasting triglyceride levels (1.5–3-fold increase):
↑Hepatic TG synthesis and secretion
↓Peripheral TG uptake and clearance
↔Total and LDL cholesterol levels unchanged
↑Proportion of small, dense highly atherogenic LDL particles
↑Fatty acid levels
↓HDL cholesterol levels (typically 10–20%)

In the German PROCAM study, 39% of patients with type 2 diabetes had fasting serum TG concentrations >2.3 mmol/L (vs 21% in non-diabetics) and 27% had HDL-cholesterol levels <0.9 mmol/L (vs 16% in non-diabetics).

The dyslipidaemia of type 2 diabetes is frequently accompanied by other metabolic and biochemical abnormalities indicative of insulin resistance, chronic low-grade inflammation (e.g. increased high-sensitivity C-reactive protein (hsCRP) and elevated cytokines such as interleukin-6 and tumour necrosis factor-α) and a prothrombotic state (increased levels of fibrinogen and PAI-1). Collectively,

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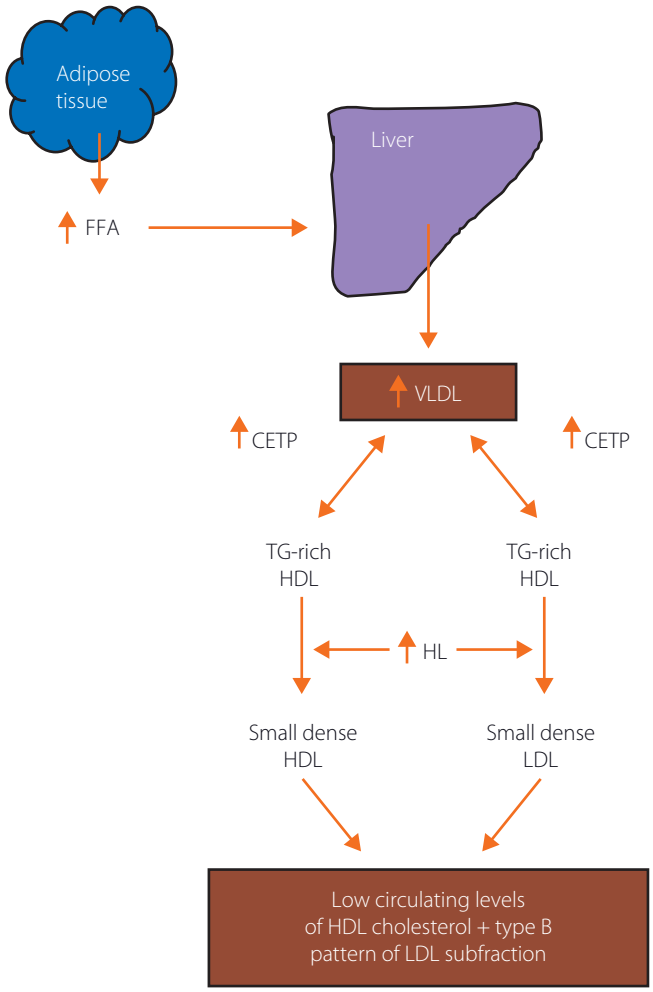

Figure 18.1 The pathogenesis of diabetic dyslipidaemia involves increased release of free fatty acids (FFAs) from expanded adipose tissue depots (obesity), which in turn fuels the hepatic synthesis of TG-rich VLDL cholesterol particles. The increase in circulating VLDL is a reflection of increased synthesis and secretion of VLDL from the liver, and decreased lipoprotein lipase-mediated clearance in peripheral tissues. Cholesterol ester transfer protein (CETP, which is increased in diabetes) transfers TG from VLDL cholesterol to HDL and LDL cholesterol in exchange for cholesterol, thus generating TG-rich HDL and LDL particles. These particles are a substrate for hepatic lipase (HL), which cleaves TG, leaving small dense HDL and LDL cholesterol.

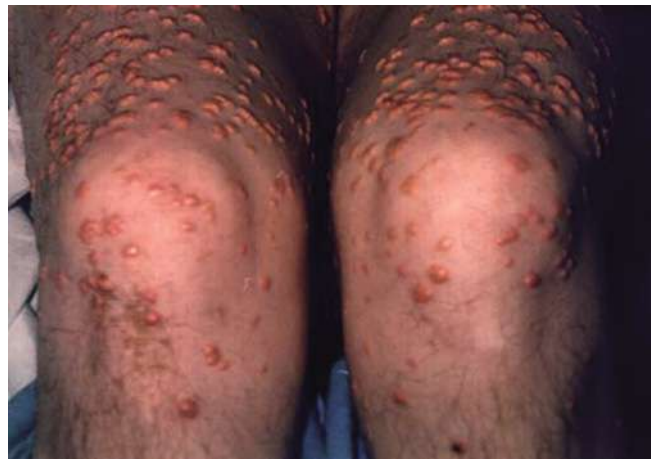

Figure 18.2 Eruptive xanthomata. This young patient with type 1 diabetes presented with ketoacidosis, severe hypertriglyceridaemia and eruptive xanthomata. Courtesy of Pictures in Lipidology, MedNet, www.mednet.gr/pim/lipid.htm.

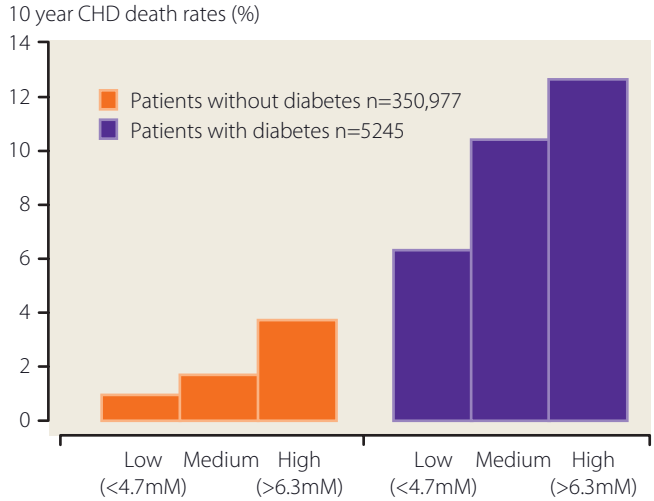

Figure 18.3 The MRFIT screening study enrolled >360,000 men in the 1960s–1970s, and showed the relationship between serum total cholesterol (classified as low, medium or high) and 10-year CHD mortality for subjects with and without diabetes. For any given level of cholesterol, CHD mortality is much higher in men with diabetes. CHD, coronary heart disease.

these abnormalities interact to substantially increase the risk of cardiovascular disease (Figure 18.1).

Type 1 diabetes

In non-obese, well-controlled type 1 diabetes, serum lipid and lipoprotein concentrations are similar to those in people without diabetes. In poorly controlled type 1 diabetes, hypertriglyceridaemia can occur because insulin deficiency causes increased lipolysis, overproduction of non-esterified fatty acids and VLDL, and decreased activity of endothelial lipoprotein lipase, which reduces clearance of triglyceride-containing VLDL and chylomicrons. Very high triglyceride levels (>20 mmol/L) can occur in patients with poorly controlled or newly presenting type 1 diabetes, often in association with ketoacidosis. Complications include eruptive xanthomas in the skin (Figure 18.2), acute pancreatitis and lipaemia retinalis (a milky appearance of the retinal vessels seen on ophthalmoscopy). The main determinants of hyperlipidaemia in type 1 diabetes are age, obesity, poor glycaemic control and nephropathy.

Cholesterol as a powerful CV risk factor

The relationship between total cholesterol levels and CHD mortality was first identified in the screening database of

male subjects for the Multiple Risk Factor Intervention Trial (MRFIT) (Figure 18.3). Over 360,000 healthy men were screened, and for both subjects with and without diabetes there was a continuous relationship between cholesterol and CHD death rates over the subsequent 10-year period. This observational epidemiology provided evidence for cholesterol as a risk factor, and suggested that, among patients with diabetes, for any given level of cholesterol the CHD mortality was 3–4-fold higher.

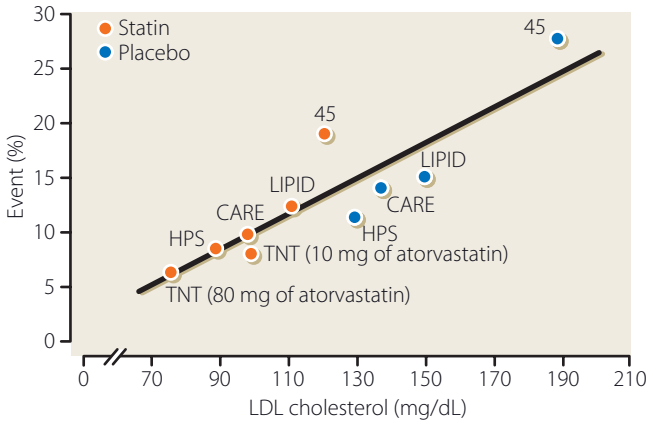

Figure 18.4 The importance of total and LDL cholesterol as a cardiovascular risk factor has been confirmed using combined data from several large statin trials. This graph illustrates the CV event rates according to achieved LDL cholesterol levels in the statin and placebo-treated groups. These trials included some patients with diabetes, and were a mix of primary and secondary prevention, but there is clearly a strong linear relationship with no apparent lower cut-off; it would seem that the lower the LDL cholesterol, the lower the risk of fatal or non-fatal CV events. Adapted from La Rosa et al. N Engl J Med 2005; 352: 1425.

Statins (HMG-CoA reductase inhibitors) are the drugs of first choice for lowering cholesterol levels and CHD risk, especially in patients with diabetes (Figure 18.4). Examples include simvastatin, rosuvastatin and atorvastatin. They work by inhibiting an early step in cholesterol synthesis, reducing hepatic cholesterol production by up to 50%, which secondarily upregulates LDL receptor synthesis and thus promotes the removal of LDL cholesterol and VLDL remnant particles from the blood. LDL-cholesterol levels fall by up to 50% and triglycerides by about 20%. Second- and third-generation statins are more effective at lowering triglyceride levels. The drugs are generally safe and well tolerated, but generalised muscle aches and pains are more common than previously thought. Myositis is a rare adverse effect, but is more common when statins are used with fibrates, nicotinic acid or cyclosporin.

Evidence-based use of statins

The initial placebo-controlled trials of statins for primary and secondary cardiovascular prevention included only a small proportion of patients with diabetes. Subsequently, the CARDS trial (atorvastatin versus placebo) was undertaken solely in patients with type 2 diabetes (Figure 18.6), and the larger Heart Protection Study (HPS) included approximately 25% of patients with diabetes. These trials have demonstrated that statins have a powerful effect on lowering cardiovascular mortality and morbidity among patients with

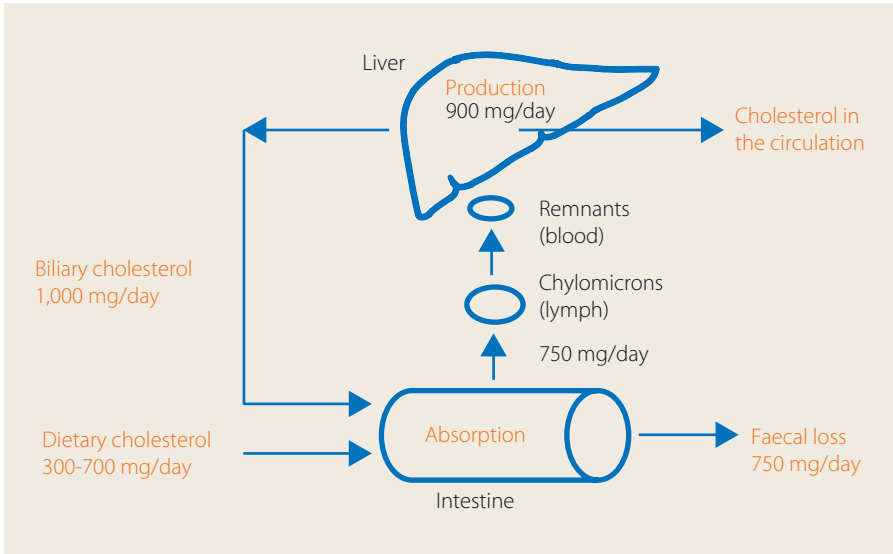

Figure 18.5 Circulating cholesterol is derived from two sources: *de novo* synthesis in the liver (statins block the rate-limiting enzyme in cholesterol synthesis, HMG-CoA reductase), and intestinal absorption of dietary cholesterol and cholesterol contained in bile. Intestinal (re)absorption of cholesterol is blocked by ezetimibe, which can be used in combination with a statin to maximise cholesterol reduction. Other cholesterol-lowering drugs include nicotinic acid, which blocks lipolysis in adipose tissue, thereby lowering free fatty acid levels and hepatic VLDL-TG synthesis.

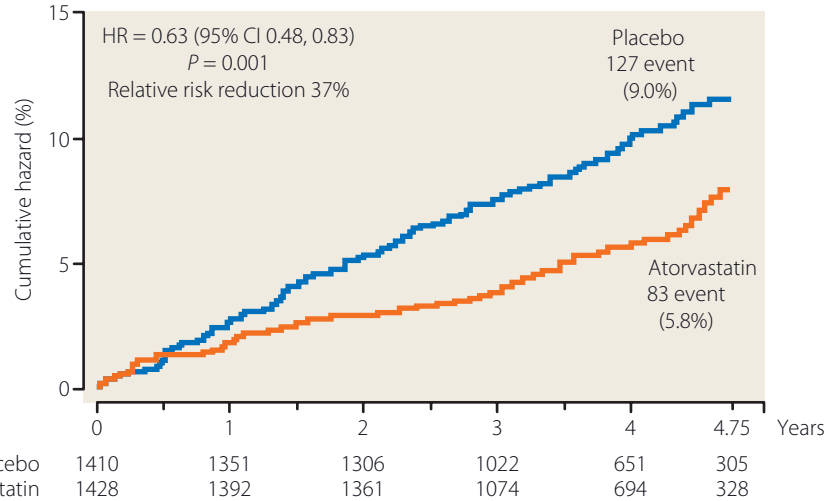

Figure 18.6 The Collaborative Atorvastatin Diabetes Study (CARDS) enrolled 2800 patients with type 2 diabetes + one other risk factor and LDL-cholesterol <4.2 mmol/L, but no prior history of a macrovascular event. The trial was stopped after 3.9 years because of the overwhelming benefit (37% relative risk reduction) of atorvastatin 10 mg versus placebo on the primary outcome of fatal and non-fatal CV events.

CASE HISTORY

A 62-year-old woman with obesity and type 2 diabetes presents for annual review. She is taking NPH insulin twice daily and metformin 1 g bid, with a past history of angina, gallstones and type 2 diabetes for 8 years. Her fasting blood tests show total cholesterol 4.8 mmol/L, HDL-cholesterol 0.65 mmol/L, LDL-cholesterol 3.5 mmol/L and triglycerides 3.8 mmol/L. HbA_{1c} 8.8%. She is already taking simvastatin 40 mg od, aspirin 75 mg, bendroflumethiazide 2.5 mg, ramipril 10 mg and atenolol 100 mg. BP 166/92 mmHg. Examination shows no signs of hypothyroidism. Renal and liver function are normal; she takes no alcohol. Her dietary compliance is eratic.

Comment: This lady has the typical pattern of dyslipidaemia associated with obesity, insulin resistance and type 2 diabetes, in particular the low HDL and high fasting triglycerides. Improving her HbA_{1c} will help improve these lipid abnormalities, and both thiazide diuretics and β-blockers can adversely affect HDL/TG levels. She has established angina, and therefore her CV risk is very high. Despite simvastatin 40 mg, her total and LDL-cholesterol levels are above target. Dietetic input would be helpful, but she is likely to require further changes to her lipid-lowering treatment: (1) add-on treatment with ezetimibe 10 mg od to block cholesterol absorption; (2) a switch to atorvastatin or rosuvastatin, which are more potent statins that also lower TG levels; or (3) it may be worth trying a higher dose of simvastatin, e.g. 80 mg od.

Box 18.2 Relative risk reduction per 1 mmol/L reduction in LDL-cholesterol

• All-cause mortality	9%
• Major fatal or non-fatal CV events	21%
• MI or coronary death	22%
• Coronary revascularisation	25%
• Stroke	21%

diabetes, even at relatively low baseline levels of cholesterol, and the relative risk reductions in major CV events are at least as high in diabetics compared with non-diabetics. Most clinical guidelines now recommend statin therapy for all patients with diabetes; target levels of lipids should be a total cholesterol <4 mmol/L and LDL-cholesterol <2 mmol/L. Given that most patients have baseline untreated levels of total cholesterol >6 mmol/L, these targets are often difficult to achieve using standard doses of first-generation statins such as simvastatin 40 mg.

A meta-analysis of cholesterol-lowering therapy in 18,686 patients with diabetes has quantified the risk reductions per 1 mmol/L reduction in LDL-cholesterol. In individual patients, statin therapy will typically reduce LDL-cholesterol by 1–2 mmol/L. There is no conclusive evidence that statin therapy prevents diabetes.

Fibric acid derivatives (e.g. fenofibrate) are useful for the treatment of hypertriglyceridaemia and mixed hyperlipidaemia, lowering serum TG and increasing HDL cholesterol. Their mechanism of action involves binding to the nuclear receptor, peroxisome proliferator activated receptor (PPAR-α), which forms a complex with another nuclear receptor, RXR and modulates several genes that control lipoprotein metabolism (e.g. increasing triglyceride breakdown). Several trials show that fibrates reduce CHD events in diabetes and they appear particularly beneficial in patients with features of the metabolic syndrome. In the ACCORD study, however,

LANDMARK CLINICAL TRIALS

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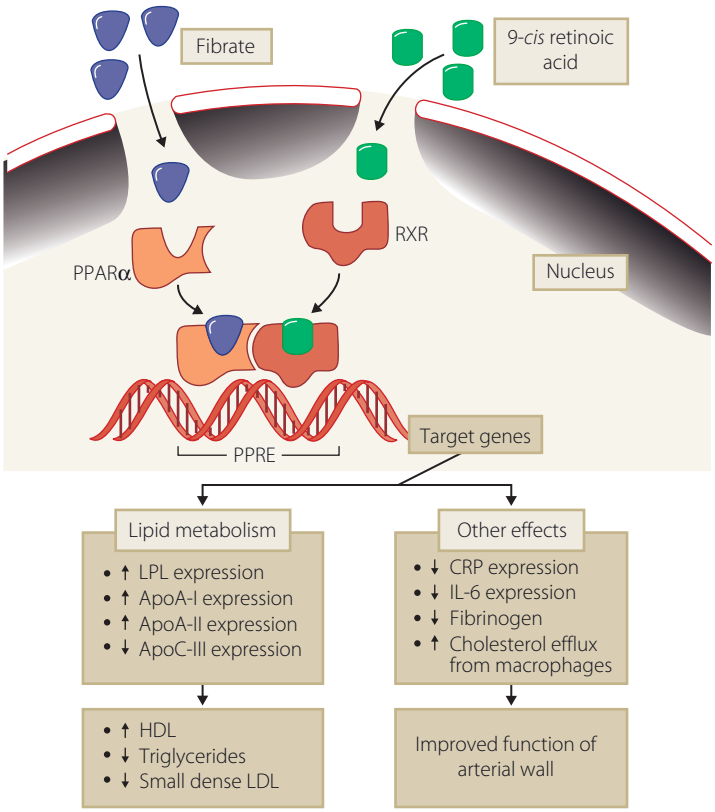

Figure 18.7 The mechanism of action of fibrates. PPRE, peroxisome proliferator response element; LPL, lipoprotein lipase; CRP, C-reactive protein; IL-6, interleukin-6; RXR, retinoid X receptor.

KEY WEBSITES

- www.diabetes.org/diabetescare
- www.bmj.com/cgi/content/full/326/7394/874
- www.gpnotebook.co.uk/simplepage.cfm?ID=x20020430093741021840
- www.dtu.ox.ac.uk/index.php?maindoc=/LDS/index.php
- SIGN Guidelines: www.SIGN.ac.uk

combination therapy of fenofibrate and simvastatin did not result in a further lowering of CV mortality in patients with type 2 diabetes compared with simvastatin alone. Only a small subgroup with high TG and low HbA_{1c} benefitted.

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Chapter
19

Hypertension in diabetes

KEY POINTS

- Hypertension is more common in people with diabetes; both conditions are components of the metabolic syndrome.
- Hypertension increases the cardiovascular risk in diabetic patients by 2–3-fold.
- Insulin resistance and oxidative stress provide two common potential causative mechanisms for hypertension and diabetes.
- The internationally accepted definition of hypertension in people with diabetes is now 140/90 mmHg and this level should be the target for all those on antihypertensive therapy.
- Diet and lifestyle interventions can have a significant impact on blood pressure and should be recommended first-line therapy for all.
- Most patients will require three or more drugs to achieve target blood pressure; agents which block the renin angiotensin system, calcium channel blockers or diuretics are first line.

Diabetes and hypertension have been termed the 'bad companions' for cardiovascular disease risk. Diabetes alone increases this risk 2–4-fold; in the presence of hypertension, the risk for coronary heart disease is further trebled and for stroke, doubled. There is also a close relationship with microvascular disease; in the UKPDS, for every 10 mmHg increase in systolic pressure, there was a 13% increase in the combined microvascular endpoint (with a 12% increase in myocardial infarction). Moreover, up to 50% of patients with type 2 diabetes are hypertensive or on antihypertensive therapy at diagnosis. In cross-sectional studies, up to 75% of adults with diabetes are hypertensive, increasing to 80% if they have microalbuminuria and over 90% if they have clinical nephropathy. For patients with type 1 diabetes, 30–43% of adults have hypertension but this is almost always in the presence of nephropathy.

Causative links

Type 2 diabetes and hypertension are constituents of the so-called metabolic syndrome which is underpinned by insulin resistance. There are several plausible reasons why this might lead to hypertension as well as glucose intolerance (Box 19.1). However, not all epidemiological studies have demonstrated a positive link between fasting plasma insulin levels and blood pressure (or cardiovascular risk); moreover, patients with insulinomas, who have high circulating plasma insulin levels, do not have high blood pressure. There are also ethnic differences in estimates of insulin resistance and blood pressure levels.

Box 19.1 Potential causative links between insulin resistance and hyperinsulinaemia and hypertension

- Sodium retention secondary to stimulated renal tubular reabsorption
- Raised intracellular sodium secondary to increased Na^+/K^+ ATPase
- Hypertrophy of vascular smooth muscle cells by direct trophic action
- Increased intracellular calcium leading to increased contractility of vascular smooth muscle cells
- Increased sympathetic nervous system stimulation
- Decreased vascular endothelial nitric oxide generation

Recently, the common role of oxidative stress for both hypertension and diabetes has been proposed (Box 19.2). Again, there are plausible mechanisms linking the two.

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Box 19.2 Potential causative links between oxidative stress and hypertension

- Quenching of nitric oxide
- Generation of vasoconstrictor lipid peroxidation products (e.g. F_2 isoprostanes)
- Depletion of tetrahydrobiopterin (BH_4), a nitric oxide synthase co-factor
- Direct endothelial cell damage leading to increased permeability
- Direct vascular smooth muscle cell damage
- Increased intraceullar calcium leading to increased contractility of vascular smooth muscle cells
- Stimulation of inflammation and growth factors

However, oxidative stress is hard to measure in humans, there are no data on the benefit or otherwise of antioxidant therapies, and the observed reduction in some measures of oxidative stress in response to antihypertensive therapy does not prove causality.

As can be seen from Box 19.2 and Figure 19.1, there is some overlap of potential mechanisms and it is possible that both insulin resistance and oxidative stress play a role, with a different predominance in individual patients.

For type 1 diabetes, hypertension is almost invariably a consequence of nephropathy and the processes that lead to it. Many of these will share potential mechanisms with insulin resistance and oxidative stress. Interestingly, the DCCT/EDIC 8-year follow-up showed a significantly lower number of patients with hypertension in the original intensively treated

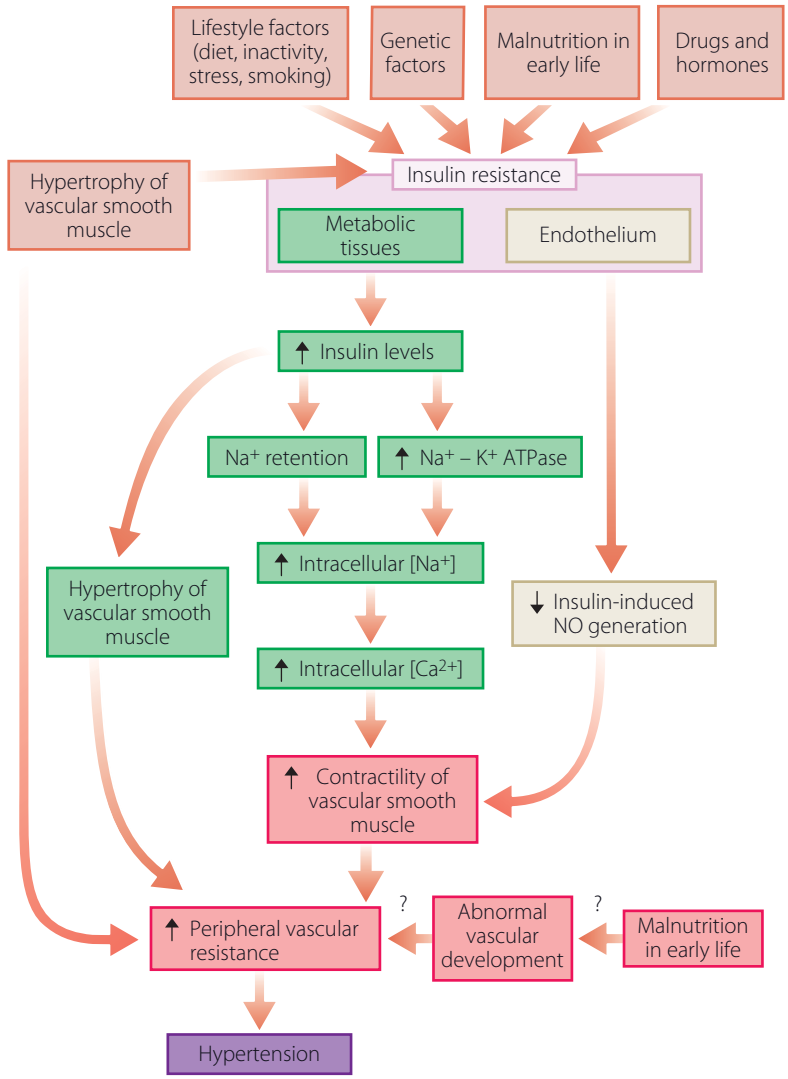

Figure 19.1 Possible mechanisms of hypertension in conditions of insulin resistance. NO, nitric oxide.

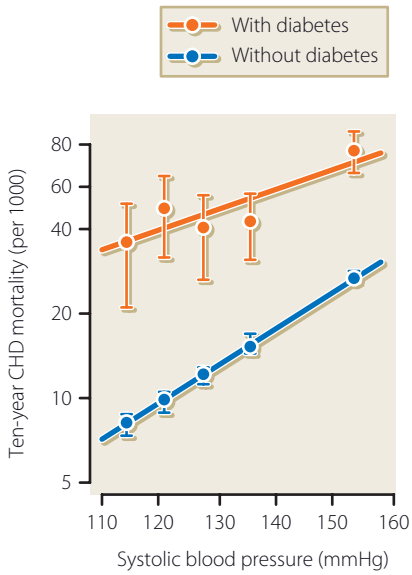

Figure 19.2 Synergistic effects of diabetes and hypertension on deaths from coronary heart disease (CHD). Data from 342,815 subjects without diabetes and 5163 subjects with diabetes aged 35–57 years, free from myocardial infarction at entry. From Pickup & Williams. *Textbook of Diabetes*, 2nd edition. Blackwell Publishing Ltd, 1997.

arm (29.9% versus 40.3%), almost certainly as a consequence of fewer cases of nephropathy in this cohort.

Definition of hypertension

With the increasing numbers of antihypertensive agents and large trials, the close relationship between level of blood pressure and cardiovascular disease risk has resulted in the definition being revised downwards, from 160/95 mmHg in the 1980s to 140/90 mmHg today.

For every 20/10 mmHg increase in blood pressure above 115/75, the risk for cardiovascular disease in the population doubles. For people with type 2 diabetes, there is an 18% increase in risk of myocardial infarction, and 29% for stroke for every 10 mmHg increase in blood pressure. However, intervention trials only show benefit for reduction of systolic and diastolic pressure to a level of about 130/80 mmHg (Figure 19.2).

Diagnosis of hypertension

Patients should have blood pressure measured in a standardised way with readings above 140/90 mmHg on at least two occasions before they are diagnosed with hypertension (Box 19.3). Ambulatory blood pressure or home assessment can be used in cases of doubt but diagnostic readings in these circumstances are 10/5 mmHg lower (120/75 mmHg). Initial management should include a thorough basic examination and investigations (Box 19.4).

Box 19.3 Recommended practice for measuring blood pressure

- Use a calibrated and validated instrument
- Measure after 5 minutes in a seated position, feet on floor
- Arm should be free of tight clothing and at heart level
- Cuff bladder should cover >80% of arm circumference
- Two measurements should be taken
- Check both arms (always use the arm with higher reading)
- Check standing blood pressure to detect autonomic neuropathy and/or drug-induced postural hypotension

Box 19.4 Assessment and investigation of the patient with hypertension

- Measurement of height and weight (for BMI) or waist circumference
- Examination of the:
  - heart for evidence of left ventricular hypertrophy
  - lungs for heart failure
  - abdomen for pulsatile masses, renal enlargement or bruits
- Auscultation for carotid and femoral arterial bruits
- Examination of peripheral pulses (to exclude co-arctation or peripheral vascular disease)
- Investigations to include ECG, urinalysis (including for microalbuminuria), serum electrolytes, urea and creatinine (and calculation of eGFR), fasting blood lipid profile, chest X-ray or echocardiogram to confirm left ventricular hypertrophy

Management

Lifestyle changes can be remarkably effective. Table 19.1 lists those known to have an impact on blood pressure but most of these data have been gleaned from populations without diabetes or from mixed populations with and without type 1 and type 2 diabetes .

Some drugs and behaviours are known to increase blood pressure (Box 19.5).

Hypertension is a feature of endocrinopathies that also cause glucose tolerance such as Cushing's syndrome, acromegaly and phaeochromocytoma. These rare conditions should be considered and excluded (see Chapter 8).

Drug treatment

Lifestyle changes should be tried for at least 3 months before commencing medication. However, if blood pressure is >20/10 mmHg above target, drug treatment should be started immediately, and will usually require two agents initially.

Table 19.1 Lifestyle changes and the magnitude of reported reduction in blood pressure

Modification	Systolic/diastolic blood pressure effect (mmHg)
Weight loss	2.0/1.0 per kg
Dietary Approaches to Stop Hypertension (DASH) diet	8.0/6.0
Potassium intake >3.5 g/d	1.8./1.1
Sodium intake <2.4 g (6 g sodium chloride)/day and normal diet	5.0/2.7
Alcohol ≤30 mL ethanol (3 units)/day men ≤15 mL ethanol (1.5 units)/day women	3.3/2.0
Exercise 30–60 minutes moderate × 4–7/ week	4.0/2.0
Dietary fibre supplement(11.5 g/day)	1.1/1.3
Multiple modifications (DASH diet, weight loss, low sodium intake, physical activity) – 9 week trial	12.1/6.6

Box 19.5 Drugs and behaviours that increase blood pressure

Drugs
- Corticosteroids
- Cyclo-oxygenase (COX-2) inhibitors
- Non-steroidal anti-inflammatory drugs
- Erythropoietin
- Oral contraceptive pill
- Serotonin reuptake inhibitors
- Monoamine oxidase inhibitors

Behaviours
- Alcohol excess
- Tobacco (smoking/ snuff)
- Liquorice

Drugs which block the RAS

The RAS has been closely linked to the development of micro- (particularly nephropathy) and macrovascular complications. Activation both locally at the tissue level and systemically has been described in people with diabetes. Angiotensin II (AII) is a potent vasoconstrictor and has profibrogenic properties in both the kidney and myocardium. Aldosterone causes salt and water retention and is also profibrogenic. Moreover, several of the breakdown products of angiotensin I (AI) and II have vasoactive properties and our understanding of the RAS shows it to be much more complicated than originally realised. The rate-limiting step for AII production from the RAS is renin activation. Although renin is an enzyme, together with its precursor prorenin it now appears to have its own receptor (Figure 19.3).

Angiotensin-converting enzyme (ACE) is responsible for most AII production from AI, but other enzymes such as chymases may also operate and be upregulated in the presence of ACEI drugs. ACE2 is a newly described enzyme not inhibited by ACEI and responsible for production of angiotensin 1–7.

By blocking AII action at the type 1 receptor, angiotensin receptor blocking agents (ARB) may upregulate the type 2 receptor but also increase angiotensin 1–7 production via ACE2.

Finally, both spironolactone and eplerenone block aldosterone action by direct antagonism at its receptor.

With the development of a direct renin inhibitor (aliskiren), blockade of the RAS is possible at almost all levels. Theoretically, the choice of agent should be determined by where in the RAS it is active and the likely consequences of blockade in terms of physiological outcome. In practice, however, because the agents were developed historically, there is much more information about ACEI and ARB.

ACEI

In experimental animals, ACEI reduce glomerular intracapillary pressure and subsequent glomerulosclerosis. In humans, they reduce microalbuminuria over and above their blood pressure lowering effect. In type 1 diabetes, a meta-analysis of 12 trials in 698 normo- or mildly hypertensive patients showed that ACEI treatment gave an odds ratio of 0.38 (95% CI 0.25–0.57) for progression to clinical nephropathy, and 3.07 (2.15–4.44) for regression to normoalbuminuria. At 2 years, albuminuria was 50.5% (29.2–65.5%) lower in treated patients versus placebo. In type 1 patients with clinical nephropathy, captopril use for 4 years was associated with a 50% reduction in the numbers doubling serum creatinine or who reached a combined endpoint of death, dialysis or kidney transplantation (Figure 19.4). There are few other studies of antihypertensive therapy using cardiovascular endpoints in type 1 diabetes.

For patients with type 2 diabetes at high risk of vascular disease, ramipril use for 4.5 years in the MICRO-HOPE Study reduced overall albumin:creatinine ratio and the numbers developing microalbuminuria and clinical nephropathy (incidence reduced by 13% and 14% respectively). There was also a 25% (95% CI 12–36%) relative risk reduction in fatal and non-fatal MI and stroke. More recently, the ADVANCE study of a perindopril and indapamide combination showed a 21% and 18% risk reduction in new microalbuminuria and worsening nephropathy respectively in 11,140 type 2 patients at high vascular risk. However, the observed risk reduction for fatal and non-fatal MI and stroke was not statistically significant at 8% (95% CI –4 to 19%). Most of the patients in these studies were hypertensive. Why the results differ is not clear but may relate to the fact that many control patients in ADVANCE were taking open label perindopril.

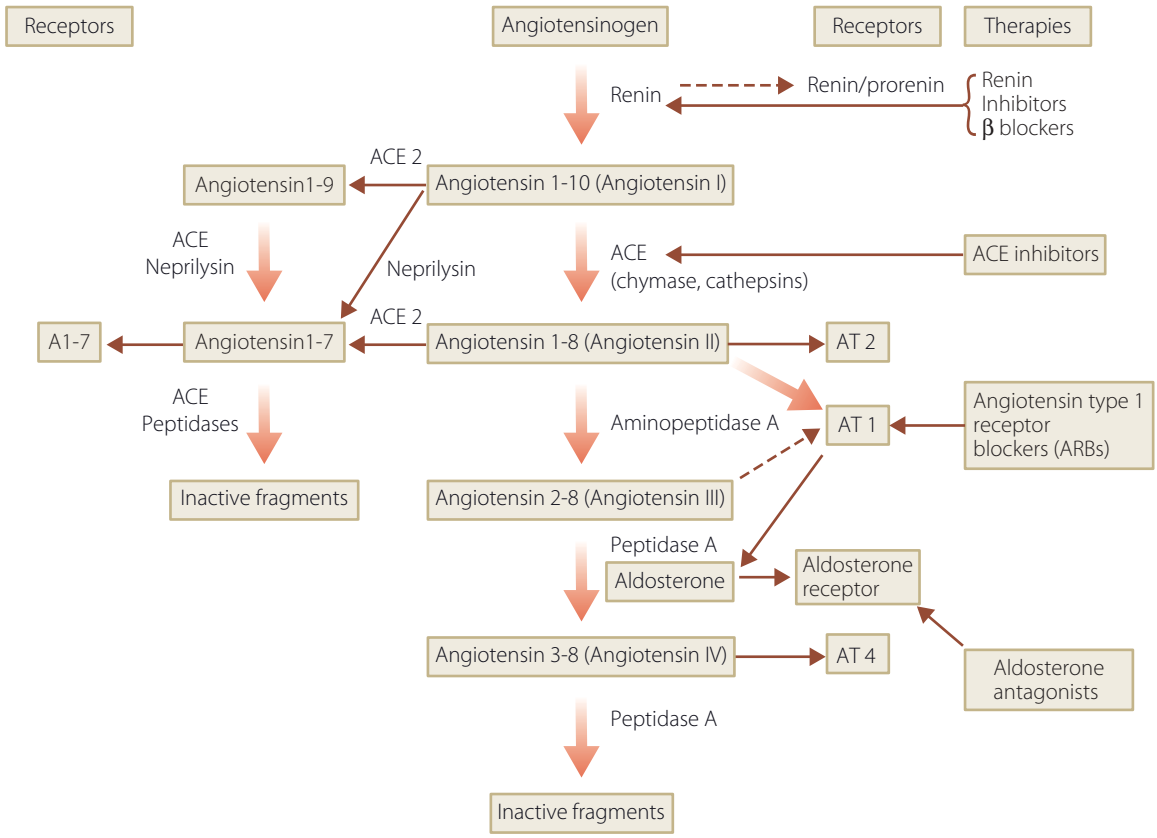

Figure 19.3 Schematic diagram of the renin-angiotensin system. Dotted lines refer to possible or minor actions. Angiotensin 1–7 acts via a separate receptor system and antagonises AT1 actions. AT1 activation results in vasoconstriction, aldosterone release, cell growth, matrix accumulation, inflammation and sympathetic nervous system activation. AT2 activation antagonises some AT1 actions, promotes apoptosis, and possibly promotes inflammation. AT4 activation results in vasodilatation, decreased renal tubular sodium transport, and possibly inflammation. Renin/prorenin receptor activation promotes fibrosis and AII production (not yet confirmed in humans). ACE, angiotensin converting enzyme; AT, angiotensin II type receptor.

ARB

Short-term studies in type 1 diabetes suggest equal potency for albuminuria reduction with similar blood pressure lowering for ARB and ACEI. ARB have been most extensively used in type 2 diabetes where a similar reduction in microalbuminuric patients developing clinical nephropathy on the ARB irbesartan to the meta-analysis of ACEI in type 1 diabetes was seen (HR 0.32; 95% CI 0.15–0.65).

For clinical nephropathy, two large trials showed a significant reduction of 16–20% in the numbers reaching a combined endpoint of doubling of serum creatinine, end-stage renal disease or death. However, neither of these studies of ARB has shown a significant impact on cardiovascular mortality or morbidity alone.

Renin inhibitors

Aliskiren is the only agent currently in this class and has been shown to reduce both blood pressure and albuminuria when used in combination with an ARB. No data are available on renal or cardiovascular endpoints.

Aldosterone antagonists

Spironolactone and eplerenone have been shown to benefit patients with heart failure and who are already on an RAS-blocking agent. In diabetes, they further reduce albuminuria when added to either an ACEI or ARB, although with a risk of hyperkalaemia. There are no hard endpoint data on their use in diabetic patients.

Side effects

All RAS-blocking agents can cause hyperkalaemia and regular serum potassium monitoring is required when initiating or adjusting therapy. An acute reduction in GFR can occur as part of the lowering of glomerular pressure.

An increase in serum creatinine of up to 35% of baseline is acceptable but above this either a reduction in concomitant diuretic dose or investigation for possible renal artery stenosis should be considered. Although many type 2 patients at postmortem have evidence of renal artery atheroma and stenosis, this is functional in only a minority of individuals. If there is a suspicion of stenosis from a rapid deterioration

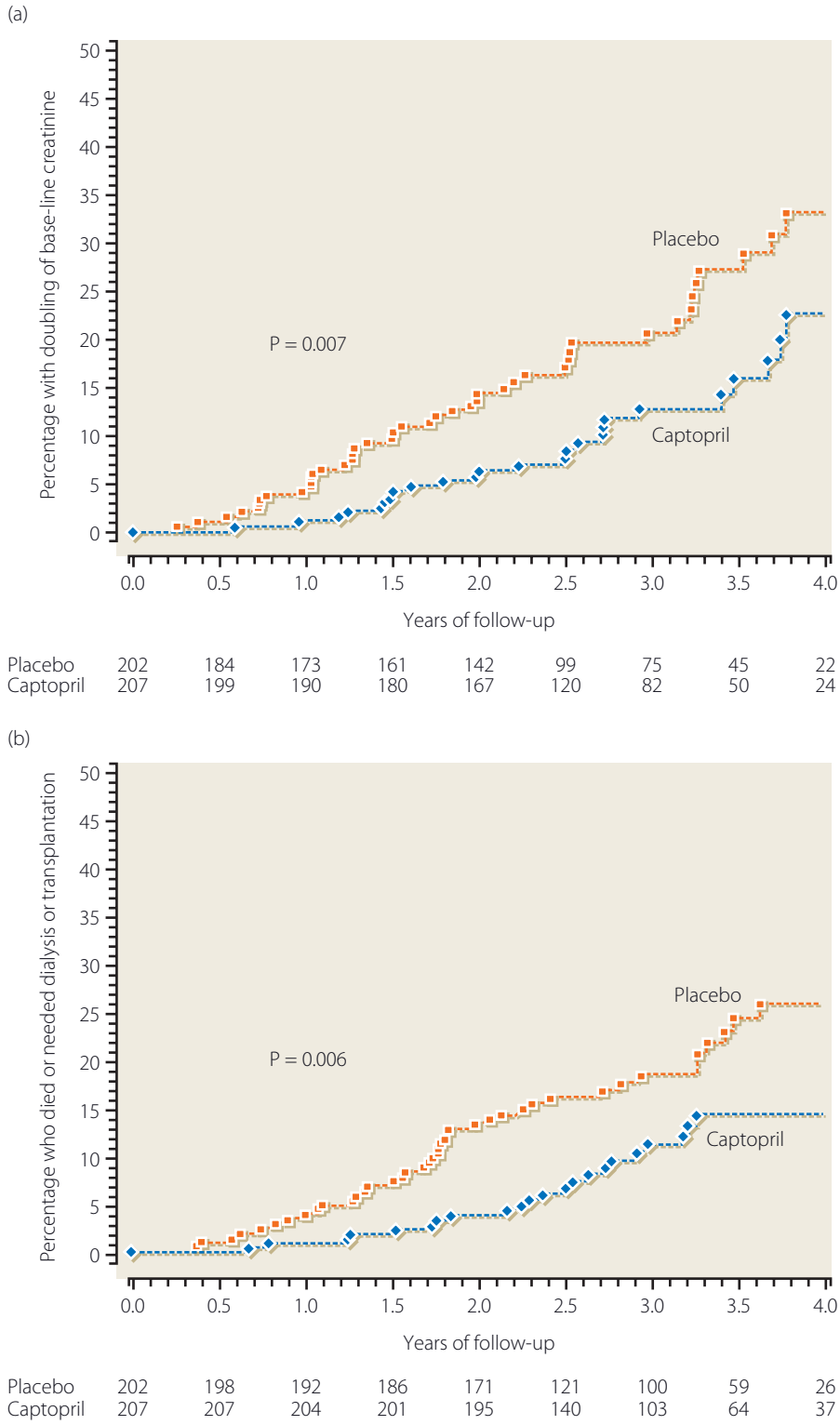

Figure 19.4 Cumulative incidence of percentage of patients doubling serum creatinine from baseline (*upper panel*) and percentage dying, needing dialysis or a kidney transplant (*lower panel*) in 405 patients with type 1 diabetes and clinical nephropathy and well-controlled hypertension treated with captopril or placebo. From Lewis et al. N Engl J Med 1993; 329: 1456–1462.

in renal function after RAS blockade, renal arterial Doppler ultrasound or renal angiography should be undertaken. Trials have shown no real benefit of angioplasty or stenting on rate of decline of GFR. Some patients may experience hypotension with the first dose of an RAS-blocking drug. Because of this the first dose should be given at night.

Combination/dual blockade

Because of the potential of a theoretical lack of complete RAS blockade using either an ACEI or an ARB alone, studies using both drugs together have been undertaken in diabetic patients with nephropathy. Most of these are of short duration and whilst they have shown an increased benefit in terms of lowering blood pressure and albuminuria, there was a significant incidence of hyperkalaemia. The recently published ONTARGET study of long-term dual blockade (telmisartan plus ramipril) versus either agent alone in over 25,000 patients, nearly 7000 of whom had type 2 diabetes, found worse renal outcomes, so at present combination therapy cannot be recommended routinely.

Hyporeninaemic hypoaldosteronism (also known as type IV renal tubular acidosis) is more common in people with diabetes with developing nephropathy and is probably a result of tubulointerstitial disease. It often only becomes apparent when patients are challenged with RAS-blocking agents and they become markedly hyperkalaemic.

Calcium channel blockers

There are two groups: dihydropyridine and non-dihydropyridine; both are vasodilators and useful in systolic hypertension (Table 19.3). However, they can increase albuminuria in nephropathy and are less effective than ARB in preserving renal function in patients with type 2 diabetes and clinical nephropathy.

The non-dihydropyridines also slow heart rate and for this reason they should not be used with β-blockers. They

Table 19.2 RAS-blocking agents

Class	Indications	Contraindications	Precautions/side effects
ACEI	Nephropathy (type 1 diabetes) Heart failure Younger patients <55 years Post myocardial infarction	Renal artery stenosis Hyporeninaemic hypoaldosteronism Aortic stenosis Pregnancy (or risk of)	First dose hypotension Acute deterioration in renal function Hyperkalaemia Angio-oedema (especially Afro-Caribbean) Cough (10–15%)
ARB	Nephropathy (type 2 diabetes) Intolerance of ACEI (cough, angio-oedema) Heart failure	Renal artery stenosis Hyporeninaemic hypoaldosteronism Aortic stenosis Pregnancy (or risk of)	Acute deterioration in renal function Hyperkalaemia
Renin inhibitors	Not established	Renal artery stenosis Hyporeninaemic hypoaldosteronism Aortic stenosis Pregnancy (or risk of)	GI side effects Hyperkalaemia
Aldosterone antagonists	Resistant hypertension Heart failure	Renal impairment (relative)	Hyperkalaemia GI side effects Gynaecomastia (spironolactone)

Table 19.3 Calcium channel-blocking agents

Class	Indications	Contraindications	Precautions/side effects
Dihydropyridines	Systolic hypertension Afro-Caribbean	Heart failure Aortic stenosis	Peripheral oedema Flushing
Non-dihydropyridines	Angina	Heart block β-Blocker use	Constipation Bradycardia Postural hypotension

can worsen heart failure. Verapamil has been shown to be less effective in reducing albuminuria than the ACEI trandolapril.

Diuretics

These also fall into two main groups: thiazides and loop diuretics (Table 19.4). Thiazides are very effective first-line agents in uncomplicated essential hypertension, as shown in the ALLHAT trial. However, they do have side effects, including glucose intolerance, and have been linked to the development of hyperosmolar hyperglycaemic state (HHS; see Chapter 12). In patients with an eGFR <60 mL/min/1.73 m^2 they are rarely effective in producing a diuresis and more potent loop diuretics are required. Diuretics act in synergy with RAS-blocking agents.

β-Blockers

These drugs reduce cardiac output, slow heart rate and reduce renin release in the kidney (Table 19.5). They are of proven benefit in angina, post-MI and in heart failure. Non-cardioselective β-blockers can worsen bronchospasm and are contraindicated in people with asthma. They can also blunt some symptoms of hypoglycaemia and exacerbate symptomatic peripheral vascular disease. For these reasons only cardioselective β-blockers should be used in diabetes. β-Blockers are associated with the development of glucose intolerance and type 2 diabetes and are no longer first-line therapy in the latest British Hypertension Society Guidelines.

LANDMARK CLINICAL TRIAL

UK Prospective Diabetes Study Group. Tight blood pressure control and risk of macrovascular and microvascular complications in type 2 diabetes: UKPDS 38. BMJ 1998; 317: 703–713.

The UKPDS has been referred to many times in this handbook, but this report was the first to demonstrate not only the link between hypertension and micro- and macrovascular complications, but also that blood pressure lowering *per se* could benefit both types of tissue damage, notably retinopathy.

One thousand one hundred and forty eight patients who were hypertensive (>160/94 mmHg) or on antihypertensive therapy at time of diagnosis of type 2 diabetes were randomised to less tight (n = 390, target <180/105 mmHg) or tight (n = 758, <150/85 mmHg) blood pressure management. In the event, achieved mean BP was 154/87 and 144/82 mmHg for the less tight and tight cohorts respectively.There was a 21% (95% CI 41, –7%; p NS) relative risk reduction (RRR) in MI and 44% (65,11%; p = 0.013) for stroke; for the combined microvascular endpoint (renal failure, death from renal disease, vitreous haemorrhage or retinal photocoagulation) the reduction was 37% (56,11%; p = 0.0092). For microalbuminuria and clinical nephropathy, after 6 years the RRR was 29% and 39% respectively.

Subsequent analysis and papers revealed a 13% increase in the microvascular endpoint, 12% for MI, and 19% for stroke for every 10 mmHg increase in systolic BP. Recently, the 10-year post original study follow-up showed that this benefit of tight control did not persist once the less tight cohort were managed to the same BP target (i.e. no 'memory' effect, unlike for glycaemia).

It is hard to overemphasise the impact the UKPDS has had on the management of type 2 diabetes.

Table 19.4 Diuretics

Class	Indications	Contraindications	Precautions/side effects
Thiazides	Heart failure Addition to RAS blockers Elderly	Gout	Hypokalaemia/hyponatraemia Hyperuricaemia Postural hypotension Erectile dysfunction
Loop diuretics	Heart failure eGFR <60 Addition to RAS blockers	Hypovalaemia Gout	Constipation Bradycardia Hypokalaemia/hyponatraemia Postural hypotension Hyperuricaemia

Table 19.5 β-Blockers

Class	Indications	Contraindications	Precautions/side effects
Cardioselective	Post MI Heart failure Angina	Heart block Asthma (relative) Severe peripheral vascular disease Less effective in elderly Hypoglyaemic unawareness (relative)	Bronchospasm Cold hands/feet Altered hypoglycaemic symptoms (rare) Fatigue

CASE HISTORY

A 59-year-old man with type 2 diabetes of 9 years' duration was referred to our clinic because of difficult-to-control hypertension. He was overweight (BMI 31 kg/m^2) and despite being prescribed ramipril 10 mg, bendroflumethiazide 5 mg and amlodipine 5 mg, his blood pressure was 164/102 mmHg. His glycaemic control was also outside target, his HbA_{1c} was 8.4% on gliclazide 80 mg bd. His ECG suggested left ventricular hypertrophy confirmed on chest X-ray. Fundoscopy showed some AV nipping and a few microaneurysms. Examination was otherwise normal apart from his obesity. Investigations showed normal biochemistry, eGFR was 84 mL/min/1.73 m^2, albumin:creatinine ratio was 9 mg/mmol.

A careful history revealed that he had developed a persistent cough since starting ramipril; he had read the patient information which warned him of this side effect and had discontinued the tablets. He had some prostatic symptoms and consequently only took his diuretic intermittently. Because he was a shift worker he ate mainly convenience foods and his estimated sodium intake was around 8 g/d (20 g sodium chloride). He had never had a formal dietary review or diabetes education.

He was highly motivated because he did not want to go onto insulin and his mother had recently suffered a disabling stroke.

His BP was confirmed at 164/102 mmHg which is well over the threshold (20/10 mmHg above target) for immediately commencing medication. He was started on an ARB and his amlodipine was changed to an α-blocker (he was found to have benign prostatic hypertrophy). His diuretic was maintained and he was ultimately switched to an ARB/diuretic combination when doses were stabilized. Formal dietary review led to a significant reduction in his sodium intake and he was able to lose 4 kg in weight over 6 months. His BP came down to 140/86 mmHg.

Comment: There are several points here. Many people with type 2 diabetes are on multiple therapies and find it hard to comply, hence our use of a combination tablet. Many patients do not take their medication as prescribed, often because of side effects. A really careful drug history is essential in these situations. Cough is much less common (but still occurs) on ARB and this patient required a RAS-blocking agent because of his microalbuminuria. Although α-blockers are not recommended as monotherapy, they are effective for minor prostatic symptoms and enabled this man to continue his diuretics. This is important because they have a synergy with RAS blockers, but neither is effective if dietary sodium intake is high. It is possible to use potassium chloride instead (Lo-salt), but careful monitoring of serum potassium would be required because of the propensity for retention on RAS blockers. Education and awareness of the role of sodium in hypertension and its treatment are crucial. This man was well motivated and the information, support and follow-up he received helped him to significantly reduce his cardiovascular risk (30% for MI, 45% for stroke).

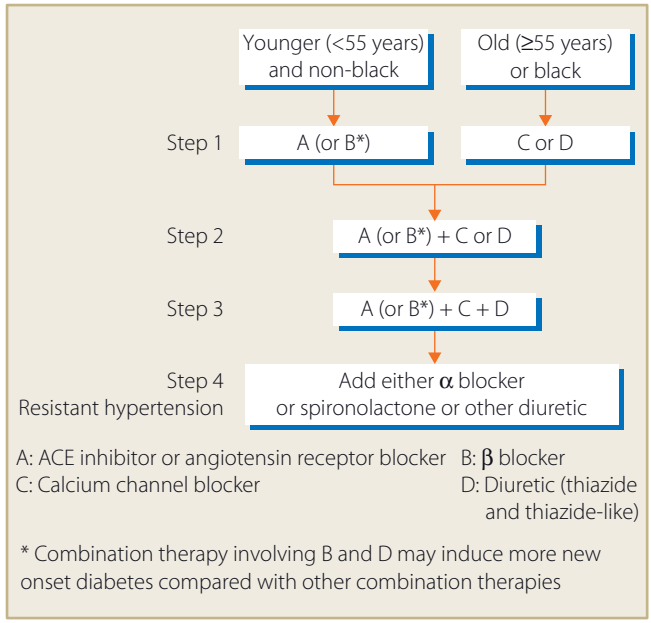

Figure 19.5 Suggested strategy for hypertension management from the British Hypertension Society. (NB: international guidelines still consider β-blockers as a possible first-line choice.)

Other agents

α-Blocking drugs were associated with more heart failure in the ALLHAT study and should not be used as monotherapy. They may be helpful in men with prostatic symptoms by improving urine flow.

Centrally acting drugs are limited to patients who cannot tolerate first-line agents. However, they have problems with drowsiness, postural hypotension and depression. Methyldopa is completely safe in pregnancy and is useful as an alternative to contraindicated agents such as RAS blockers.

KEY WEBSITES

- British National Formulary: www.bnf.org-section2cardiovasculardisease
- National Diabetes Audit: www.ic.nhs.uk/webfiles/Services/NCASP/audits%20and%20reports/ 7121_National%20Diabetes%20Audit_final.pdf
- ALLHAT trial: www.nhlbi.nih.gov/health/ALLHAT/articles.htm
- National Collaborating Centre for Chronic Conditions and NICE Guidance: www.nice.org-clinicalguidance34
- British Hypertension Society Guidelines: www.bhsoc.org/Hypertension_management_Guidelines.stm
- World Health Organization/International Society for Hypertension Guidelines: www.who.int/ cardiovascular_diseases/guidelines/hypertension/en/
- Joint National Committee on Prevention, Detection, Evaluation and Treatment of High Blood Pressure (JNC 7): www.nhlbi.nih.gov/guidelines/hypertension/
- SIGN Guidelines: www.SIGN.ac.uk

Combination therapy

The UKPDS showed that most patients require three or more agents to achieve what would be regarded now as the modest target of 144/82 mmHg. Current data from the Diabetes Audit in the UK show that approximately 30% of people with diabetes had a recorded blood pressure ≤135/≤75 mmHg in 2007–8 which is similar to data from the USA (28–36% of treated people with type 2 diabetes had a blood pressure <130/80). Even in clinical trials the current target for diabetes is challenging; <30% of the 5137 diabetic patients in the ASCOT-BPLA trial achieved a blood pressure <130/80 mmHg.

Current British Hypertension Society recommendations are for either an RAS or calcium channel-blocking agent or thiazide as first line, with the addition of another class if target is not reached (Figure 19.5). Other guidelines still include β-blockers as first line. Most suggest titration of dose of each class to the maximum effective tolerated level before adding another agent, although this does run the risk of more side effects. In order to reduce the numbers of tablets, combination medications have been developed (such as RAS blockers and diuretics, β-blockers and diuretics) in an attempt to improve compliance.

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Chapter

20 Macrovascular disease in diabetes

KEY POINTS

- Macrovascular disease (stroke, peripheral arterial disease and coronary disease) is 3–5-fold more common in patients with diabetes; atheroma tends to be more diffuse and distal, and to readily undergo plaque rupture.
- Multiple risk factor modification is essential to reduce the risk of macrovascular complications. Lowering HbA_{1c} is important but may not be as powerful as BP and lipid lowering.
- The biochemical mechanisms by which high glucose damages vascular tissues include protein kinase C activation, AGE formation and oxidative stress.
- The benefits of tight glycaemic control on macrovascular outcomes may take 10–20 years, as illustrated by the UKPDS, but this 'legacy effect' means that tight glycaemic control is especially important in the early years after diagnosis.
- Small differences in BP translate into big differences in CV outcome, therefore optimal BP targets are lower in patients with diabetes.
- There is uncertainty about the use of low-dose aspirin for primary prevention in patients with type 2 diabetes; the benefits are unclear and the risks are not insignificant (randomised trials are in progress).

Atherosclerosis

For any given age, level of cholesterol or BP, the risk of atherosclerotic cardiovascular disease (CVD) is 3–5-fold higher among patients with diabetes compared with subjects without diabetes. Macrovascular complications include fatal and non-fatal coronary heart disease (CHD) events, stroke and peripheral arterial disease (PAD). CVD accounts for most (>75%) of the premature mortality and shortened life expectancy among patients with diabetes. It affects both genders equally, and in particular the protective effect of premenopausal status is lost in women with diabetes. Within the diabetic population, hypertension and especially proteinuria (nephropathy) have a multiplying effect on CVD risk and there is a strong inverse relationship between urinary albumin excretion rate and survival (Figures 20.1 and 20.2). Some ethnic groups are particularly susceptible to CVD complicating diabetes (e.g. South Asians in the UK and blacks in the USA), while others are relatively protected (e.g. Native Americans, such as the Pima Indians, and Hispanic whites in the USA).

Histologically, atherosclerotic disease in patients with diabetes is similar to that in people without diabetes, but plaques tend to be more diffuse in nature and involve more distal, smaller arteries, which often makes revascularisation (angioplasty/stenting or bypass) less feasible. In patients with diabetes, atherosclerotic disease occurs at a younger age and progresses more rapidly, and plaque rupture leading to superimposed thrombus and major vessel occlusion is more common (Figure 20.3). Outcomes from acute myocardial infarction (AMI) and stroke are all consistently worse in patients with diabetes compared with people without diabetes, e.g. rates of coronary reperfusion and reocclusion, left ventricular function and sudden death. There is also an inflammatory component to atherosclerotic disease progression and plaque rupture, and several studies have shown a relationship between the risk of CVD events and circulating inflammatory biomarkers such as high-sensitivity C-reactive protein (hsCRP).

Peripheral arterial disease in patients with diabetes typically involves multiple vessels with diffuse, distal narrowing, and there is a 40-fold increased risk of lower limb amputation. The smaller arteries and arterioles are damaged further by microvascular disease affecting the vasa vasorum (the tiny nutrient vessels which supply oxygen to the arterial wall itself), which makes the medial layer of arteries prone to calcification, known as 'Mönckeberg's medial sclerosis', which is often seen in the digital arteries of patients with diabetes and nephropathy and/or neuropathy (Figure 20.4).

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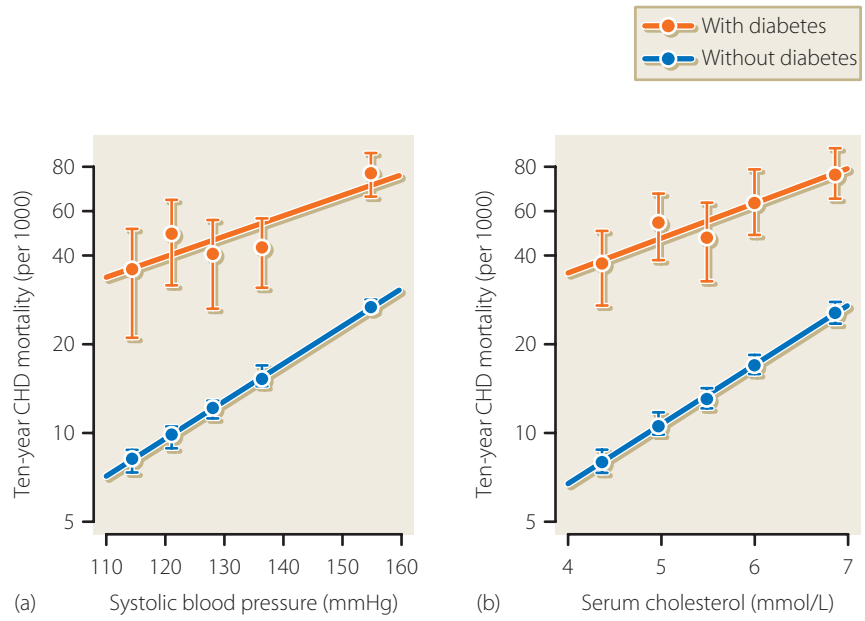

Figure 20.1 Relationships between systolic BP (a) and serum cholesterol (b) and CHD mortality for subjects with and without diabetes in the Multiple Risk Factor Intervention Trial (MRFIT) screening programme. For any given level of BP or lipids, the risk of death from CHD is 3–5-fold higher among patients with diabetes. This excess risk is evident from the time of diagnosis of diabetes. Data from Stammler et al. Diabetes Care 1993; 16: 434–44.

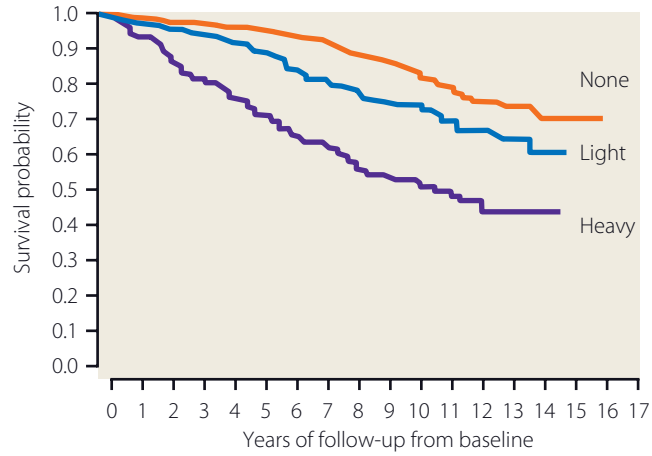

Figure 20.2 Among patients with diabetes, those who develop nephropathy and micro- or macroproteinuria have an even higher risk of fatal or non-fatal CVD events. From the WHO Multinational Study of Vascular Disease in diabetes, urinary albumin excretion rate is a powerful prognostic indicator of CVD risk. Leakage of protein at the glomerulus probably reflects widespread endothelial barrier dysfunction and atherosclerotic disease activity.

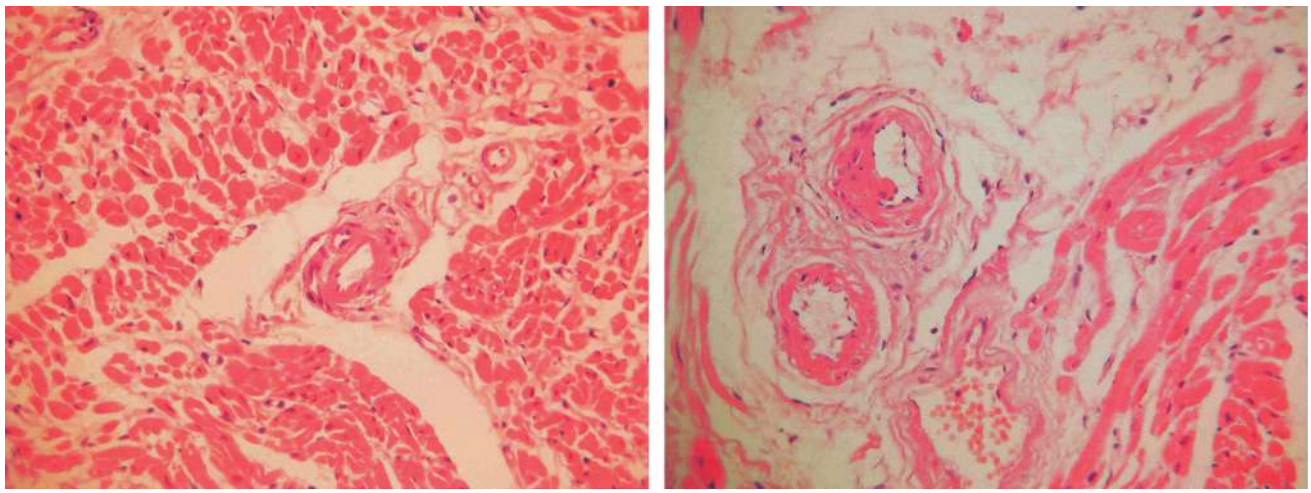

Figure 20.3 Arteriolar changes in diabetes in the myocardium of a woman who died from macrovascular disease associated with diabetic nephropathy. Basement membrane thickening, vascular smooth muscle hypertrophy and intravascular thrombus reflect widespread atherosclerosis accelerated by diabetes, hypertension and proteinuria.

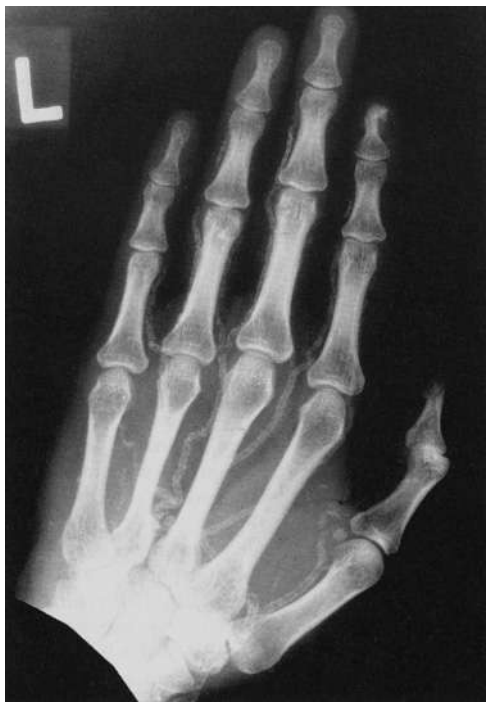

Figure 20.4 Medial calcification of the digital arteries in a patient with diabetes and widespread arterial disease and nephropathy.

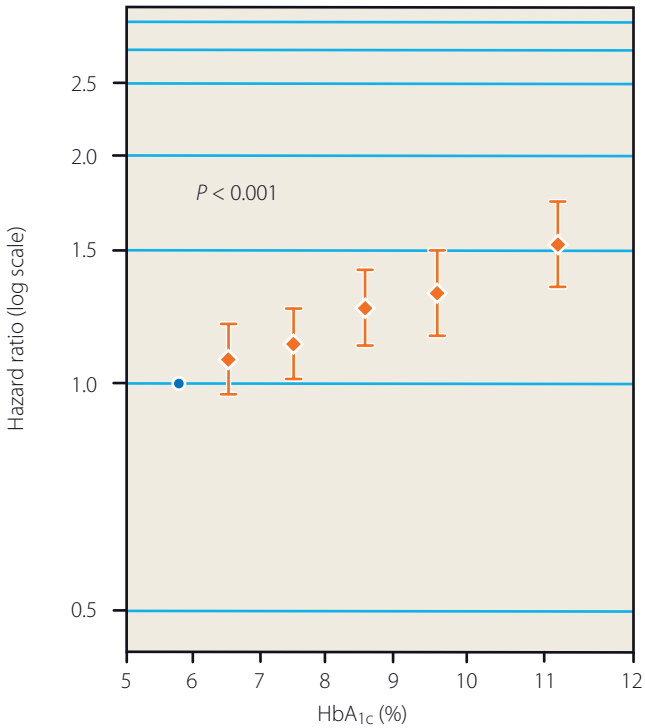

Figure 20.5 New Zealand cohort study showing the relationship between CVD mortality and HbA_{1c} among 48,000 patients with type 2 diabetes. Adapted from Elley et al. Diabetic Med 2008; 25: 1295–1301.

CASE HISTORY

A 57-year-old man with obesity and long-standing type 2 diabetes (15+ years) presents with macrovascular complications. He is known to have hypertension, diabetic nephropathy and dyslipidaemia, but on his annual review he presents with symptoms of intermittent claudication and cold feet. Clinical examination shows loss of pedal pulses and some early ischaemic ulceration at the tips of his toes on the left foot. Measurement of ABPI is 0.56 in the left leg and 0.65 in the right leg, but duplex scanning shows diffuse distal disease and arterial calcification in both legs, especially the left, with evidence of critical ischaemia. In addition, there is a proximal 75% stenosis of the left superficial femoral artery that is amenable to percutaneous intervention and stenting. Two days following this procedure, perfusion to the left foot is improved but he develops atypical chest pain and ECG shows a non-ST elevation myocardial infarction (serum troponin-I 0.18). He is treated in hospital with aspirin, clopidogrel and enoxaparin (7 days).

Comment: This man has features of the metabolic syndrome, and proteinuria as well as hypertension increase his macrovascular risk. ABPI can be unreliable in patients with diabetes. Although his ABPI measurements confirm PAD, 0.56 and 0.65 probably underestimate the severity of his disease. Stenting of a proximal lesion in the left leg is aimed at preserving tissue viability, healing the ischaemic ulceration and preventing sepsis and amputation. His symptoms of AMI were not typical – which is often the case in diabetes – but biomarkers and ECG confirmed non-ST elevation infarction. This is treated with combination antiplatelet therapy and short-term low molecular weight heparin. Optimum secondary prevention requires a statin, tight BP control, ideally with an ACE inhibitor, and antiplatelet therapy. A low-dose β-blocker for cardioprotection will probably have minimal adverse effect on his PAD.

Glycaemic vascular injury

Observational epidemiological studies have shown a continuous linear relationship between HbA_{1c} and CVD mortality which extends into the non-diabetic range of glucose levels, but the excess macrovascular risk in diabetes reflects multiple components of the diabetes syndrome as well as hyperglycaemia (e.g. BP, lipids, proteinuria and inflammatory markers) (Figure 20.5). In addition, there is some concern that HbA_{1c} may underestimate the link between glycaemia and macrovascular outcomes; postprandial glucose levels may be a better indicator of CVD risk, but a major trial of prandial glucose lowering with nateglinide failed to show a benefit on CV outcomes.

There are four principal mechanisms by which hyperglycaemia causes the structural and functional vascular abnormalities associated with diabetes: (1) non-enzymatic glycation of tissue proteins and formation of advanced glycosylation endproducts (AGEs); (2) metabolism of glucose

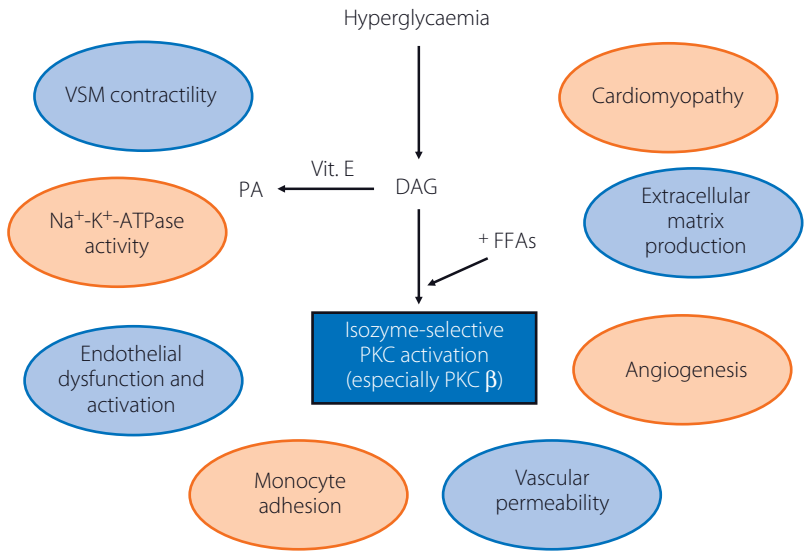

Figure 20.6 DAG-mediated activation of protein kinase C-β results in phosphorylation and altered function of numerous proteins, enzymes and/or receptors involved in endothelial and vascular smooth muscle function, cardiac hypertrophy, contractility and fibrosis. Inhibitors of PKCβ (e.g. ruboxistaurin) have undergone clinical trials to block hyperglycaemia-induced vascular disease in patients with diabetes. Free fatty acids (FFA) enhance DAG-PKC activation, and vitamin E can help reduce DAG via conversion to phosphatidic acid (PA).

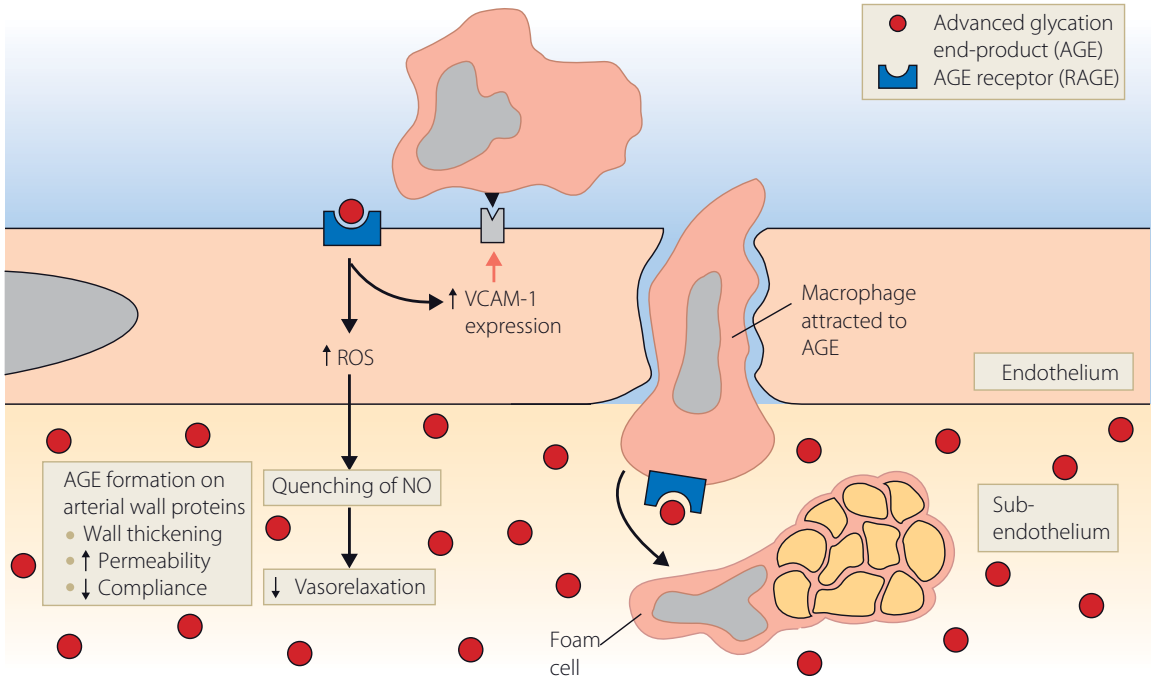

Figure 20.7 Advanced glycation endproducts (AGEs) have an number of unwanted effects on vascular structure and function. In particular, they bind to specific receptors (RAGEs) and, via decreased nitric oxide bio-availability, increase arterial stiffness and reactive oxygen species (ROS) formation. AGEs also attract macrophages and promote foam cell formation. Foam cells contribute to atherosclerotic disease progression.

via the aldose reductase pathway; (3) excess formation of reactive oxygen species (ROS) leading to oxidative stress and formation of highly atherogenic endproducts such as oxidised-LDL; and (4) increased *de novo* synthesis of diacylglycerol (DAG) from intermediate steps in glycolysis, which in turn leads to activation of protein kinase C, especially PKCβ. These pathways are not mutually exclusive, and indeed all four probably contribute and interact to influence the development, progression and complications from macrovascular disease (Figures 20.6, 20.7).

Evidence for glucose-lowering in CVD prevention

There is considerable interest in the effects of glucose-lowering therapy on macrovascular disease outcomes. In the original UKPDS population, intensive versus conventional

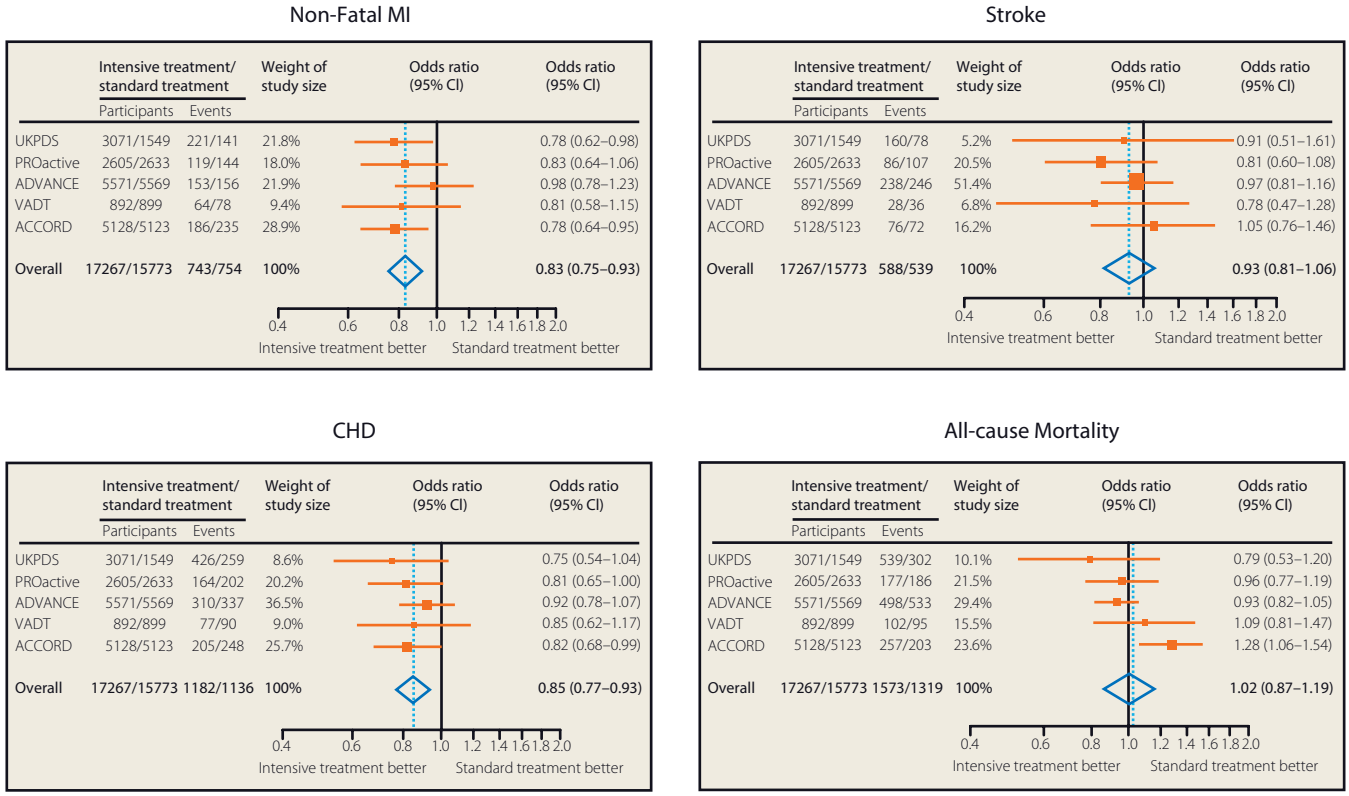

Figure 20.8 A meta-analysis of five prospective randomised controlled trials of intensive glucose lowering in a total of 33,040 patients with type 2 diabetes. On average, HbA_{1c} was 0.9% lower in intensively treated patients, which resulted in modest significant benefits in terms of preventing CHD and non-fatal, acute myocardial infarction, but all-cause mortality and stroke events were not significantly different between intensive and conventional glycaemic control. These effects contrast with BP-lowering and cholesterol-lowering interventions which have a more powerful effect on macrovascular outcomes in patients with diabetes. Adapted from Ray et al. Lancet 2009; 373: 1765–1772.

glycaemic control strategies (average HbA_{1c} 7.0% versus 7.9%) had no significant effect on diabetes-related deaths (principally due to CVD), but more recent and much larger randomised controlled trials have provided a total study population of >33,000 patients from which to assess the benefits versus harms of intensive glucose lowering. Overall, the meta-analysis showed that intensive glycaemic control (on average HbA_{1c} was 0.9% lower in intensively treated patients) resulted in a 17% reduction in non-fatal myocardial infarction, but no significant effect on stroke or all-cause mortality (Figure 20.8).

The cardiovascular benefits of tight glycaemic control in the first few years after diagnosis of type 1 and type 2 diabetes may not be evident until 10+ years later. This has been well illustrated by the DCCT-EDIC trial in type 1 diabetes and by the UKPDS in type 2 diabetes. In both trials, long after study closure, and despite near-identical post-trial HbA_{1c} levels in the two groups, those patients who were previously assigned to intensive glycaemic control obtained lasting benefits on survival. This has been described as a legacy effect, and reinforces the importance of tight glycaemic control in the early stages of type 1 and type 2 diabetes (Figure 20.9).

Recent analyses have shown that low HbA_{1c} (<6.7%), as well as high HbA_{1c}, is associated with increased all-cause mortality and cardiac events, raising further doubts about the safety of intensive glycaemic control (Currie et al, 2010).

Macrovascular disease remains the leading cause of death among patients with diabetes. The presentation of ischaemic heart disease in diabetes includes angina, AMI and heart failure, as it does in the non-diabetic population. However, angina and AMI may be relatively painless ('silent') in patients with diabetes. Both short and long-term mortality from myocardial infarction are increased in diabetes, largely through the increased risk of heart failure and reocclusion causing reinfarction. Nevertheless, considerable progress has been made over the last 10–20 years in improving outcomes from macrovascular events (Figure 20.10).

Multiple risk factor intervention

Tight control of BP and lipids is arguably more important than tight glycaemic control in preventing deaths from macrovascular disease, but in practice a multifactorial intervention strategy, aggressively lowering all three risk factors,

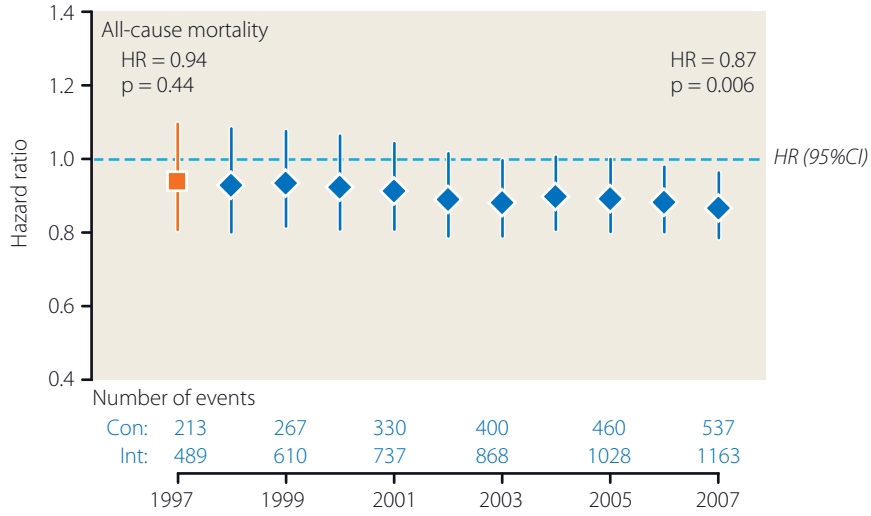

Figure 20.9 The legacy effect of tight glycaemic control in participants in the UKPDS. At the end of the study (1997), there was a non-significant reduction in all-cause mortality in the intensively treated patients. After study closure, average HbA_{1c} levels in both cohorts of patients converged and were similar, but 10 years later (2007) those patients who were previously assigned to the intensive control group had significantly better survival compared with those who were assigned to conventional glycaemic control. Adapted from Holman et al. N Engl J Med 2008; 359: 1577–1589.

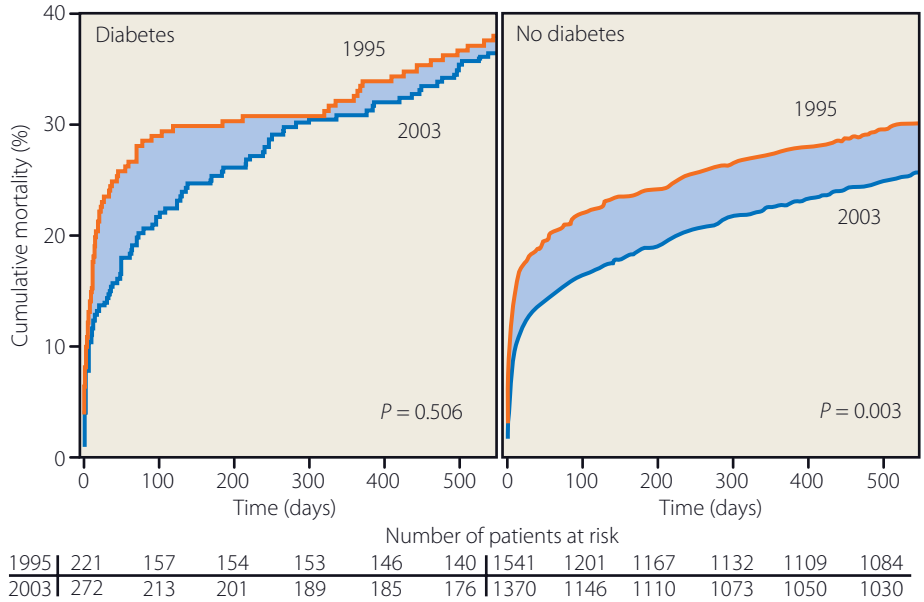

Figure 20.10 This figure illustrates survival rates among patients with and without diabetes in Leeds, UK, following acute myocardial infarction, comparing 1995 with 2003. Survival is clearly worse among subjects with diabetes compared with subjects without diabetes. In 2003, short-term outcomes among patients with diabetes recovering from acute myocardial infarction are much improved compared with 1995, but after 1 year there is minimal difference between 2003 and 1995. Thus, early outcomes have been improved more than late outcomes in this high-risk population. The data emphasise the need for vigorous secondary prevention. Adapted from Cubbon et al. Eur Heart J 2007; 28: 540–45.

is the mainstay of best practice for cardiovascular protection (Figure 20.11). Thus, international guidelines set tough targets for patients treated for diabetes that include BP < 130/80 mmHg, LDL-cholesterol < 2.0 mmol/L (total cholesterol < 4.0 mmol/L) and HbA_{1c} < 6.5–7%. In those with established nephropathy, optimum BP targets are even lower.

Transient ischaemic attacks and stroke are also common in diabetes, and mortality and disability after a stroke are higher in people with diabetes compared to people without diabetes. Admission glucose is a prognostic indicator in acute stroke, but glucose-lowering in the early stages post-stroke has not been shown to improve outcomes (Figure 20.12).

The role of low-dose aspirin in the (primary) prevention of macrovascular events among asymptomatic patients with diabetes is still unclear and the major international guidelines offer differing advice (Figure 20.13). In those patients who have symptoms (e.g. angina or claudication), aspirin confers significant benefits for secondary prevention, but primary prevention is more doubtful, bearing in mind that

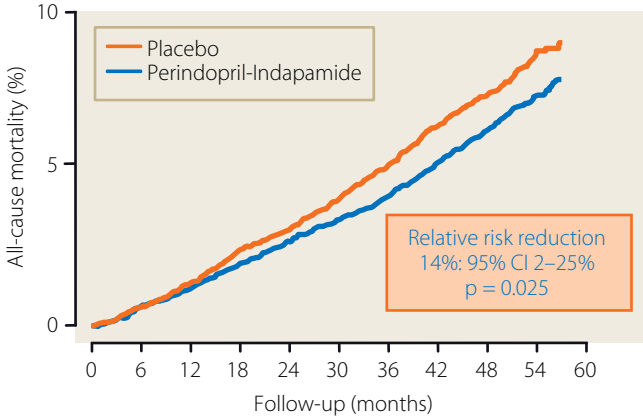

Figure 20.11 The ADVANCE study randomised approximately 20,000 high-risk patients with type 2 diabetes to usual care + add-on angiotensin converting enzyme (ACE) inhibitor/diuretic combination (perindopril + indapamide) or add-on placebo, on top of usual BP-lowering therapies. Baseline BP for the study population was quite good (average BP 140/77 mmHg), and the active therapy resulted in a modest further BP reduction, 6/2 mmHg on average over 5 years. This effect translated into a 14% risk reduction in all-cause mortality, due largely to a reduction in macrovascular events. The treatment effect may have been at least partly BP independent, but the trial emphasises that small differences in BP matter. Adapted from Patel et al. Lancet 2007; 370: 829.

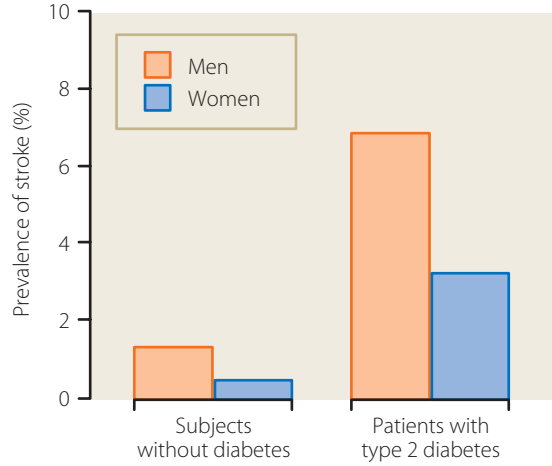

Figure 20.12 Age-adjusted prevalence of previous stroke among type 2 diabetes patients compared with subjects without diabetes (45–64 years of age). Small vessel cerebral ischaemia, as well as internal carotid artery stenosis, are more common among patients with diabetes. Data from Pyörälä et al. Diabet Metab Rev 1987; 3: 463–42.

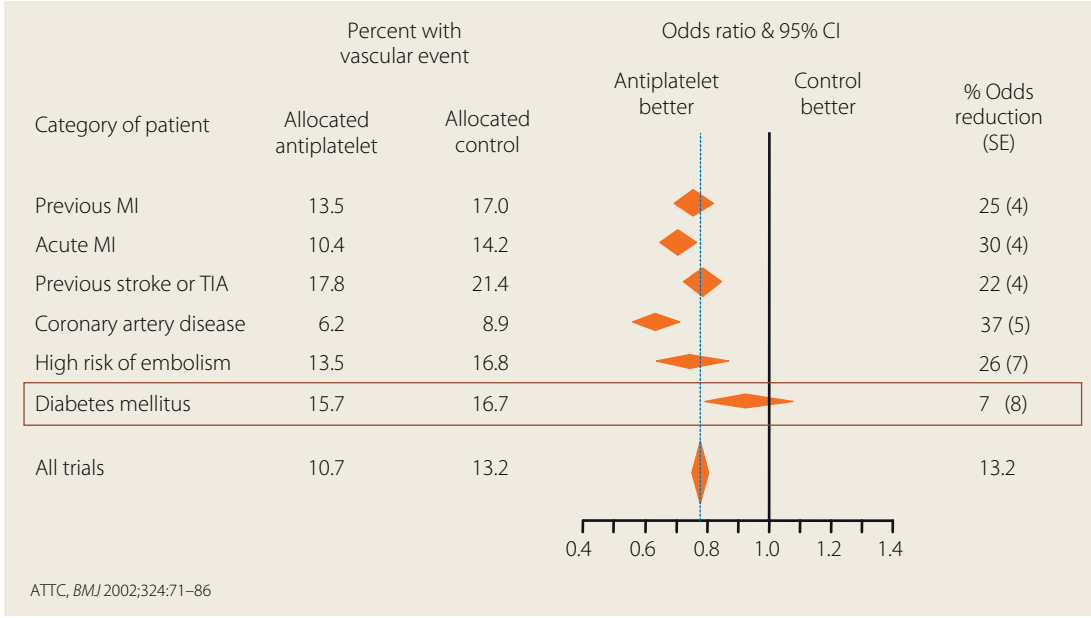

Figure 20.13 From the Antithrombotic Trialists Collaboration, there is no clear evidence for the routine use of low-dose aspirin for primary prevention of macrovascular disease in patients with diabetes, but international guidelines do not all agree. In contrast, low-dose aspirin is highly effective in those patients with previous AMI, stroke or symptomatic angina. Adapted from Antithrombotic Trialists Collaboration. BMJ 2002; 324: 71–6.

low-dose aspirin is not without side effects. The ongoing ASCEND trial is evaluating aspirin for primary prevention.

Peripheral arterial disease (PAD) in the legs typically presents with intermittent claudication (i.e. calf pain on walking) (Figure 20.14). Buttock pain may occur if the iliac vessels are affected and PAD may be associated with erectile dysfunction (Leriche's syndrome). Decreasing claudication distance or rest pain may indicate critical ischaemia. PAD in people with diabtes tends to be more diffuse and distal in nature, therefore less amenable to percutaneous intervention

LANDMARK CLINICAL TRIALS

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(i.e. angioplasty or stenting). People with diabetes have an approximately 16-fold higher risk of lower limb amputation than people without diabetes and about 20% of those with PAD die within 2 years of the onset of symptoms, mostly from myocardial infarction. Because of increased calcification and stiffness, measurements of Ankle Brachial Pressure Index (ABPI; ankle systolic BP divided by branchial systolic BP) may be artificially raised and therefore underestimate the severity of PAD in patients with diabetes. Fibrate therapy has been shown to reduce amputation rates in people with diabetes and PAD.

Coronary heart disease and diabetes

In patients admitted with AMI, blood glucose should be controlled tightly using IV insulin infusion (Figure 20.15). The Diabetes Mellitus Insulin Glucose Infusion in Acute Myocardial Infarction (DIGAMI) study showed a 30%

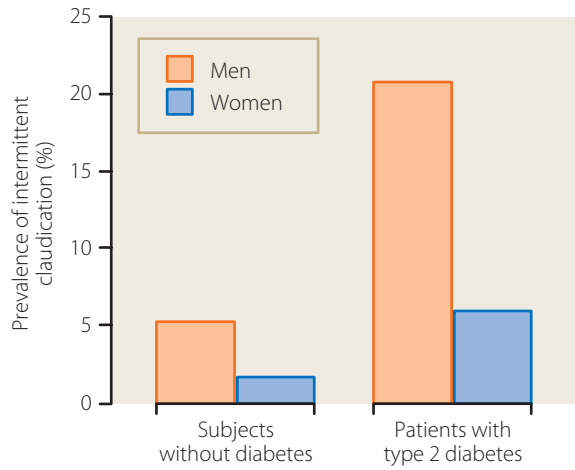

Figure 20.14 Age-adjusted prevalence of intermittent claudication in patients with type 2 diabetes (45–64 years of age). Data from Pyörälä et al. Diabet Metab Rev 1987; 3: 463–42.

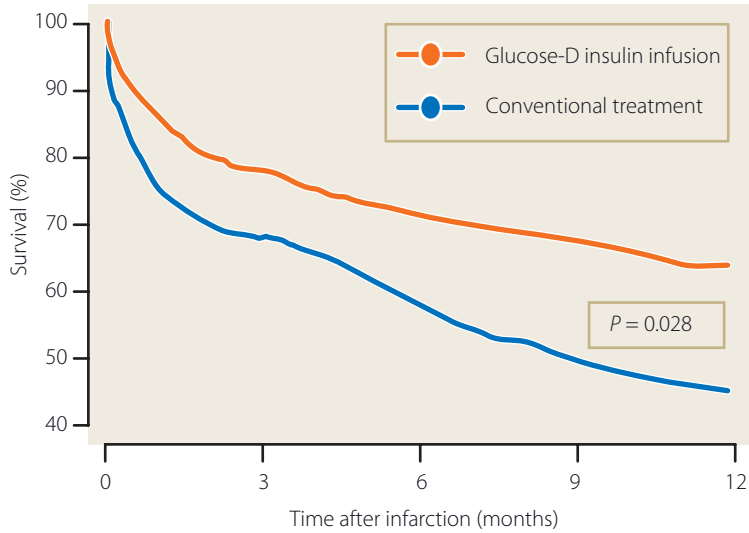

Figure 20.15 In patients found to be hyperglycaemic on admission with acute myocardial infarction, IV insulin-glucose infusion to maintain tight glucose control reduced mortality compared with a conservative approach. Reducing free fatty acid levels (which are toxic to the myocardium) is one mechanism likely to underlie this effect. From Malmberg et al. J Am Coll Cardiol 1995; 26: 57–5.

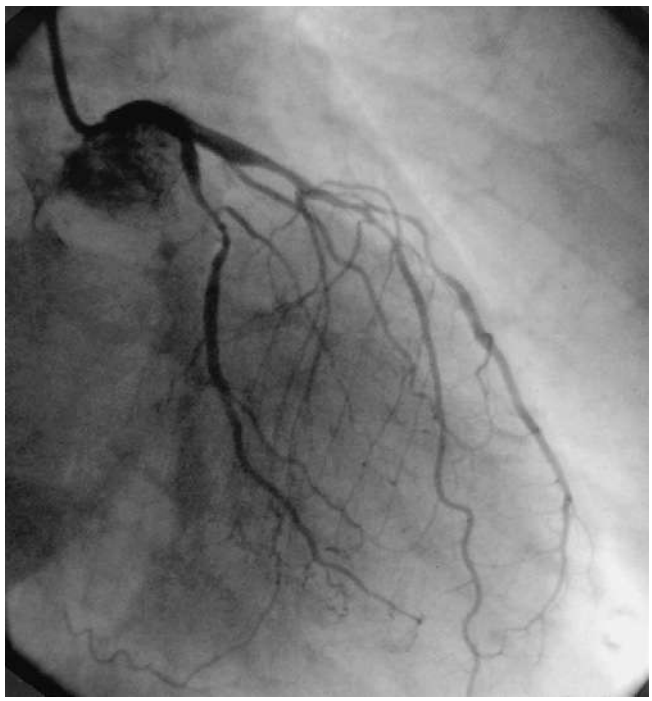

Figure 20.16 Diffuse coronary artery disease in a 49-year-old woman with type 1 diabetes. There is widespread narrowing of the mid-portions of the left anterior descending coronary artery and circumflex artery.

KEY WEBSITES

- http://diabetes.niddk.nih.gov/dm/pubs/stroke/
- www.americanheart.org/presenter.jhtml?identifier=3044762
- www.diabetes.org/diabetes-heart-disease-stroke.jsp

reduction in mortality in patients with diabetes treated with insulin soon after infarction, compared with conventional management. This involves an insulin–glucose solution infused intravenously to maintain blood glucose levels of 7–11 mmol/L for at least 24–48 hours.

Until recently, the optimum management of patients with diabetes and stable ischaemic heart disease was uncertain. In particular, there has been uncertainty about the extent to which asymptomatic patients with diabetes should be screened for coronary artery disease and about the role of revascularisation, on prognostic grounds, in patients with stable and/or minimal angina symptoms. The BARI-2D study (a randomised trial of therapies for type 2 diabetes and coronary artery disease) randomised patients with established macrovascular disease who were eligible for either percutaneous coronary intervention (PCI) or coronary artery bypass grafting (CABG). In a 2 × 2 factorial design, patients were assigned to undergo either prompt revascularisation or medical therapy, and separately randomised to either insulin sensitisation treatment or insulin provision treatment to achieve $HbA_{1c} < 7\%$. Overall, there was no significant difference in the rates of death and major cardiovascular events between patients who had prompt revascularization versus those managed by medical therapy, and nor was there a difference in CV outcomes between the two strategies of HbA_{1c} lowering. Thus, revascularisation is likely to be used mainly for those patients with an acute coronary syndrome and those with unstable or troublesome symptoms despite medical treatment. In the DIAD study, screening of asymptomatic patients with diabetes for coronary disease using myocardial perfusion imaging was of no clinical benefit.

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Chapter

21 Foot problems in diabetes

KEY POINTS

- The population incidence of diabetic foot ulcers is 1–4%, and the risk of amputation (toe, foot or leg) in patients with diabetes is 10–30-fold increased.
- Foot ulcers frequently arise because of the combination of neuropathy and ischaemia, complicated by infection. Diabetic neuropathy is a major risk factor for foot ulcer formation.
- Ulcers are classified as neuropathic, ischaemic or neuroischaemic. Neuropathic ulcers are often painless and on the plantar surface or over high-pressure areas.
- Ankle Brachial Pressure Index (ABPI) is a simple measurement for detecting PAD (ABPI <0.9) or critical ischaemia (ABPI <0.5) but may be falsely elevated in diabetics with calcified vessels.
- The NICE risk stratification system for assessing diabetic foot ulcers is useful.
- Debridement, antibiotic use and off-loading are important aspects of treatment for ulceration.

The high risk diabetic foot

The lifetime risk of a person with diabetes developing foot ulceration is around 25%. Recent studies suggest that the population-based incidence of diabetic foot ulcers is 1–4% with a prevalence of 4–10%. The risk of amputation is 10–30-fold higher in people with diabetes compared with the general population, and global estimates suggest that every year one million people with diabetes undergo some sort of lower limb amputation. The majority of limb amputations (85%) are preceded by foot ulceration, and the mortality rate following an amputation is reported to be in the region of 15–40% at 1 year and 39–80% at 5 years. The risk of foot ulceration may be lower in South Asians compared with Europeans living in the UK.

Diabetic foot ulcers are caused mainly by neuropathy (motor, sensory and autonomic) and/or ischaemia, and frequently complicated by infection. Loss of pain sensation can damage the foot directly (e.g. from ill-fitting shoes) and motor neuropathy leads to a characteristic foot posture – raised arch, clawed toes and pressure concentrated on the metatarsal heads and heel. Skin thickening (callus) is stimulated at these pressure points and the haemorrhage or necrosis, which is common within callus, can break through to form an ulcer. Callus formation is therefore an important predictor of ulcers (Figure 21.1).

Box 21.1 The 'diabetic foot' refers to a mix of pathologies

- Diabetic neuropathy
- Peripheral arterial disease
- Charcot's neuroarthropathy
- Foot ulceration
- Osteomyelitis
- Limb amputation

Diabetic neuropathy is present in at least half of patients over 60 years of age, and increases the risk of foot ulceration sevenfold. Since peripheral nerve damage is often insidious and asymptomatic, regular inspection of the foot by patients themselves and healthcare professionals is essential to identify early signs of impending ulceration. Sensory neuropathy often renders the diabetic foot 'deaf and blind'. Therefore, effective and simple education about footwear, and strategies to minimise ulcer risk, are important aspects of diabetes care, especially in high-risk individuals with a history of previous ulceration and/or several risk factors (Box 21.2).

Handbook of Diabetes, 4th edition. By © Rudy Bilous & Richard Donnelly. Published 2010 by Blackwell Publishing Ltd.

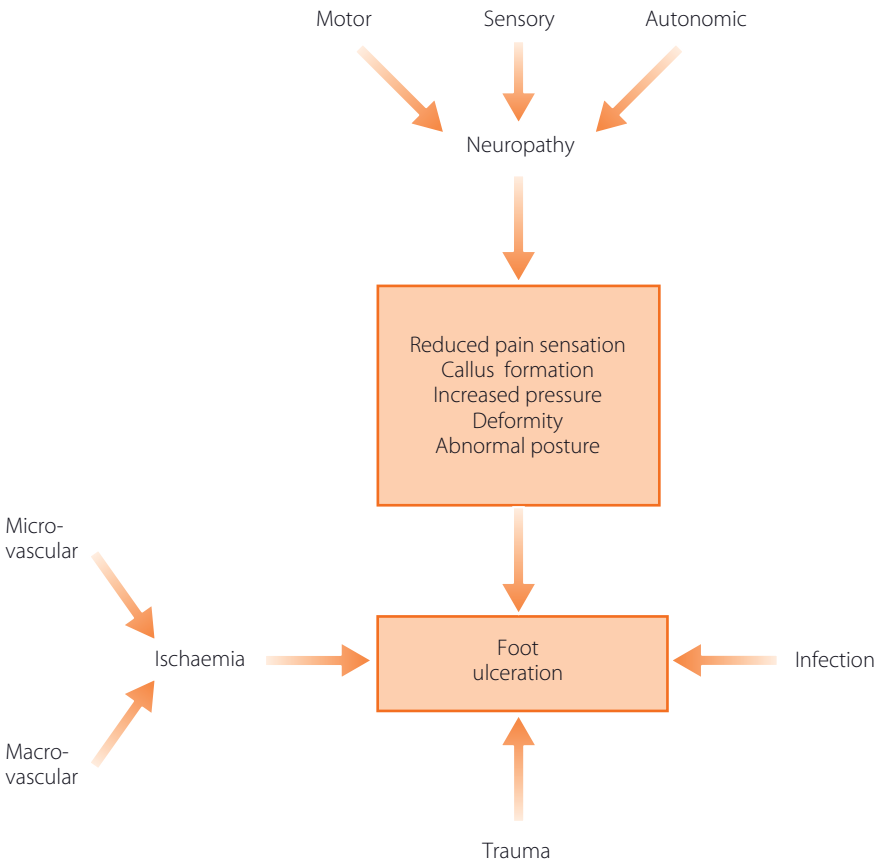


Figure 21.1 Major components and mechanisms in the aetiology of foot ulceration.

Box 21.2 Risk factors for diabetic foot complications

- Neuropathy
- Peripheral arterial disease
- Trauma
- Infection
- Poor glycaemic control
- Ill-fitting footwear
- Older age, smoking, low socio-economic status

Motor neuropathy leads to muscle atrophy, foot deformity, altered biomechanics and a redistribution of foot pressures. This in turn leads to ulceration. Sensory neuropathy affects pain and discomfort, which predisposes the foot to repetitive trauma. Autonomic nerve damage leads to reduced sweating, which leads to dry and cracked skin and fissures, and so allows the entry and spread of infection. Damage to the sympathetic innervation of the foot leads to arteriovenous shunting and distended veins. This bypasses the capillary bed in affected areas and may compromise nutrition and oxygen supply. Microvascular disease may also interfere with nutritive blood supply to the foot tissues.

Box 21.3 Foot screening assessment tool for routine use in the clinic

• Deformity or bony prominences	Yes/No
• Skin not intact (ulcer)	Yes/No
• Signs of neuropathy:	
• Monofilament undetectable	Yes/No
• Tuning fork undetectable	Yes/No
• Cotton wool undetectable	Yes/No
• Abnormal pressure/callus	Yes/No
• Loss of joint mobility	Yes/No
• Circulation impaired:	
• Posterior tibial A. pulse absent	Yes/No
• Dorsalis pedis A. pulse absent	Yes/No
• Discolouration on dependency	Yes/No
• Other features:	
• Previous ulcer	Yes/No
• Amputation	Yes/No
• Inappropriate footwear	Yes/No

Foot is at risk if any of these are answered yes

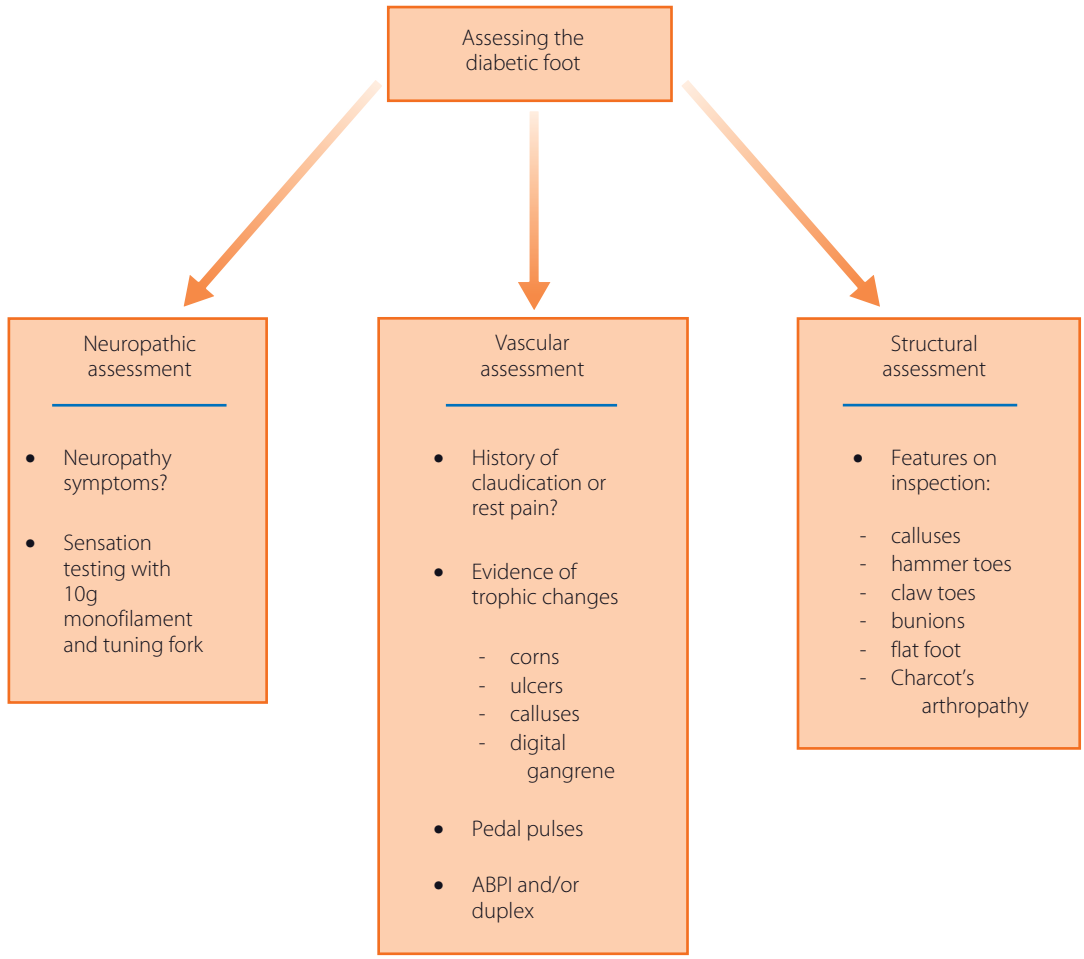


Figure 21.2 Assessing the diabetic foot for neuropathic, vascular and structural abnormalities.

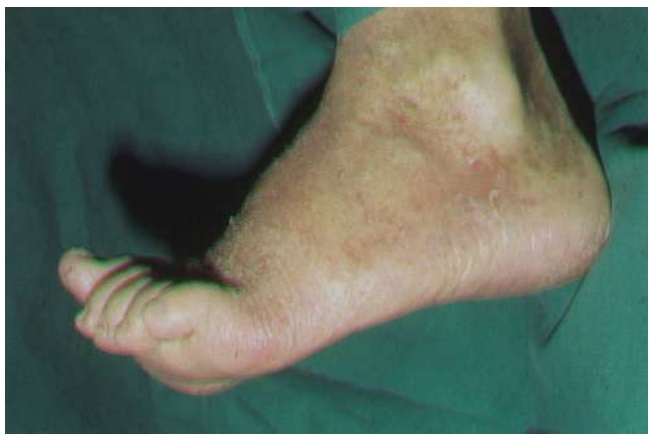


Figure 21.3 Characteristic deformities in a neuropathic foot: clawed toes, dry skin and prominent veins.

Foot ulcers

Most ulcers can be classified as neuropathic, ischaemic or neuroischaemic (Figures 21.4–21.6). Neuropathic foot ulcers frequently occur on the plantar surface of the foot in high-pressure areas, e.g. overlying the metatarsal heads, or in other areas overlying a bony deformity. They account for >50% of diabetic foot ulcers and are often painless with a 'punched out' appearance. Ischaemic or neuroischaemic ulcers are more common on the tips of the toes or the lateral border of the foot. Neuropathic ulcers with overlying callus and necrosis should be regularly debrided, and infection should be treated promptly with antibiotics.

Peripheral arterial disease (PAD) in the lower limb is often diffuse and distal, involving the tibioperoneal trunk and crural arteries, and vascular insufficiency may be overlooked until signs of critical ischaemia develop. Cutaneous trophic changes such as corns, calluses, ulcers or frank digital gangrene occur (Figure 21.7). Ulceration is typically painful and at the distal extremities of the toes. The ABPI is easily measured and useful (ABPI < 0.9 indicates PAD; critical ischaemia is often reflected by ABPI <0.5), but it can be falsely elevated and underestimate the degree of arterial disease in patients with diabetes and calcified vessels. Measurements of toe pressure and transcutaneous oxygen pressure ($TcPO_2$) are also helpful. The probability of an ulcer healing is determined

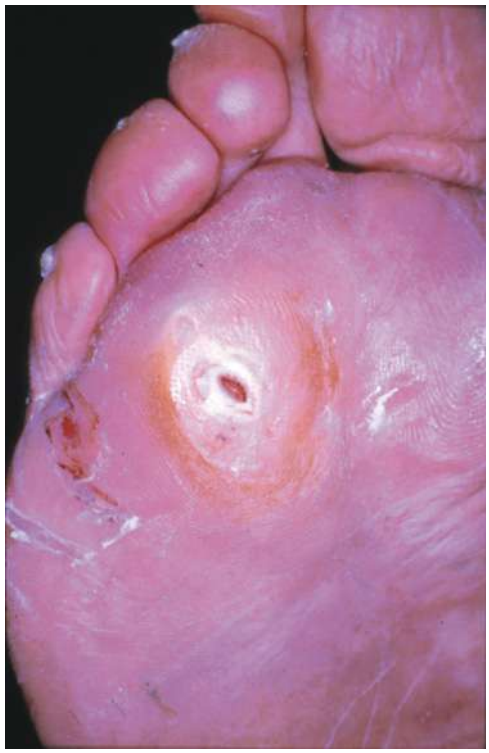


Figure 21.4 Typical neuropathic ulcer with surrounding callus.

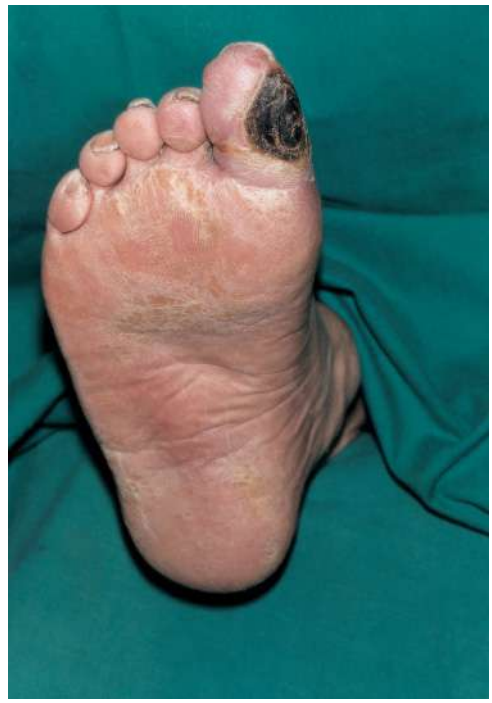


Figure 21.5 Neuroischaemic damage caused by tightly fitting shoes.

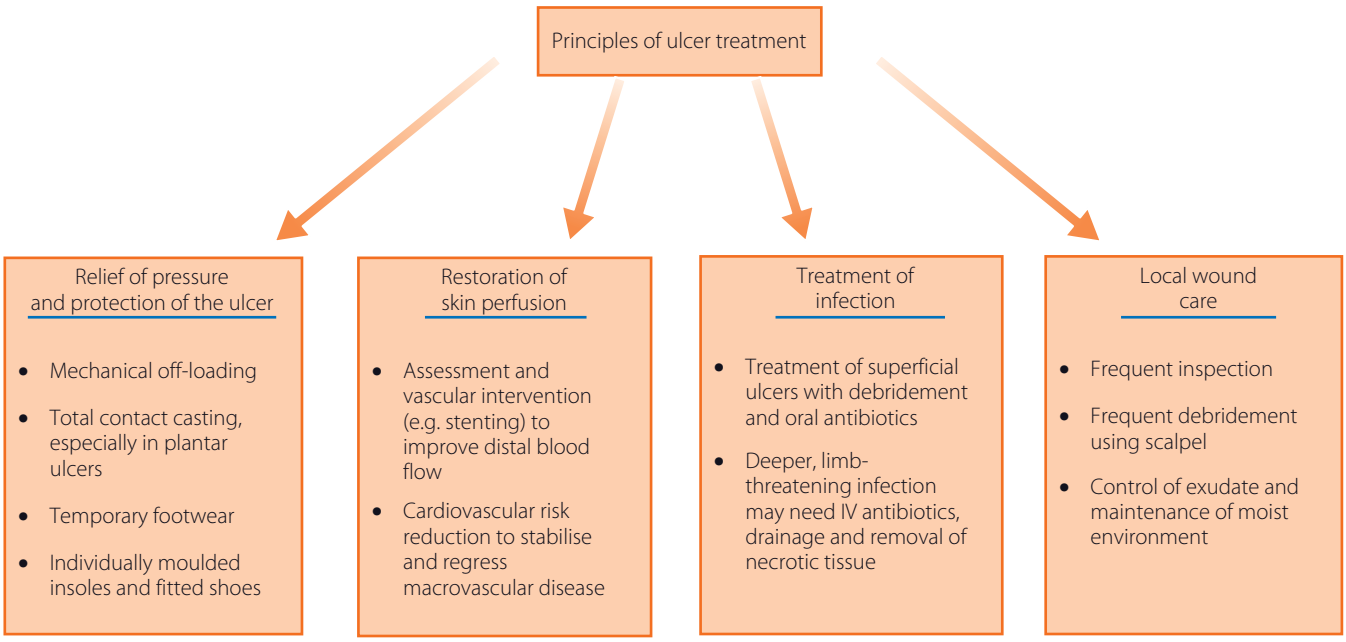


Figure 21.6 Principles of ulcer treatment, in addition to providing education and good metabolic control.

by perfusion, as indicated by measurements of ABPI, toe pressure and $TcPO_2$.

Charcot's arthropathy is a rare complication of severe neuropathy in long-standing diabetes (Figure 21.8). The initiating event may be an injury (perhaps unnoticed) that causes bone fracture in the mid-foot. Repeated minor trauma in pain-insensitive feet and possibly enhanced blood flow caused by sympathetic denervation result in decreased bone

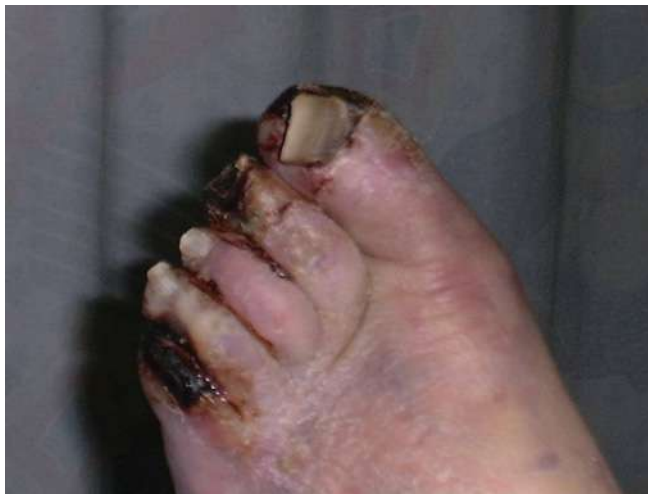
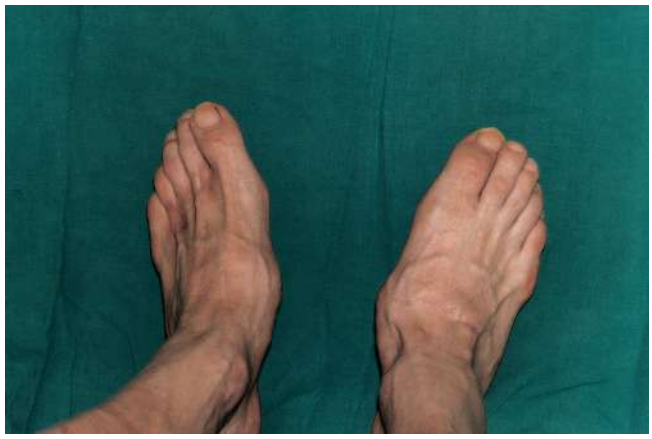
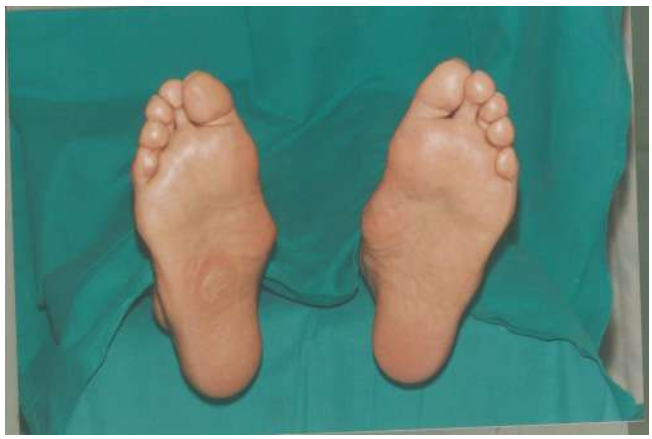


Figure 21.7 Critical ischaemia, ulceration and gangrene affecting the extremities.



(a)



(b)

Figure 21.8 Bilateral Charcot's neuroarthropathy in the cuneiform-metatarsal area has resulted in the characteristic deformity of the mid-foot: (a) dorsal and (b) plantar views.

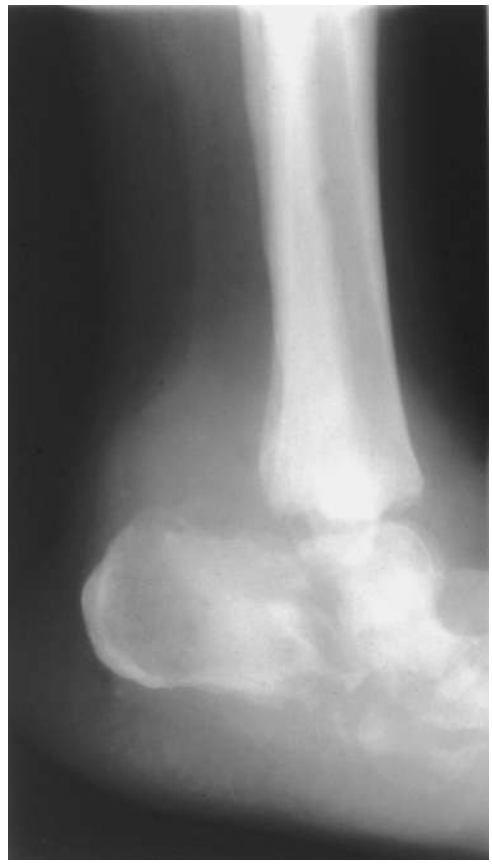


Figure 21.9 Plain X-ray of a Charcot foot demonstrates gross destruction, deformity and instability of the ankle joint + effusion. The 'bag of bones' appearance. Courtesy of Professor G Williams, University of Bristol, Bristol, UK.

density and bony destruction. Excessive osteoclast activity causes bone resorption, coalescence and remodelling, which lead to the characteristic deformity and instability. Over months, the patient may notice the foot changing shape or the sensation of the bones crunching on walking. In the later stages a large effusion may surround disrupted joints and bone fragments – often giving the 'bag of bones' appearance on plain X-ray (Figure 21.9). Total contact casting is the most effective treatment, until the hyperaemia and swelling have settled, and bisphosphonates (potent inhibitors of osteoclast activation) are used in the acute phase of Charcot's neuroarthropathy.

Risk stratification and ulcer treatments

The UK National Institute for Health and Clinical Excellence (NICE) has suggested a risk stratification system for diabetic foot ulceration and appropriate follow-up (Table 21.1). Educating patients about footcare, footwear and self-inspection is essential. Early intervention at the first sign of ulceration is important, and those patients with a history of

CASE HISTORY

A 56-year-old man with type 1 diabetes since the age of 15 presents for annual review. He has required laser photocoagulation to the left eye, but has no history of macrovascular disease. HbA_{1c} is 8.1%, BP 138/86 mmHg and LDL-cholesterol 2.7 mmol/L. He is on a basal-bolus regime of insulin. On questioning him, he denies any foot symptoms but on examination using a 10 g monofilament and tuning fork, he has markedly reduced sensation. Inspection reveals a 1 cm 'punched out' ulcer with surrounding callus on the plantar surface of the right foot (Figure 21.12).

Comment: It is common for patients with severe neuropathy to report no symptoms in the feet (they have very little sensation), so it is important to remove the socks and shoes and inspect the feet. This is a typical neuropathic foot ulcer (punched-out appearance, painless, surrounding callus). It requires cleaning, debridement of callus using a scalpel, oral antibiotics and off-loading. Given the duration of diabetes and microvascular complications in the eye, this patient would be at very high risk of foot ulcer. There is also some deformity of the mid-foot on the photo, which raises the possibility of Charcot's neuroarthropathy being present (an X-ray would be helpful).

LANDMARK CLINICAL TRIALS

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Table 21.1 NICE risk stratification system with appropriate frequency of foot assessments (NICE clinical guideline 10, 2004; 10: 45)

Risk category	Clinical features	Frequency of foot assessment
Low risk	Normal sensation Palpable pulses	Annual
At risk	Evidence of neuropathy and/or absent pulses	3–6 monthly
High risk	Neuropathy or absent pulses and signs of deformity, or skin changes or previous ulceration	1–3 monthly
Ulcerated foot (very high risk)	Foot ulcer	Active care by multidisciplinary foot team

previous ulcers are at the highest risk for recurrent ulcer formation.

Off-loading refers to interventions that relieve pressure from the wound area and redistribute pressure to healthy areas of skin. The simplest method of off-loading is strict bedrest but this is impractical, difficult to enforce and associated with other complications (e.g. deep venous thrombosis). Total contact casting (TCC) is the most effective and evidence-based method for off-loading (Figure 21.10); studies have shown that TCC accelerates the healing of non-infected neuropathic ulcers. TCC is contraindicated in patients with significant peripheral arterial disease, infected ulcers or osteomyelitis. TCC facilitates mobility, but needs changing regularly, limits patients (e.g. in terms of bathing) and does not easily allow regular inspection of the ulcer. Thus, removable devices for off-loading can be used, but compliance is reduced if the patient can easily remove the boot.

Management of infected foot ulcers includes cleaning the wound and regular debridement of necrotic, unhealthy and infected material. Weekly debridement using a scalpel is associated with quicker ulcer healing. Larval therapy has also been used to promote healing; medicinal maggots secrete enzymes that digest the necrotic tissue and facilitate healing. The optimal type of dressing is unclear, and in small randomised trials simple dry dressings have been as effective as anything else. The most important pathogens causing diabetic foot infections are the aerobic gram-positive cocci (e.g. *Staph. aureus*, β-haemolytic streptococcus and coagulase-negative staphylococci). Commonly used antibiotics include amoxicillin-clavulanic acid, cirprofloxacin, cephalexin and clindamycin (Figure 21.11).

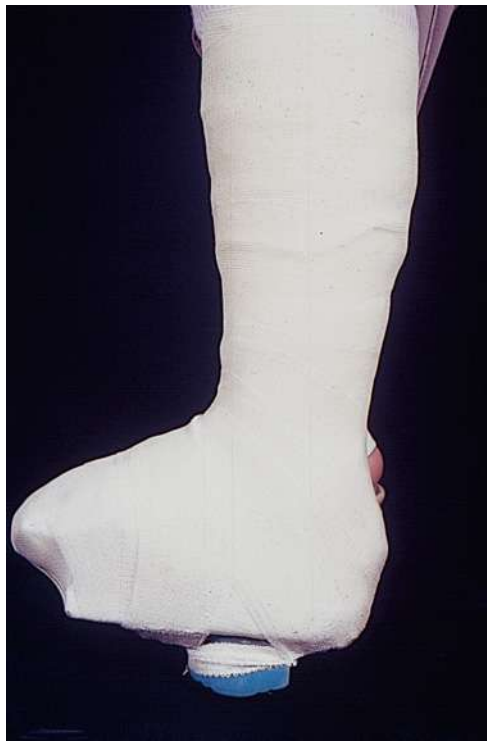

Figure 21.10 Total contact plaster cast for off-loading a neuropathic ulcer. Also used in Charcot's arthropathy.

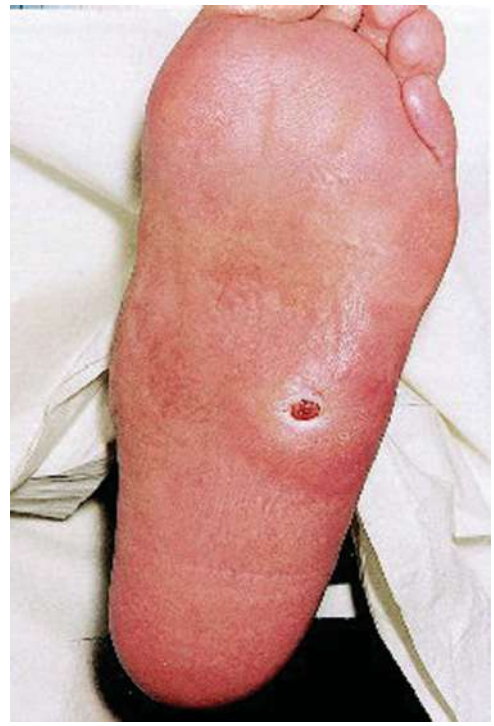

Figure 21.12 Neuropathic ulcer and mid-foot deformity.

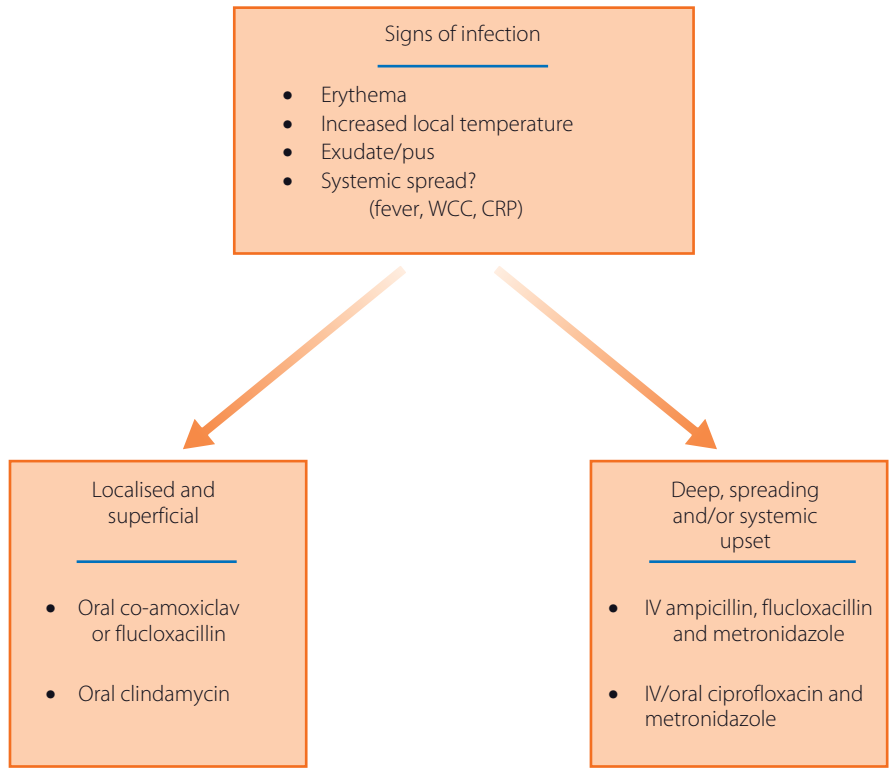

Figure 21.11 Typical approach to antibiotic use in infected foot ulcers. IV, intravenous; CRP, C-reactive protein; WCC, white cell count.

KEY WEBSITES

- www.Diabetic-foot.com.au
- www.diabetes.nhs.uk/downloads/NDST_Diabetic_Foot_Guide.pdf
- www.emedicinehealth.com/slideshow_diabetes_and_foot_problems/article_em.htm
- http://guidance.nice.org.uk/CG10
- SIGN Guidelines: www.SIGN.ac.uk

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Chapter

22

Sexual problems in diabetes

KEY POINTS

- Erectile dysfunction (ED) occurs at a younger age in men with diabetes, has a greater impact on their quality of life and may be less responsive to oral treatment.
- Nitric oxide (NO) is a key neural mediator of the normal erectile response, and modulated by cGMP. Phosphodiesterase V (PDE5) inhibitors (e.g. sildenafil) increase intracellular concentrations of cGMP.
- A thorough history and examination should be performed in men presenting with ED. It is helpful to have the partner present when discussing symptoms and possible treatments.
- PDE5 inhibitors work best if taken on an empty stomach; response rates in men with diabetes are 60–70%.
- Sexual dysfunction may be less common in women with diabetes but vaginal dryness, impaired arousal and orgasmic difficulties are frequently reported. Genitourinary infections are more common in diabetic women.
- Contraceptive advice should always be considered during the diabetes assessment to avoid unexpected pregnancy in the woman with diabetes.

Symptoms of sexual dysfunction affect both men and women with diabetes. The most common problem among men is erectile dysfunction (ED), which is defined as 'the inability to achieve or maintain an erection sufficient for sexual intercourse'. ED occurs 10–15 years earlier in men with diabetes compared with men without diabetes, has a greater impact on quality of life than in men without diabetes and is less responsive to oral treatment. The prevalence of ED among diabetic men varies from 35% to 90%, and the age-adjusted incidence is twofold higher in men with diabetes compared with those without. Advancing age and longer duration of diabetes are major risk factors for ED, but ED occurs more often in those men with macro- and/or microvascular and neuropathic complications. It is also associated with obesity, hypertension and antihypertensive therapies. In women, however, female sexual dysfunction (FSD) is related more closely to psychosocial factors than metabolic variables, and the presence of depression is a key predictor of FSD (Figure 22.1).

Erectile dysfunction is the most common sexual problem that affects men with diabetes. The age-related decline in erectile function is enhanced in diabetes, particularly in men with cardiovascular, microvascular or neuropathic complications (Figure 22.2). Depression is a common underlying problem that may predispose to, or exacerbate, ED and multiple drug therapies, especially antihypertensive drugs, often accentuate or unmask ED. One-third of men with diabetes and ED still experience morning erections, which suggests that there may also be a significant psychological component to their ED. The International Index of Erectile Function (IIEF), and its short form (IIEF-5), also known as the Sexual Health Inventory for Men (SHIM), are validated assessment tools for establishing the presence and severity of ED. In the erectile function domain of IIEF, men scoring <25 are classified as having ED and those >25 are considered not to have ED.

The principal neural mediator of the erectile response is nitric oxide (NO), which is released by vascular endothelial cells in response to cholinergic and non-cholinergic, non-adrenergic nerve fibre stimulation. NO-mediated relaxation of vascular smooth muscle in the corpus cavernosum of the penis leads to engorgement of the cavernosal space and compression of venous outflow. The postreceptor pathway that mediates NO-induced smooth muscle relaxation involves activation of the intracellular

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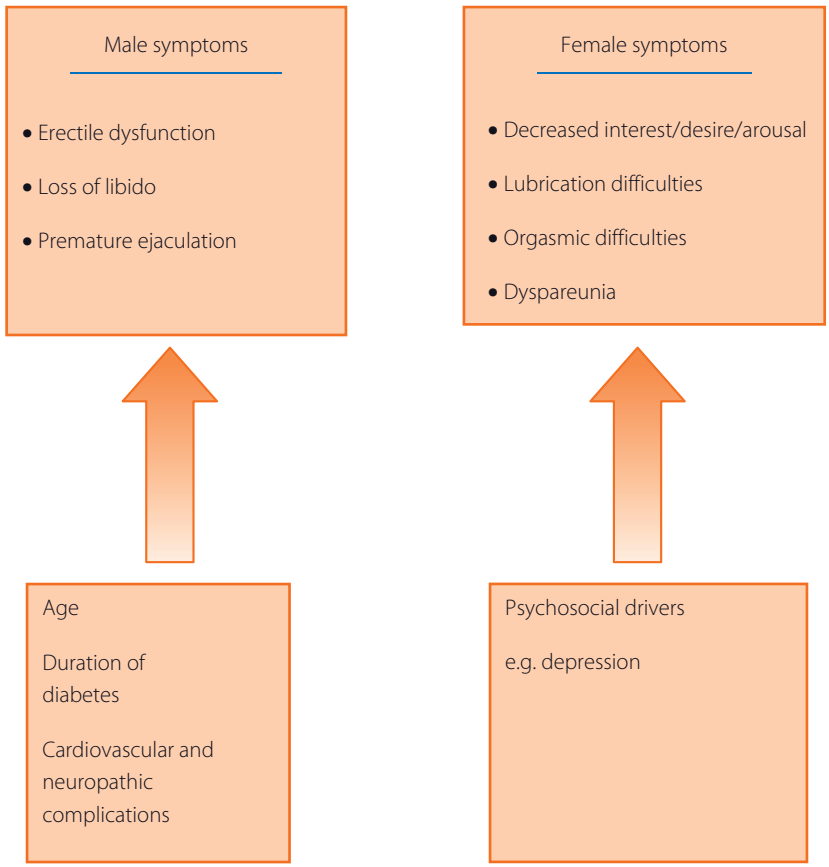

Figure 22.1 The most common symptoms of sexual dysfunction in men and women with diabetes.

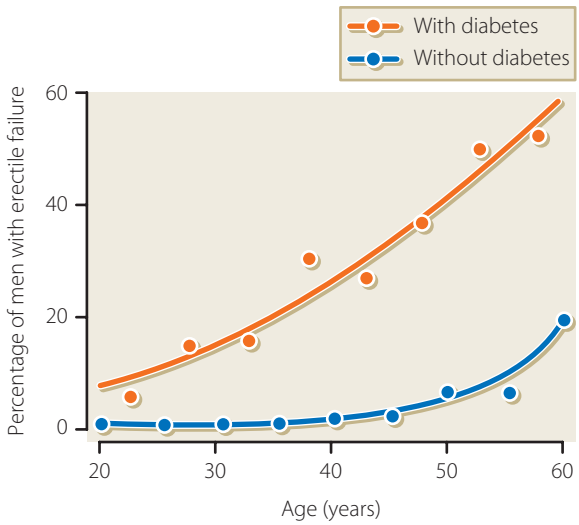

Figure 22.2 Age-related prevalence of ED in men with diabetes compared with men without diabetes. From Bancroft J. Human Sexuality and its Problems. Edinburgh: Churchill Livingstone, 1989.

enzyme guanylate cyclase and formation of the second messenger cyclic guanosine monophosphate (cGMP). cGMP is broken down by phosphodiesterase-5 (PDE5), which converts cGMP to GMP (Figure 22.3).

In men with diabetes, multiple factors can contribute to ED (Figure 22.4). Macrovascular disease, hypertension and other CV risk factors (e.g. smoking) impair blood flow to the penis and cause endothelial dysfunction (in which the bio-availability of NO and/or the smooth muscle responsiveness to NO may be reduced). Microangiopathy in diabetes affects both somatic and autonomic nerve function, leading to neuropathy. Autonomic neuropathy is strongly associated with ED. Hypogonadism is often associated with type 2 diabetes (up to 35% of men with diabetes and ED may have serum total testosterone levels <8 nmol/L). Although normal testosterone levels are needed for libido, the role of testosterone in erectile function is unclear. In addition, local and psychosocial factors can be important contributors.

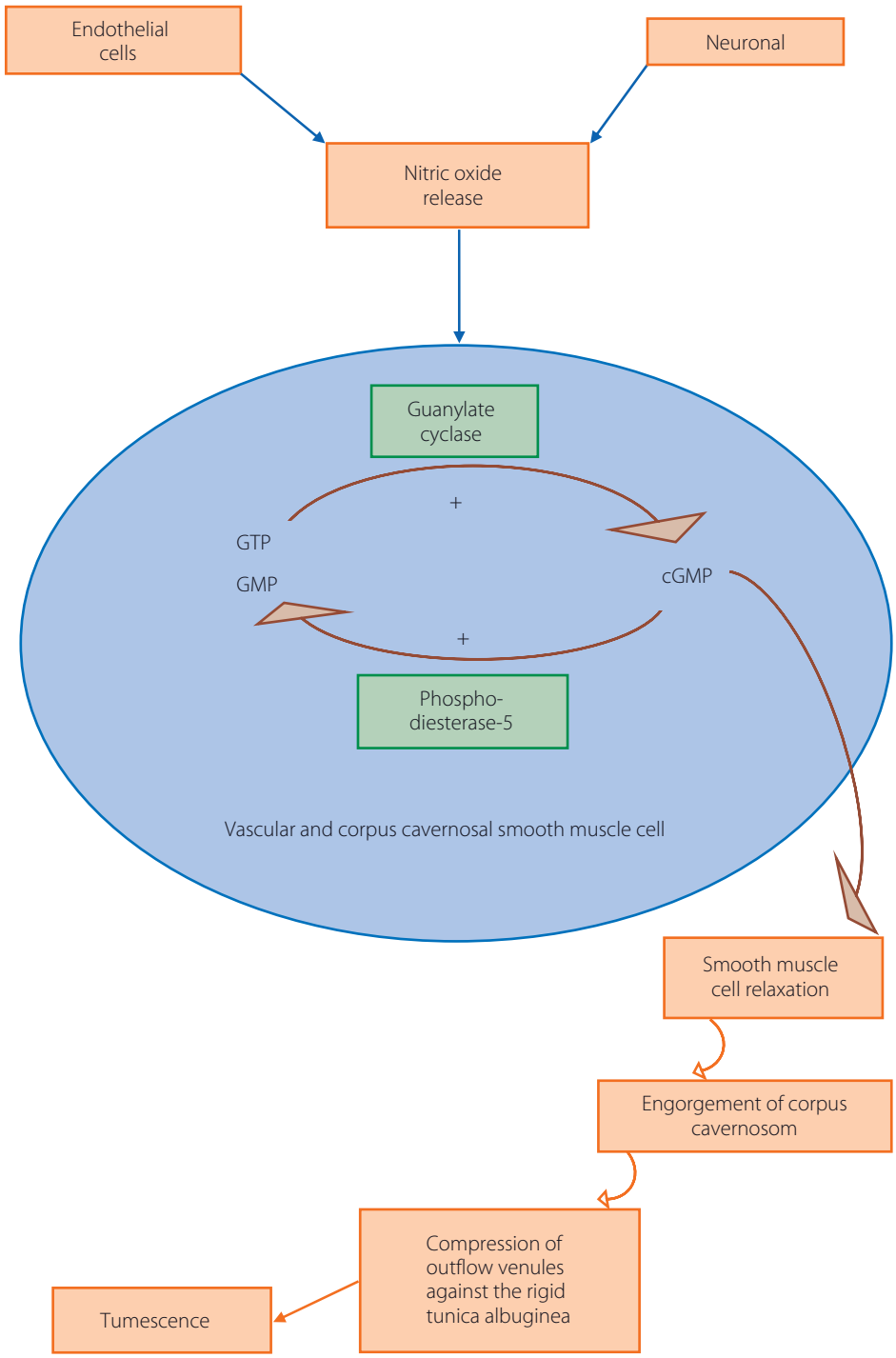

Figure 22.3 Pathways that lead to the relaxation of vascular and corpus cavernosal smooth muscle cells. NO is the principal mediator, via cGMP formation. Intracellular concentrations of cGMP are increased by phosphodiesterase-5 inhibitors.

Clinical assessment of men with ED

A detailed history should be taken in men who complain of impotence, particularly to exclude related problems, such as premature ejaculation and loss of libido, which the patient may confuse with ED, and to identify associated drugs and risk factors such as smoking (Box 22.1). Specifically asking about sexual dysfunction, especially ED in men, should be a routine part of the annual complications assessment. Patients often suffer in silence and hope that the healthcare professional will ask about sexual function and/or provide

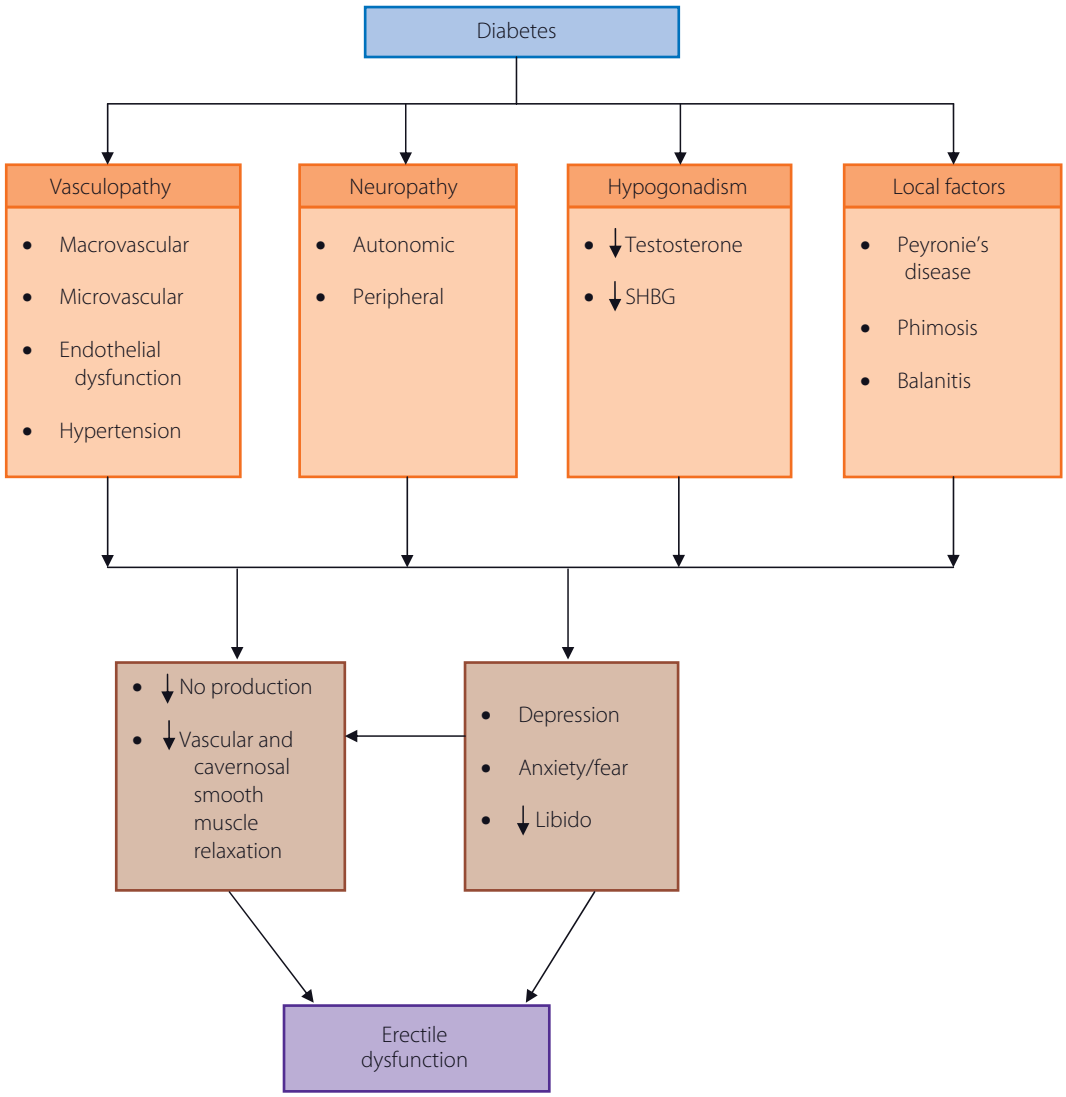

Figure 22.4 Major pathways contributing to ED in men with diabetes.

Box 22.1 Key features in the medical history of ED in a man with 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 thought 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. Impotent men often understate their sex drive for a variety of reasons
- Note drug history and smoking

an opportunity for them to indicate a possible problem. It is often helpful to have the partner present when discussing symptoms and possible treatment options. A full drug history should be taken.

Patients reporting ED should be examined. General physical examination may give clues to the aetiology (e.g. hypogonadism) or indicate associated conditions such as balanitis, phimosis or Peyronie's disease (Box 22.2). The integrity of the lower limb circulation and any features of peripheral or autonomic neuropathy should be noted. Obesity and features of the metabolic syndrome, independent of diabetes, are associated with ED.

Investigations include serum testosterone, when there is reduced libido or suspected hypogonadism, an assessment of cardiovascular, peripheral arterial, renal and lipid status, and a review of glycaemic control (Box 22.3). It is not

Box 22.2 The physical examination of a man with ED should consider the following

- Any features of hypogonadism
- Manual dexterity – if limited, may preclude physical treatment (e.g. intracavernosal injection)
- Protuberant abdomen
- External genitalia
  - Presence of phimosis, balanitis, Peyronie's disease
  - Testicular volume
- Cardiovascular disease (leg pulses, iliac and femoral bruits)

Box 22.3 Investigations in a patient with diabetes and ED

- Serum testosterone (ideally taken at 9 am) – if libido reduced or hypogonadism suspected
- Serum prolactin and luteinizing hormone (LH) – if serum testosterone subnormal
- Assessment of cardiovascular status if clinically indicated
  - Electrocardiography (ECG)
  - Serum lipids
- Glycosylated haemoglobin, serum electrolytes if clinically indicated

LANDMARK CLINICAL TRIALS

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CASE HISTORY

A 64-year-old man with a 5-year history of type 2 diabetes attends for annual complications assessment. He volunteers no specific symptoms or problems related to his diabetes, and has no past history of significant micro- or macrovascular complications. Only when asked directly about sexual function and libido does he acknowledge a loss of sex drive and frequent difficulties either achieving or maintaining an erection. His BMI is 34, HbA_{1c} 7.7% on metformin 850 mg bid, and BP 158/94 using lisinopril 20 mg and bendroflumethiazide 2.5 mg daily. He is a non-smoker. The nurse undertaking the complications assessment arranges for him and his wife to attend a follow-up appointment to explore the sexual dysfunction. The history is confirmed, although ED seems to be causing tension and distress in their relationship. Physical examination was unremarkable, but an early morning total testosterone level was low at 6 nmol/L. After discussing the relationship between diabetes and ED (which the patient's wife did not realise), they were better informed and less anxious. The treatment options were discussed and the couple opted to try a vacuum device first, combined with testosterone replacement gel.

Comment: This man has features of the metabolic syndrome, which increases the risk of sexual dysfunction and hypogonadism. There is limited scope to reduce or change his medications; the thiazide diuretic may be worse than a calcium channel blocker in aggravating ED. Patients need to be asked sensitively about sexual dysfunction, as they seldom volunteer symptoms unless the health professional gives them an appropriate prompt. Partners and patients need information about the association with diabetes. He is testosterone deficient and symptomatic (loss of libido), so replacement gel is appropriate and may help with ED. Vacuum devices can be very successful once patients become familiar with their use and overcome some embarrassment.

helpful to try and determine whether ED in men with diabetes is of psychogenic origin, but treatment options and the likely response to treatment will be influenced by the extent of arterial and/or neuropathic function and it is important to exclude any associated endocrine disease that may be contributing to ED.

Treatment options

In terms of the management of ED, general and lifestyle factors are important. Regular exercise, weight loss, reduction in alcohol intake and smoking improve endothelial function and self-confidence and raise the overall sense of well-being. Any drugs likely to worsen ED, e.g. β-blockers, may be changed or discontinued to minimise the adverse effects on erectile function. There is generally no need for a psychosexual counsellor, except when there is a failing relationship, severe anxiety (including performance anxiety) and fear of

Phosphodiesterase type 5 (PDE5) inhibitors

- Sildenafil, tadalafil, vardenafil
- Block degradation of cGMP
- More effective on an empty stomach
- Efficacy rates 60–70% in diabetic men
- Contraindicated in men taking oral nitrates

Transurethral or intracavernosal administration of vasoactive compounds

- Papaverine (non-specific PDE inhibitor)
- Phentolamine (α-blocker)
- Alprostadil (prostaglandin E1)
- Transurethral PGE1 via pellets (*M*edicated *U*rethral *S*ystem for *E*rection, MUSE) increases cAMP-mediated smooth muscle relaxation
- Intracavernosal injection of PGE1 may be more effective

Vacuum devices and penile implants

- Non-pharmacological approach using vacuum and a constriction band
- Sensation of cold penis and retrograde ejaculation are disadvantages
- Vacuum device can be very effective in those failing or unable to use PDE5 inhibitor
- Hydraulic, semi-rigid or silicone penile implants are a last resort

Testosterone supplementation

- Clinical significance of low testosterone levels in ED is uncertain
- Supplementation indicated in symptomatic patients with 9 am total testosterone level <8 nmol/L
- Several studies have shown beneficial effect on ED in hypogonadal men
- Formulations include gel, patch, implants, injections, tablets

Figure 22.5 Treatment options for men with diabetes and ED.

intimacy. Several treatment options are available. Each has advantages, disadvantages and limitations (Figure 22.5).

Phosphodiesterase-5 inhibitors work best if taken on an empty stomach, prior to sexual stimulation. Vardenafil and sildenafil have a shorter duration of action (4–6 h) than tadalafil (36–48 h). In placebo-controlled efficacy studies in men with diabetes, all three drugs have similar response rates of 60–70% (versus 15% response to placebo). Patients with diabetes often need the higher doses of PDE5 inhibitors, and all three drugs are contraindicated in men taking oral nitrates because of the risk of excessive reductions in BP. Prostaglandin E1 (PGE1) therapy via transurethral pellet or intracavernosal injection is equally effective (60%) in men with diabetes compared with men without diabetes (Figure 22.6). Priapism is a small risk.

Vacuum devices have been in use since the 1970s. A translucent tube is placed over the penis and air pumped out to draw blood into the erectile tissue. A constriction band around the base of the penis then maintains the erection (Figure 22.7). This simple non-pharmacological approach is surprisingly effective and safe, once patients have become skilled in using the device. Response rates in men with diabetes are around 70%, and the device can work in those who failed to respond to PDE5 inhibitor treatment.

Figure 22.6 Intracavernosal injection of alprostadil, self-injected.

Female sexual dysfunction

Sexual dysfunction seems to be much less common in women with diabetes than in men, but there is an increased risk of vaginal dryness and impaired sexual arousal. Menstrual irregularities are also common in women with diabetes, particularly in those with obesity and poor glycaemic control. Insulin requirements alter around the time of menstruation in about 40% of women with diabetes; the majority need more insulin, but about 10% require less. Type 2 diabetes and impaired glucose tolerance (IGT) are common in women with the polycystic ovary syndrome (PCOS), features of which include oligomenorrhoea or amenorrhoea, polycystic ovaries on ultrasound examination, obesity, hirsutism and raised circulating androgen levels (Box 22.4). Both type 2 diabetes and PCOS share an association with insulin resistance. It is thought that hyperinsulinaemia stimulates androgen synthesis and thecal hypertrophy in the ovary.

Genitourinary infections are common in women with diabetes. Vaginal candidiasis is especially frequent in poorly controlled subjects; it can be irritating and painful and may interfere with sexual activity. Treatment involves improving control, and local or oral antifungal agents, including fluconazole. Other genital infections, such as genital herpes and pelvic inflammatory disease, occur in women with diabetes, but possibly no more frequently than in the general female population. However, urinary tract infections are frequent in patients with poorly controlled diabetes, and especially in those with autonomic neuropathy and bladder distension (Box 22.5). Vulvo-vaginal candidiasis is a recognised side effect of the new SGLT2 inhibitors for treating type 2 diabetes.

Contraceptive advice is essential in diabetes. On the available evidence, low-dose (<30μg oestradiol) combined oral contraceptives can be used safely in type 1 and type 2 diabetes; all women who take the pill should have their blood pressure and serum lipids reviewed regularly. Progesterone-only pills are also suitable for use in diabetes, but they may cause menstrual irregularities. As these are not thought to be associated with vascular disease, they are often used more in older women or in those with diabetic complications or risk factors (Figure 22.8).

Box 22.4 Gynaecological factors relevant to women with diabetes or IGT

- Vaginal dryness
- Menstrual irregularities
- Infection
- Contraception
- Hormone replacement therapy
- Pregnancy
- Association with polycystic ovary syndrome (PCOS)

Figure 22.7 A vacuum device with constriction rings.

Box 22.5 Genitourinary infections in women with diabetes

- Vaginal candidiasis
- Vaginal warts, herpes
- Pelvic inflammatory disease
- Urinary tract infections

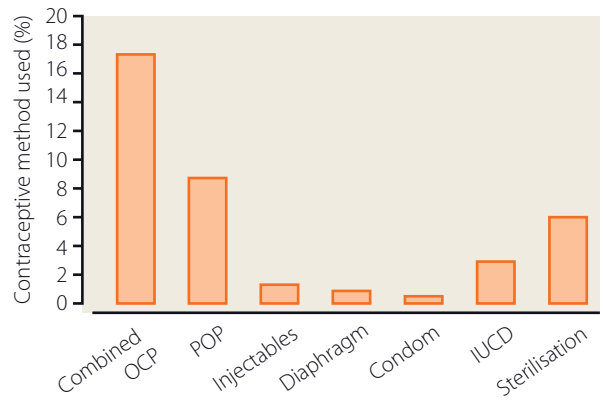

Figure 22.8 Patterns of contraceptive use in women with type 1 diabetes in the UK. OCP, oral contraceptive pill; POP, progesterone-only pill; IUCD, intrauterine contraceptive device. From Lawrensen et al. Diabetic Med 1999; 16: 395–399.

KEY WEBSITES

- http://diabetes.niddk.nih.gov/dm/pubs/sup/
- www.diabetes.co.uk/diabetes-erectile-dysfunction.html
- www.nhs.uk/Pathways/diabetes/Pages/Landing.aspx
- SIGN Guidelines: www.SIGN.ac.uk

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Chapter

23

Gastrointestinal problems in diabetes

KEY POINTS

- Gastrointestinal symptoms are common in people with diabetes and usually occur in patients with multiple microvascular complications.
- Although associated with autonomic neuropathy, there is often a poor correlation between symptoms and results of objective tests.
- The most troublesome problems are vomiting due to gastroparesis, diarrhoea and constipation. Symptoms fluctuate and usually remain stable with time.
- The cornerstones of treatment are agents that affect gastrointestinal motility but jejunal feeding is occasionally required for severe cases of gastroparesis.

Disordered gastrointestinal motor function occurs in both type 1 and type 2 diabetes and can result in symptoms of nausea, vomiting, diarrhoea or constipation, malnutrition, poor glycaemic control and delayed absorption of orally administered drugs (Figure 23.1). Gustatory sweating, typically affecting the head and neck, and postprandial hypotension may also occur. Traditionally, this has been attributed to irreversible autonomic neuropathy, but acute changes in blood glucose also play a role. For example, hyperglycaemia delays gastric emptying by up to 15 minutes, slows gallbladder contraction and small intestinal transit, and inhibits colonic reflexes (Figure 23.2); while hypoglycaemia accelerates gastric emptying (Figure 23.3). The mechanisms are unclear. Every effort to improve glycaemic control should be made in symptomatic patients, including consideration of continuous subcutaneous insulin infusion (CSII).

Symptoms

Gastrointestinal symptoms are common in diabetes, possibly more than in the general population (Table 23.1). However, there is an imprecise relationship between the symptoms and either demonstrable motor dysfunction (e.g. gastric emptying time) or autonomic neuropathy. Among the additional factors that influence symptoms are hyperglycaemia (which increases the perception of visceral sensation, such as gut fullness); and drugs such as metformin, acarbose and incretins (exenatide and liraglutide), which can cause diarrhoea and faecal incontinence. There is also a link with psychological stress and psychiatric symptoms of anxiety and depression which doubled the prevalence of GI symptoms in one cross-sectional study. It is important to exclude other endocrine disease which can cause altered gastrointestinal function such as hyper- and hypothyroidism.

Oesophagus

Oesophageal transit is delayed in about 30–50% of subjects with diabetes (mostly because of impaired peristalsis) and is associated with dysphagia, heartburn and chest pain (Figure 23.4). Endoscopy is required to exclude other disorders, such as carcinoma and candidiasis. Minimal symptoms do not require treatment; indeed, no treatment, including prokinetic drugs, has yet been shown to be effective for more severe symptoms attributable to hypomotility. Consider discontinuation of drugs such as calcium channel blockers which can worsen heartburn. Reflex oesophagitis is also exacerbated by obesity.

Gastroparesis

Delayed gastric emptying (gastroparesis) of a modest extent occurs in up to 50% of people with diabetes of long standing. Symptoms of gastroparesis are characteristically worse postprandially, include nausea, vomiting, abdominal discomfort and/or fullness and anorexia, and are reported in 5–12% of all patients with diabetes. Symptoms are often stable for up to 12 years and do not appear to be associated with mortality. They tend to be worse with solids rather than liquids.

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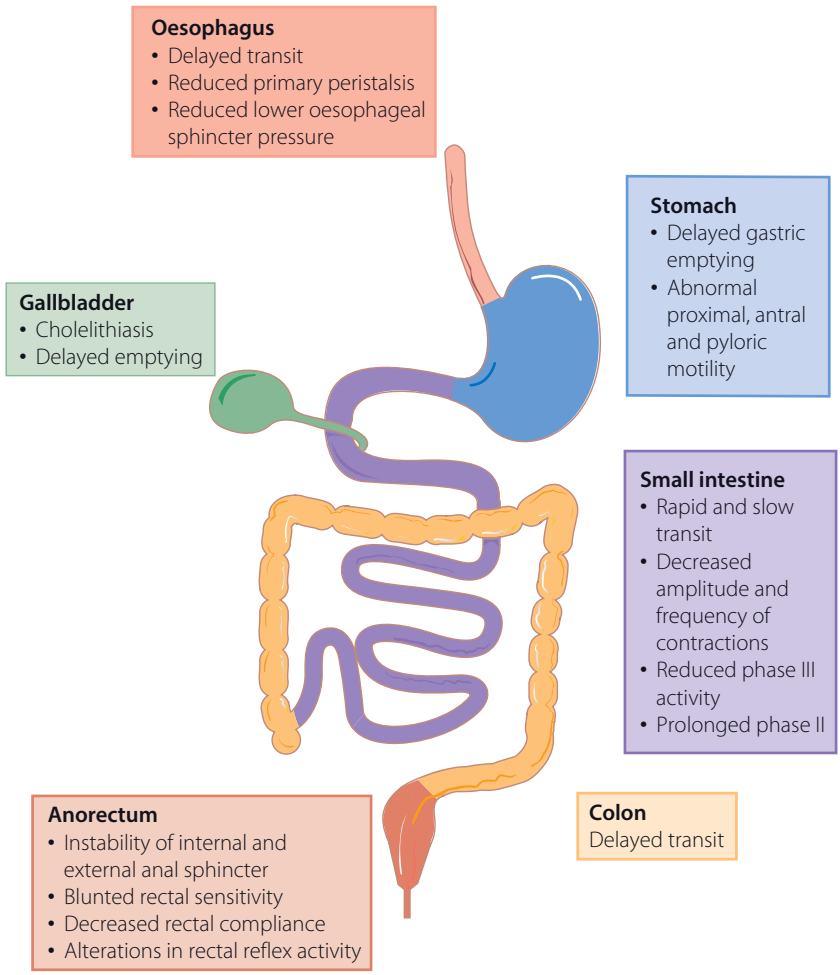

Figure 23.1 Motility disorders associated with diabetes at various levels of the gastrointestinal tract.

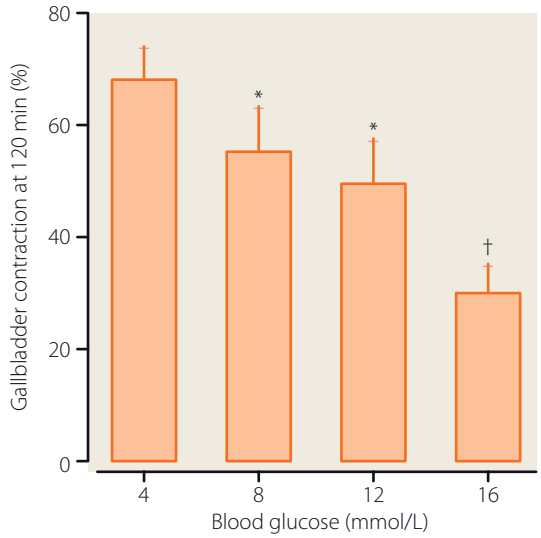

Figure 23.2 Dose-dependent effect of hyperglycaemia on postprandial gallbladder contraction in healthy subjects. *p < 0.05 compared with 4 mmol/L; p < 0.05 compared with 4, 8 and 12 mmol/L. From Rayner et al. Diabetes Care 2001; 24: 371–381.

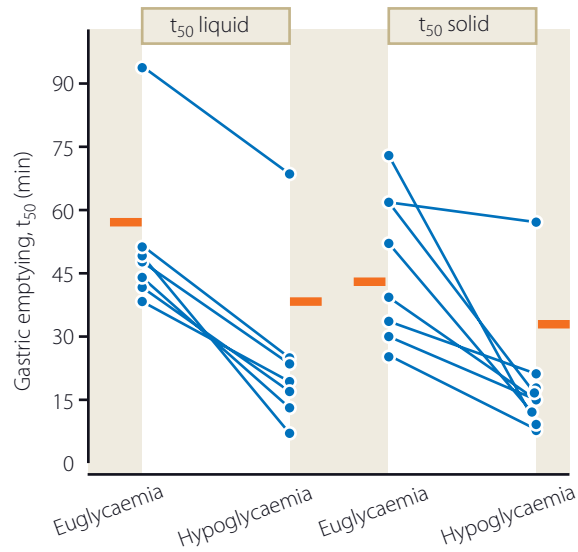

Figure 23.3 Effect of insulin-induced hypoglycaemia on gastric emptying (50% emptying, t50) of 200 g solid (processed beef and vegetables) and liquid (150 mL 100% dextrose in water) in eight subjects with uncomplicated type 1 diabetes (mean ± SD). From Scharcz et al. Diabetic Med 1993; 10: 660–663.

Table 23.1 Prevalence of gastrointestinal symptoms in diabetes mellitus and controls, based on a population-based study of 423 patients with diabetes in Australia (22 type 1, 401 type 2).

	Prevalence rate (%)		
	Controls (*n* = 8185)	**Patients with diabetes (*n* = 423)**	**Adjusted odds ratios with 95% CI**
Abdominal pain/discomfort	10.8	13.5	1.63 (1.21–2.20)
Postprandial fullness	5.2	8.6	2.07 (1.43–3.01)
Heartburn	10.8	13.5	1.38 (1.03–1.86)
Nausea	3.5	5.2	2.31 (1.45–3.68)
Vomiting	1.1	1.7	2.51 (1.12–5.66)
Dysphagia	1.7	5.4	2.71 (1.69–4.36)
Faecal incontinence	0.8	2.6	2.74 (1.40–5.37)
Oesophageal symptoms	11.5	15.4	1.44 (1.09–1.91)
Upper dysmotility symptoms	15.3	18.2	1.75 (1.34–2.29)
Any bowel symptom	18.9	26.0	1.84 (1.46–2.33)
Diarrhoea symptoms	10.0	15.6	2.06 (1.56–2.74)
Constipation symptoms	9.2	11.4	1.54 (1.12–2.13)

From Horowitz et al. J Gastroenterol Hepatol 1998; 13: S239–245.

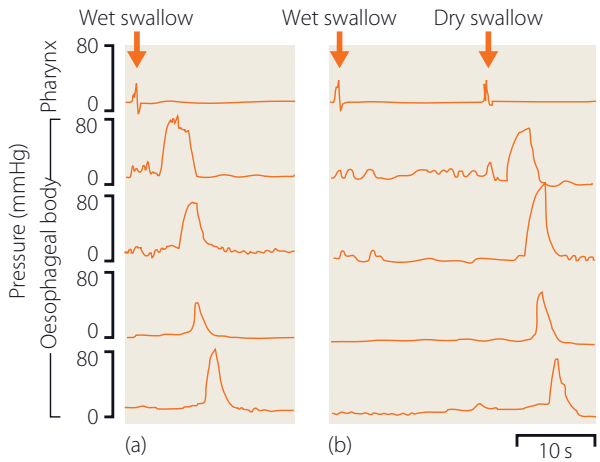

Figure 23.4 Wet swallow-induced oesophageal peristalsis in a healthy subject (a) and in a patient with long-standing insulin-dependent diabetes (b). In the subject with diabetes, the swallow-induced peristaltic wave has insufficient force to propel the water bolus distally (failed peristalsis). A subsequent dry swallow is associated with normal peristalsis, and clears the oesophagus. Adapted from Holloway et al. Am J Gastroenterol 1999; 94: 3150–3157.

The pathophysiology is a combination of vagal neuropathy and increased gastrointestinal hormone levels such as glucagon. There is often a history of long-standing poor glycaemic control.

Examination can reveal epigastric distension and a succussion splash an hour or two after a liquid meal if the stomach is grossly dilated. Radio-isotope scintigraphy is the gold standard method for measuring gastric emptying. Ideally, this should be performed during normoglycaemia and with a dual isotope assessment of both solid and liquid emptying. The drawbacks of this test are its expense and significant radiation exposure. A carbon 13 breath test has acceptable specificity and sensitivity and much less radiation.

Diagnosis is often based upon the patient history, in the context of other diabetic complications, especially autonomic neuropathy, and investigations should be carried out to rule out other conditions. Of these oesophagogastroduodenoscopy (OGD) is the most helpful. It is important to remember that some drugs can delay gastric emptying and should be avoided (Box 23.1).

Treatment of symptomatic gastroparesis is difficult; it involves improving glycaemic control, eating small meals often (reducing solid components) and administration of prokinetic drugs such as domperidone, metoclopramide and erythromycin (possibly better given intravenously for acute

Box 23.1 List of agents which can exacerbate gastroparesis

- Opiates
- Anticholinergics (including tricyclics)
- Calcium channel blockers,
- Proton pump inhibitors
- β-Adrenergic agonists
- Dopaminergic agents
- Nicotine

CASE HISTORY

A 32-year-old woman with type 1 diabetes of 20 years' duration with known diabetic nephropathy (eGFR 42 mL/min/1.73 m^2) and treated proliferative retinopathy was admitted with a severe pneumonia requiring ventilation and temporary dialysis. Her diabetes control had been poor for many years (HbA_{1c} > 12%; 108 mmol/mol) and she had suffered bouts of vomiting prior to her admission. Following transfer from the ITU, the vomiting became much worse, requiring regular IV insulin infusion and fluids with highly erratic blood glucose control.

Comment: This story is typical of diabetic gastroparesis with an intermittent but more or less stable problem of vomiting made much worse by her acute illness. The protocol used for her IV infusion resulted in regular periods of no insulin and undoubtedly contributed to her symptoms and poor glycaemic control. Because of this, she was commenced on CSII. Regular IV metoclopramide then continuous subcutaneous cyclizine infusion were given with little benefit. Nasogastric drainage and then feeding were unsuccessful and were followed by insertion of a percutaneous jejunostomy. Her condition stabilised and she left hospital after a 4-month admission.

Table 23.2 Management of diabetic gastroparesis

General measures	Oral prokinetic drugs	Endoscopy indicated if:	Severe episodes	Nutrition
Maintain good glycaemic control	Metoclopramide	Haematemesis	Usually require hospital admission	Consider intravenous for short term
Eat small frequent meals	Domperidone	Other pathology or causes of obstruction suspected	Intravenous rehydration	Consider intrajejunal via PEJ tube long term
Avoid high-fibre/high-fat meals	Erythromycin		Intravenous prokinetic drugs: Metoclopramide Erythromycin Ondansetron	Experimental treatments: Endoscopic pyloric injection of botulinum toxin Gastric pacemaker insertion
Consider homogenised diet	Cyclizine		Nasogastric tube and drainage	
Stop smoking Reduce alcohol				

Table 23.3 Drug treatments for diabetic diarrhoea

Agent	Dosage
Opioid derivatives	
Codeine phosphate	30 mg, three to four times daily
Loperamide hydrochloride	2 mg, three to four times daily
Broad-spectrum antibiotics (for bacterial overgrowth)	
Oxytetracycline	250 mg, four times daily for 5–7 days
Erythromycin	250 mg, four times daily
α2-Adrenergic agent	
Clonidine	0.3–0.6 mg, twice daily
Somatostatin analogue	
Octreotide	50–100 μg subcutaneously, two to three times daily

episodes because of tolerance). Severely affected patients may need admission to hospital for intravenous fluids, control of diabetes and possible nasogastric feeding. Placement of a feeding jejunostomy (PEJ) tube to maintain nutrition may be required, but surgical drainage and bypass should be avoided. There have been trials of gastric electrical stimulation via an implanted pacemaker but the results are inconclusive and more studies are required. Because many of these patients may have diabetic nephropathy and a diminished GFR, care must be taken with doses of drugs in order to avoid side effects.

Small bowel

Autonomic neuropathy and sometimes colonisation of the hypomotile small bowel by colonic bacteria contribute to 'diabetic diarrhoea' but other factors probably play a role. Classically, the diarrhoea is intermittent and worse at night. Bouts that last several days may be followed by remissions. The diagnosis is by exclusion, and other possible causes of diarrhoea, such as drugs (metformin, acarbose, antibiotics and alcohol), chronic pancreatic insufficiency with malabsorption, and coeliac disease must be considered.

Treatment of diabetic diarrhoea is by opioid derivatives (e.g. loperamide) or a broad-spectrum antibiotic if bacterial overgrowth is suspected or proven by hydrogen breath test. Troublesome diarrhoea, especially when watery, may respond to the α-adrenergic agonists clonidine or limidine (unlicensed indication). The long-acting somatostatin analogue octreotide may be helpful when other measures have failed (Table 23.3).

Large bowel

Constipation is also common in patients with diabetes and autonomic neuropathy and poor glycaemic control, though it is usually mild. A thorough history should be taken, including that of drug intake (many narcotics, antihypertensives and antidepressants can cause constipation). Thyroid function and serum calcium and potassium levels should be assessed to exclude metabolic disorders. Other serious pathology, such as colonic carcinoma, must be excluded. If constipation requires treatment, fibre and bulking agents are the first choice, and stimulant laxatives (e.g. senna), osmotic laxatives (e.g. lactulose) or prokinetic drugs are also usually effective.

KEY WEBSITES

- American Gastroenterology Society: www.gastro.org
- American Motility Society: www.motilitysociety.org
- SIGN Guidelines: www.SIGN.ac.uk

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Chapter

24

Skin and connective tissue disorders in diabetes

KEY POINTS

- Diabetes affects cutaneous microvascular function, collagen synthesis and structure, and therefore some characteristic skin lesions are recognised complications.
- Diabetic 'shin spots' are pigmented, atrophic macules, 2–3 mm in diameter, common over the shins.
- Necrobiosis lipoidica diabeticorum is rare but seen mainly in people with diabetes aged 40–60 years.
- Trigger finger, cheiroarthropathy, and the diabetic hand syndrome are less common examples of conditions that affect the hands in patients with diabetes.
- Acanthosis nigricans is associated with numerous conditions, including diabetes, and often occurs around the axilla, groin or neck.
- Chronic fungal infections of the nailfolds (paronychia) are common in patients with diabetes.

Diabetes affects the cellular biochemistry of skin and connective tissues, in particular collagen synthesis and structure, as well as cutaneous microvascular blood flow. Several non-infective skin conditions are associated with type 1 and/or type 2 diabetes (Box 24.1). Diabetic dermopathy ('shin spots') is relatively common (reportedly present on the legs in up to 10–15% of patients) and is probably due to microangiopathy. In contrast, necrobiosis lipoidica diabeticorum is rare (<0.3% of patients) and occurs mostly in the 40–60 year age group. Whether granuloma annulare is associated with diabetes is unclear, but the strongest evidence suggests a link with type 1 diabetes. There are also a number of skin or nail infections (fungal and bacterial) associated with diabetes, e.g. paronychia.

Diabetic dermopathy (also known as spotted leg syndrome or 'shin spots') is characterised by hyperpigmented, atrophic macules, a few millimetres in diameter, which typically occur as clusters on the shins (Figure 24.1). They are more common in older patients with diabetes, especially those over the age of 50 years (one or two such lesions also occur in up to 3% of people without diabetes). The spots slowly become well circumscribed, atrophic, brown and scaly scars. The usual site is the pretibial region, but forearms, thighs and bony prominences may be involved. There is no effective treatment, but the spots tend to resolve over 1–2 years.

Box 24.1 Non-ulcerative, non-infective skin conditions associated with diabetes

- Diabetic dermopathy ('shin spots')
- Necrobiosis lipoidica diabeticorum
- Acanthosis nigricans
- Diabetic bullae
- Granuloma annulare
- Yellow nails
- Plantar erythema

Necrobiosis lipoidica diabeticorum (NLD) is rare but occurs almost exclusively in patients with diabetes, typically in the 40–60 year age group, and is more common in women. NLD appears as bilateral red-brown papules on the anterior surface of the shins (Figure 24.2). The lesions gradually enlarge to form yellow, atrophic plaques with a translucent lustre and stippled with telangiectasia. Ulceration occurs in about 25%. The lesions are partially or completely anaesthetic. The aetiology of NLD is unknown, and treatment options include topical or systemic steroids, antiplatelet therapy, photodynamic therapy or anti-TNF drugs (e.g. infliximab).

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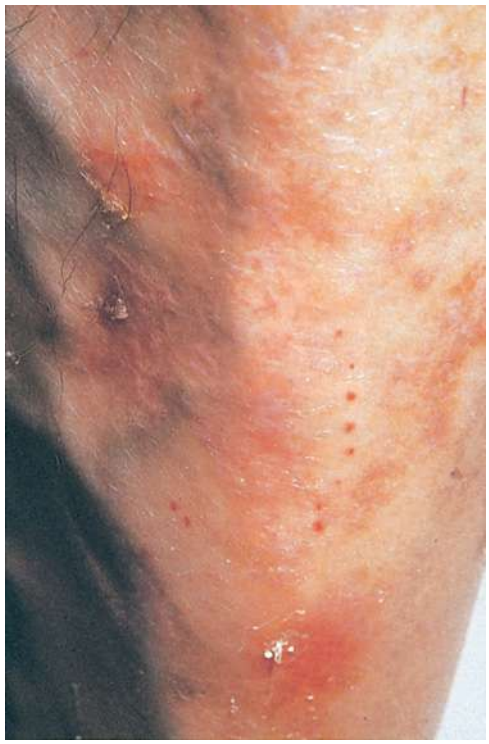

Figure 24.1 Diabetic dermopathy or 'shin spots'. Courtesy of Professor J Verbov, University of Liverpool, Liverpool, UK.

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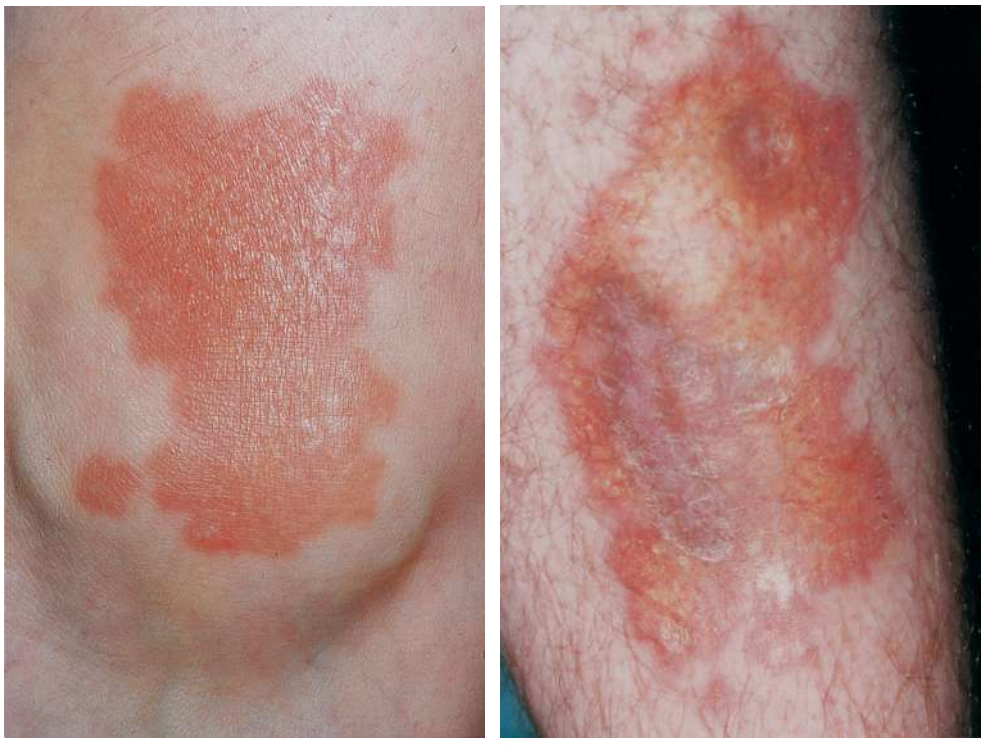


(a) (b)

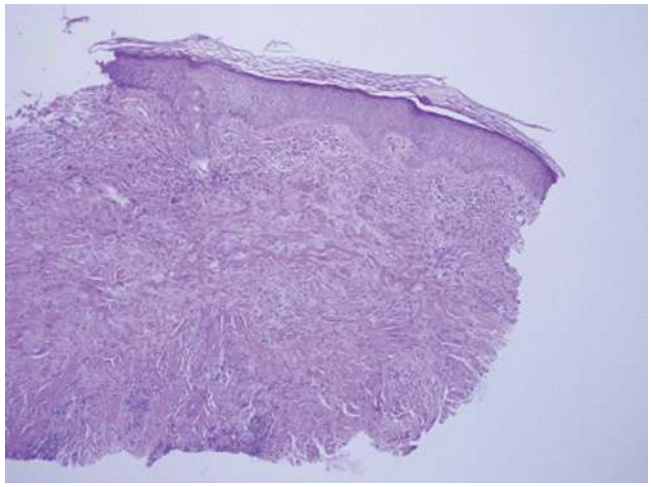
Figure 24.2 Necrobiosis lipoidica diabeticorum (NLD). (a) An early lesion on the ankle, and (b) a long-standing patch of NLD illustrating a yellow atrophic appearance with telangiectasia.

Histologically, NLD is characterised by hyaline degeneration of collagen in the dermis ('necrobiosis') with surrounding fibrosis and diffuse histiocytic infiltrate (Figure 24.3). There may be evidence of a granulomatous reaction with giant cells similar to that seen in sarcoidosis.

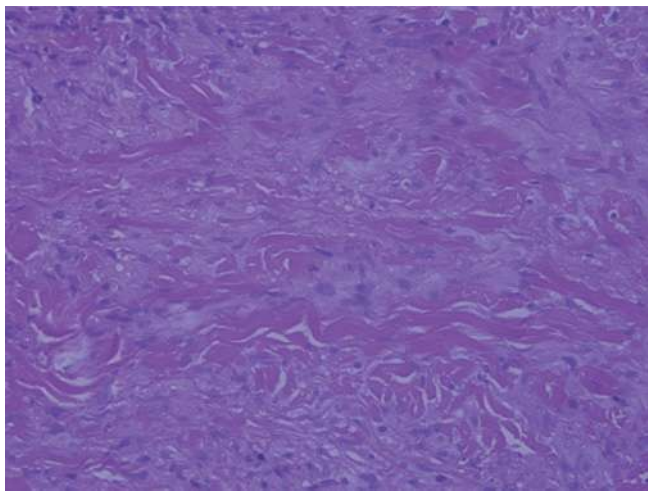
The skin is generally thickened in diabetes, probably because of glycation of dermal collagen and cross-linking to form advanced glycation endproducts (AGEs). Usually, this is clinically insignificant, but the combination of thickened, tight and waxy skin with limited joint mobility (cheiroarthropathy) is present in 30–40% of type 1 diabetic patients. This can lead to stiff and painful fingers. Thickening over the dorsum of the fingers is termed 'Garrod's knuckle pads' (Figure 24.4).

A typical sign of the 'diabetic hand syndrome' is the 'prayer sign', in which limited joint mobility because of thickened and waxy skin does not allow the patient to press their palms together (Figure 24.5).

Dupuytren's contracture occurs in up to half of patients with diabetes, especially in the elderly and those with long-standing disease; it often co-exists with cheiroarthropathy (Figure 24.6).



(a)



(b)

Figure 24.3 Histology of necrobiosis lipoidica diabeticorum (NLD). (a) Low-resolution (×100) and (b) high-resolution (×400) images from a punch biopsy. The epidermis shows a focus of mild hyperkeratosis which is focally disrupted. There is irregular necrobiosis of the dermal collagen extending from the epidermis to the deep margin of the specimen, with surrounding inflammatory infiltrate of histiocytes together with lymphocytes, plasma cells and occasional giant cells. Reproduced with permission from Lee et al. Int Med J 2007; 37: 782–783.

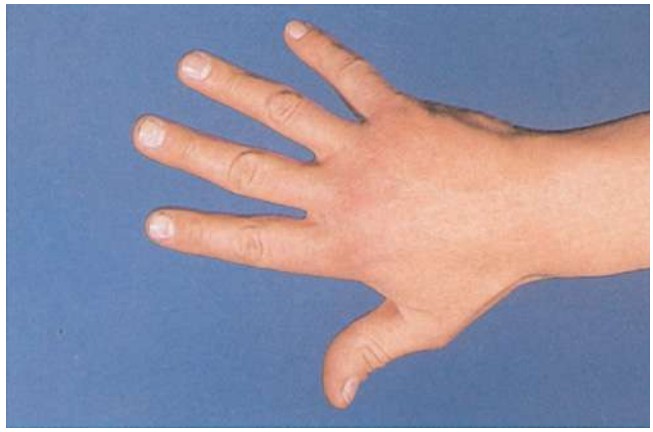


Figure 24.4 Garrod's knuckle pads.

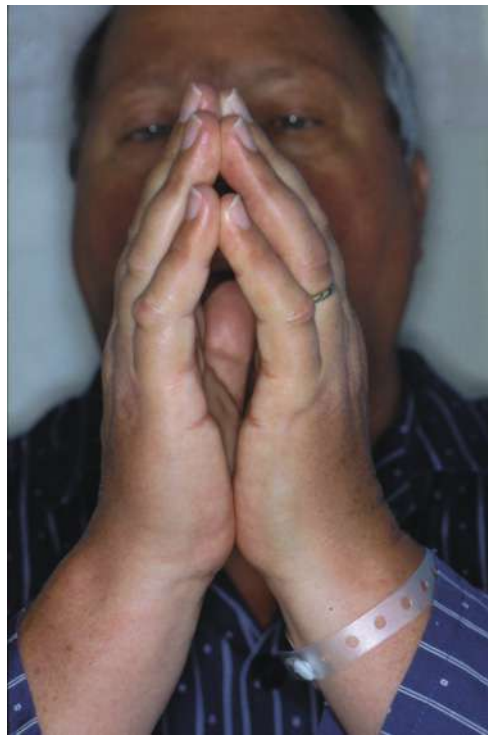


Figure 24.5 The 'prayer sign', another feature of cheiroarthropathy.

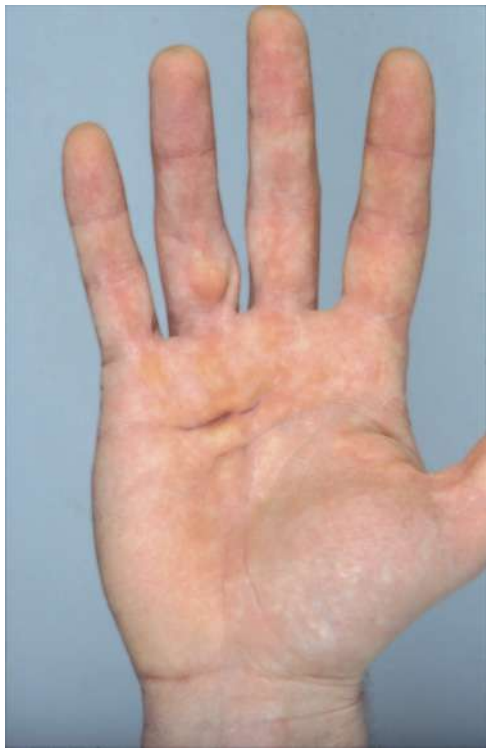


Figure 24.6 Dupuytren's contracture. Courtesy of Dr G Gill, University of Liverpool, Liverpool, UK.

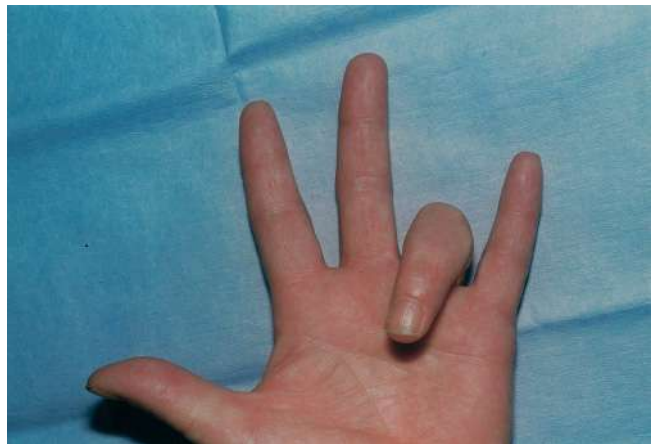


Figure 24.7 Trigger finger in a patient with diabetes.

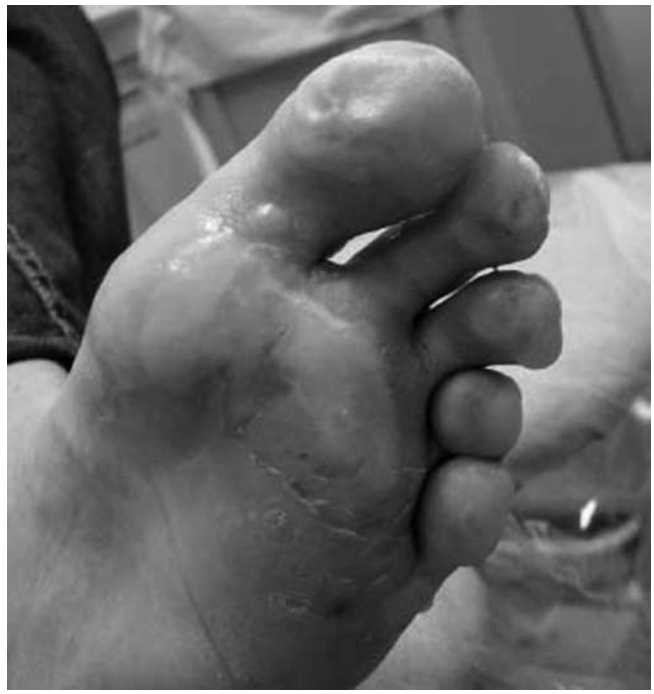


Figure 24.8 Diabetic bullae – blistering of the foot. Reproduced with permission from Bristow. Diabet Metab Res Rev 2008; 24(Suppl 1): S84–S89.

'Trigger finger' occurs when there is intermittent locking of the finger due to stenosing flexor tenosynovitis (Figure 24.7). It is often associated with diabetes. Nodular swelling and thickening of the tendon sheath can often be palpated. It responds to steroid injection. Adhesive capsulitis of the shoulder (more often called 'frozen shoulder') is another non-articular fibrosing disorder that occurs more commonly in patients with diabetes than in the general population; it results in pain and limitation of movement.

Diabetic bullae are painless blisters which appear spontaneously anywhere on the feet in patients with diabetes (Figure 24.8). The lesions are rare, but occur most often over the toes and heels and seem to be more common among adult males. The blisters can range in size from a few millimetres to centimetres in diameter. There may be an association with neuropathy and retinopathy. Histologically, the lesions usually arise as intraepidermal blisters containing clear fluid, but occasionally the blisters are subepidermal. Immunofluorescent studies have failed to identify a cause.

Acanthosis nigricans is associated with numerous conditions, including obesity, type 2 diabetes, polycystic ovary syndrome and insulinoma. It is a hyperpigmented velvety overgrowth of the epidermis, which usually occurs in the flexural areas of the axilla, groin and neck (Figure 24.9). Increased circulating insulin levels act via insulin-like growth factor-1 (IGF-1) receptors in the skin to stimulate growth.

Various other skin problems are associated with long-standing diabetes but are not specific to diabetes. These include bacterial infections (e.g. boils and sepsis caused by *Staphylococcus aureus*), *Candida albicans* infections (e.g. vulvovaginitis, balanitis, intertrigo and chronic paronychia) and tinea (dermatophyte fungal infections) (Figure 24.10). Note

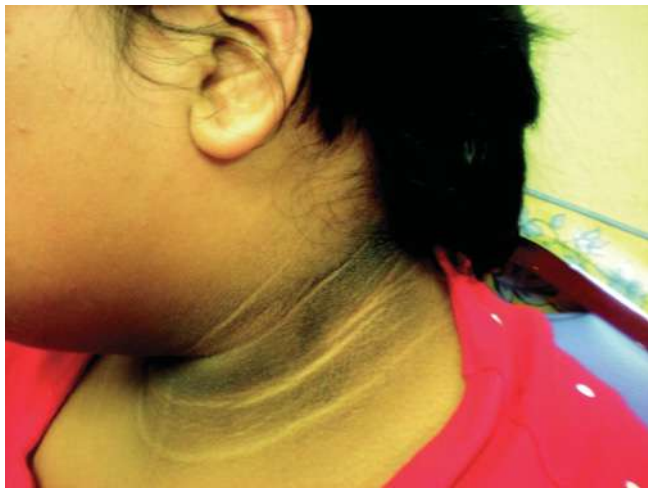


Figure 24.9 In children, acanthosis nigricans is associated with obesity (± type 2 diabetes), insulin resistance and hyperinsulinaemia. Reproduced with permission from Marimuthu et al. Arch Dis Child 2009; 94: 477.

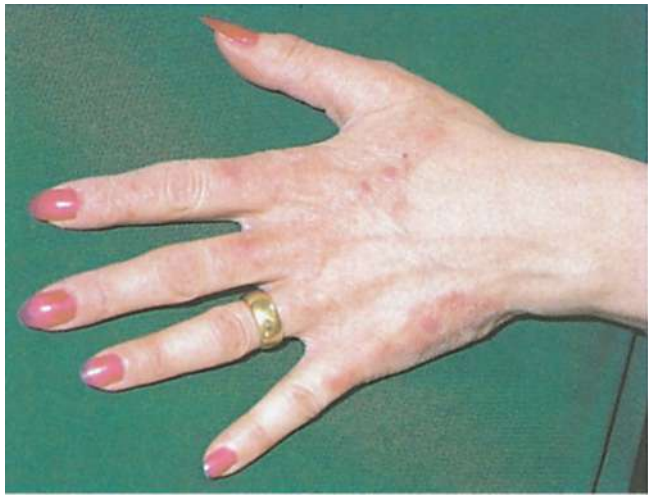


Figure 24.10 Tinea manus, showing the characteristic erythematous, scaly margin.

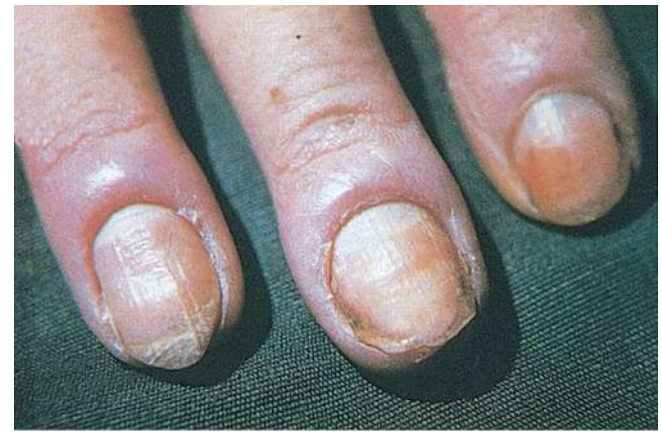


Figure 24.11 Chronic paronychia caused by *Candida albicans*.

also the occurrence of neuropathic and ischaemic foot ulcers in diabetes (see Chapter 21), and the dry skin caused by decreased sweating with autonomic neuropathy.

Chronic paronychia presents with swelling and erythema around the nailfolds, with a discharge (Figure 24.11). Severe involvement may produce onycholysis. Treatment is by keeping the fingers dry and the use of antifungal drugs; systemic drugs such as terbinafine, as well as topical medications, may be necessary.

KEY WEBSITES

- http://diabetes.webmd.com/guide/skin-problems
- www.diabetes.org/type-1-diabetes/skin-complications.jsp
- www.telemedicine.org/dm/dmupdate.htm
- SIGN Guidelines: www.SIGN.ac.uk

CASE HISTORY

A 62-year-old man with type 2 diabetes of 11 years' duration, complicated by hypertension and diabetic nephropathy, presented to his family doctor with a skin lesion over the front of his left shin. HbA_{1c} 8.6% on insulin + metformin. The plaque lesion had been present for 8 months and was gradually enlarging. It was giving few, if any, symptoms. Examination confirmed an 8 cm irregular atrophic patch with yellowish pigmentation, which the family doctor first thought was a fungal infection. There were no other skin rashes, and the feet and lower limb circulations were generally good. Topical antifungal cream had no effect and the patient was referred to the dermatologist, who diagnosed necrobiosis lipoidica diabeticorum. A punch skin biopsy confirmed a chronic granulomatous dermatitis, typical of NLD.

Comment: NLD can be confused with fungal infection. If there is diagnostic uncertainty, a skin biopsy should be performed, as in this case. The differential diagnoses histologically include sarcoid and cutaneous lymphoma. NLD is typical in this age group and this location; it may occur bilaterally on the legs. Secondary ulceration is not uncommon. The lesion may not improve with better glycaemic control. Rarely, squamous cell carcinoma can arise from NLD. Steroids (topical cream or intralesional injection) are the mainstay of treatment, but photodynamic therapy and anti-TNF drugs have been used with some success.

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Chapter

25 Psychological and psychiatric problems in diabetes

KEY POINTS

- As with any chronic disease diagnosis, children and adults with newly diagnosed diabetes can develop adjustment disorders.
- Adults with both type 1 and type 2 diabetes have around twice the prevalence of depression of the age-matched non-diabetic population. Anxiety is also common and can exacerbate glycaemic control. Cognitive dysfunction can be demonstrated in children and adults with diabetes and is related to chronic hyperglycaemia.
- Hypoglycaemia can cause short-term memory loss but there are no conclusive data relating severe episodes to long-term cognitive dysfunction.
- Eating disorder is a particular problem for girls with type 1 diabetes but abnormal eating behaviours are also common in type 2 diabetes.

Particular groups of patients with diabetes are at risk of different psychological problems (Table 25.1). Many children show remarkable resilience to the diagnosis of diabetes, but about one-third have some temporary psychological distress, mostly 'adjustment disorders' such as difficulty in sleeping, depression, social withdrawal and anxiety. This generally subsides within 6 months. Surprisingly little is known about psychological problems in adults with recent-onset diabetes.

Psychological problems in diabetes

Most children and adolescents function well psychologically during the course of their diabetes, although there is an increased frequency of psychiatric disorders by 10 years' diabetes duration, mainly severe depression and anxiety. Prevalence studies in adults with diabetes have revealed that depression and anxiety are about twice as high as in the general population and affect between 15% and 25%. The highest rates are in hospitalized patients, those with macrovascular disease, chronic foot ulceration, proliferative retinopathy and previous psychopathology; females are more susceptible than males. A longitudinal study of 500 type 2 patients who were seen three times over 18 months suggested that depressive symptoms remained relatively stable and were treated, but diabetes-related distress fluctuated and was not as well recognised or addressed. There is a weak relationship between metabolic control and mood disorder (Table 25.2). Depression may precede and predict the development of type 2 diabetes (Figure 25.1).

Table 25.1 Groups with diabetes at risk of developing psychological problems

Group with diabetes	Psychological problem
Children and adolescents at onset of diabetes (little known about adults with recent-onset diabetes)	Temporary adjustment disorder – somatic complaints, social withdrawal, sleeping disorder, anxiety, depression
Older adults with established diabetes, especially when hospitalized, in females and those with past psychopathology	Higher frequency of depression (but comparable to other chronic illnesses)
Patients with macrovascular disease, chronic foot ulceration and proliferative retinopathy	Depression, poor quality of life, psychological distress
Children with repeated hypoglycaemia (especially when onset of diabetes is <5 years of age)	Mild impairment of cognitive functioning – visuospatial/verbal defects, etc.
Later-onset children and adolescents	Verbal IQ and academic achievement lowered
Adults with chronic hyperglycaemia	Defects in psychomotor tasks, attention, learning and memory

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Table 25.2 Interactions between metabolic control and concurrent depression

Concurrent depression	Poor glycaemic control
Worsens metabolic control	Worsens depression
Poor concordance with therapy	Reduces response to antidepressants
Reduced quality of life	
Increased healthcare expenditure	

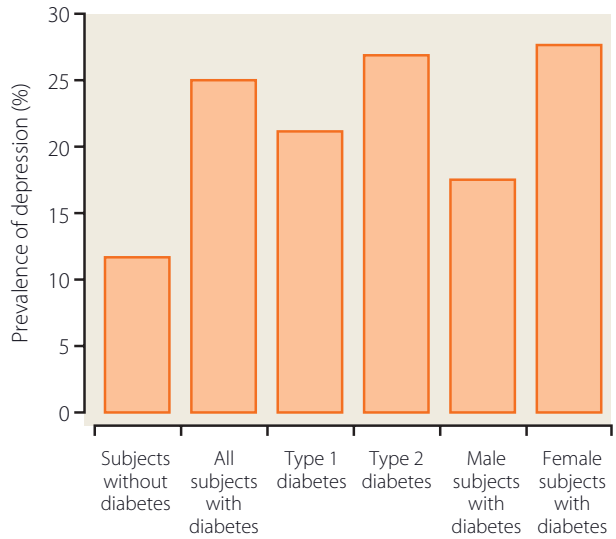

Figure 25.1 The increased prevalence of depression in subjects with diabetes compared with subjects without diabetes. The data are from a meta-analysis of 42 studies. From Anderson et al. Diabetes Care 2001; 24: 1069–1078.

The features of moderate or severe depression should be recognised by diabetologists (Box 25.1), although cases are often missed in the setting of a diabetic clinic and because some symptoms of depression overlap with those of diabetes (e.g. weight loss, lethargy and loss of libido).

Anxiety is also more frequent in those with diabetes. Some of the symptoms of anxiety, such as sweating, tremor, palpitations, nausea and headache, may be confused with hypoglycaemia by both patients and doctors (Box 25.2). Fear of hypoglycaemia is a major problem and may be severe enough to meet the criteria for phobia. Fear of needles can also cause significant anxiety in diabetes. Anxiety may exacerbate hyperglycaemia or cause hypoglycaemia in diabetes through the effects of stress hormones, such as catecholamines and cortisol, and by the disruption of self-care behaviours.

Cognitive dysfunction

Some studies have found that children diagnosed under the age of 5 or 6 years are most at risk of cognitive dysfunction with defects in visuospatial ability (copying, solving jigsaws),

Box 25.1 Depressive symptoms

Symptoms must be present for at least 2 weeks to make the diagnosis

- Depressed mood most of the day, nearly every day (also anxiety, irritability)
- Loss of interest or enjoyment
- Decreased appetite and weight loss
- Loss of libido
- Insomnia (early morning wakening, initial insomnia or interrupted sleep) or hypersomnia
- Fatigue or loss of energy
- Psychomotor retardation
- Poor concentration
- Reduced self-esteem and confidence
- Thoughts of hopelessness, worthlessness or guilt
- Suicidal ideas or attempts

Box 25.2 Typical anxiety symptoms

Emotion	• Fear, anxiety, panic
Physical symptoms	• Sweating, tremor, tachycardia, breathlessness, muscular tension, difficulty swallowing, numbness, tingling, nausea, dizziness, dry mouth, headache, epigastric discomfort, etc.
Thoughts	• Catastrophic thoughts, e.g. 'I'm going to die', 'I'm going to collapse', 'I'm going to make a fool of myself', 'I'm going to lose control' • Overestimation of danger
Behaviour	• Avoidance of specific situations • Escape from situations • Safety-seeking behaviour, e.g. never going into situations alone

which by adolescence can progress to impaired learning and memory, verbal ability and school achievement (Figure 25.2). Links have been made with number of episodes of severe hypoglycaemia because the developing brain might be more vulnerable to insult. However, not all studies support this and there is increasing evidence that chronic hyperglycaemia might be a greater problem. Other factors such as school attendance (which might be affected in those having recurrent hypoglycaemia) and home problems (including psychosocial) have to be taken into account and were often neglected in earlier studies.

In adults with type 1 diabetes and older adults with type 2 diabetes, chronic hyperglycaemia is associated with defects in psychomotor tasks, attention, learning and memory (Table 25.3). The reasons are probably multiple: micro-

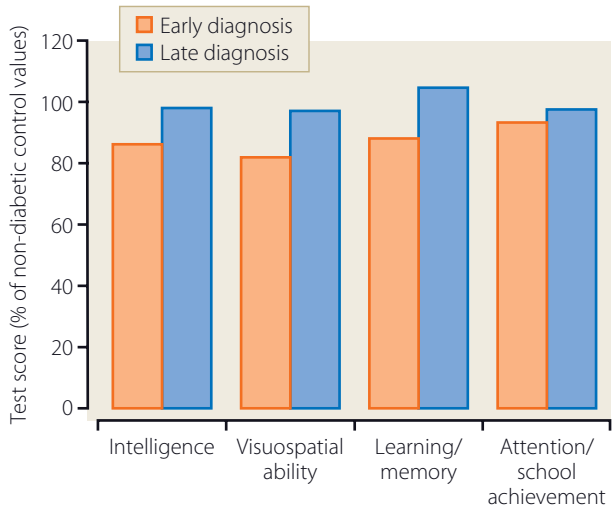

Figure 25.2 The impairment of cognitive ability in 125 adolescents with type 1 diabetes diagnosed at <5 years of age (early diagnosis), compared with those diagnosed at >5 years of age (late diagnosis). From Ryan et al. Pediatrics 1985; 75: 921–927.

Table 25.3 Changes in cognitive domains strongly linked to type 1 and type 2 diabetes

Type 1 diabetes	Type 2 diabetes
Slowing of information processing	Memory:
	Verbal
	Visual retention
	Working
	Immediate recall
	Delayed recall
Psychomotor efficiency	Psychomotor speed
Attention	Executive functioning
Visuoconstruction	
Mental flexibility	

vascular damage to central nervous system neurones, macrovascular (cerebrovascular) disease, amyloid deposits as in Alzheimer's (Apo ε 4 deficiency), insulin resistance and possibly hypoglycaemia may all play a role. There are no data conclusively linking hypoglycaemia alone to cognitive dysfunction in adults with diabetes. A meta-analysis has shown an increased risk of both vascular and Alzheimer's dementia in adults with type 2 diabetes for reasons which are not clear. Prospective studies are under way to explore this relationship.

Treatment

Treatment of depression begins with general measures such as sympathetic discussion, advice about improving glycaemic control and attention to specific causes of anxiety, such as fear of blindness, infertility, impotence, amputation, etc. (Box 25.3). Sleep disorders are common and may be helped by taking regular exercise and avoiding daytime naps, large

Box 25.3 Treatment of depression

- General measures (diabetic control, sympathetic discussion, specific anxieties, attention to sleep disorders)
- Antidepressant drugs for non-responders and for moderate/severe depression
- Consider cognitive behaviour therapy or other psychological interventions

CASE HISTORY

A 17-year-old girl with type 1 diabetes of 6 years' duration was referred to our clinic for further management of her insulin pump therapy. Her family had bought the pump after a local appeal for funds because her diabetes control was so erratic and she had had multiple admissions for DKA. She was needle phobic and admitted she disliked blood glucose tests so much that she only performed them very occasionally. She had to spend an hour or so before each cannula change in order to will herself to insert it. Consequently she changed the cannulae infrequently. Her BMI was 19 kg/m^2 and her HbA_{1c} was 12%. She had poor dentition with active periodontal disease, enamel erosion and caries. She did not wish to see the dietitian. Interrogating her pump showed that she did not give mealtime boluses often and there were occasions when the pump was disconnected for long periods.

When this was pointed out she became very defensive and left the clinic. It later transpired that she was very concerned about her body image and was worried about the potential for weight gain with glycaemic correction. She disconnected the pump when she went to night clubs because she did not want others to notice it and it would not fit under her clothes discreetly. For all these reasons, an agreement was reached to discontinue CSII on safety grounds. She agreed to a single daily injection of long-acting and occasional short-acting analogues. Her glycaemic control remains poor with HbA_{1c} levels above 11%. She would not acknowledge any problem with diet and declined to see a psychologist.

Comment: This girl has a difficult combination of needle phobia and almost certain eating disorder, probably at the anorexia part of the spectrum, although her poor dentition raises the possibility of bulimia (stomach acid corrodes tooth enamel). Insulin pump therapy is fraught with hazard in this situation; without regular blood monitoring, it is hard to set basal rates and detect metabolic decompensation which can occur more quickly on CSII. She is at risk of this because she is not changing the cannula frequently, raising the likelihood of local infection which will block insulin absorption, and she is disconnecting the pump for long periods. For these reasons, CSII had to be discontinued on safety grounds. Addressing the eating disorder and needle phobia requires active engagement from the patient and until she is willing to do this, there is little prospect of any improvement in her diabetes. At present, she attends clinic once or twice a year on her terms.

meals, tobacco, alcohol and caffeine-containing drinks in the evening.

Meta-analysis of psychological interventions (including cognitive behavioural therapy, counselling, family systems therapy and psychoanalysis) shows a significant impact on glycaemic control and psychological distress for children and adolescent patients with type 1 and adults with type 2 but not adults with type 1 diabetes (HbA_{1c} reductions 0.48%, 0.76% and 0.22% respectively). A more recent randomised controlled trial of a combination of cognitive behavioural therapy and motivational enhancement versus motivational enhancement alone or usual care showed a reduction in HbA_{1c} for the combination treatment of 0.46% at 12 months but no effect of either intervention on quality of life or psychological distress.

Moderate or severe depression usually requires antidepressant medication (Box 25.4). NICE guidance for type 1 diabetes does not specify a particular therapy, but most reviews recommend selective serotonin reuptake inhibitors (e.g. fluoxetine, sertraline) because they have the advantages of low cardiotoxicity, greater safety in overdose, less sedation, lack of weight gain and lack of anticholinergic side effects. Tricyclic antidepressants can raise blood glucose levels, cause sedation and weight gain, and have some cardiotoxicity and anticholinergic side effects (e.g. dry mouth, blurred vision, hesitancy or urinary retention). Some tricyclics, such as imipramine, nortryptiline and lofepramine, have weaker sedative properties and are useful in withdrawn or apathetic patients; tricyclic drugs with sedative action (e.g. amitriptyline) are more suitable for agitated or anxious patients. Monoamine oxidase inhibitors are currently little used.

Box 25.4 Antidepressant drugs

First choice: selective serotonin reuptake inhibitors (e.g. fluoxetine, sertraline)

Second choice: tricyclic antidepressants

- Amitriptyline: sedative, use in agitated or anxious patients
- Imipramine, lofepramine: less sedative, use in withdrawn or apathetic patients

Eating disorders

It is difficult to estimate precise prevalence,but there is general agreement that eating disorder may complicate up to 5% of (mainly female) adolescent type 1 diabetes which is probably at least twice the rate seen in the non-diabetic population. There is also a high prevalence of abnormal eating behaviours in type 2 diabetes. Eating disorder is associated with poorer long-term outcome in terms of complications, probably because of its link to omission of insulin, erratic glycaemia and recurrent DKA. The management is extremely difficult and requires multidisciplinary team work from the mental health and diabetes teams. Early recognition and referral are recommended by NICE.

KEY WEBSITE

- National Collaborating Centre for Chronic Conditions and NICE Guidance: www.nice.org-clinicalguidance15
- SIGN Guidelines: www.SIGN.ac.uk

FURTHER READING

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Part

3

The spectrum and organisation of diabetes care

Chapter

26 Specific circumstances that affect diabetes control

KEY POINTS

- Regular exercise is a key component of good diabetes self-management; often walking is the most practical form of exercise. Long-term mortality is lower among diabetics who take regular exercise, even if there is limited effect on short-term glycaemic control.
- Drugs that may worsen hyperglycaemia include steroids, diuretics and β-blockers. These may unmask type 2 diabetes at times of concomitant illness, e.g. chest infection.
- Infections are common in patients with diabetes, e.g. UTIs, respiratory tract infections and cutaneous abscesses, and may not be symptomatic.
- Managing patients with diabetes during planned or emergency surgical procedures requires care to avoid hypo- or hyperglycaemia.
- Risk stratification of patients with diabetes undergoing surgery helps guide their management in the perioperative period.

Exercise

Regular physical exercise is an important component of the management and prevention of type 2 diabetes (Figure 26.1). Aerobic exercise, in particular, and resistance exercise improve insulin sensitivity and glycaemic control. Blood glucose and lipid profiles improve, as well as insulin sensitivity, but in type 2 diabetes exercise does not usually cause hypoglycaemia and extra carbohydrate is unnecessary. Regular exercise accelerates weight loss, but it should be combined with an appropriate diet and tailored to the individual patient's capabilities. Moderate exercise in the form of walking (e.g. 30–60 minutes per day) is often the most practical recommendation. Subjects with type 2 diabetes and moderate or high fitness have a long-term mortality that is 50–60% lower than individuals with diabetes and low cardiorespiratory fitness.

Supervised, progressive resistance exercise training may be of greater benefit in Asian patients with type 2 diabetes. For example, a typical protocol supervised by physiotherapists three times per week might include a range of movements, e.g. biceps and hip flexion, shoulder flexion, finger grip, knee extension and heel rise, and be gradually increased over time (Figure 26.2). Exercise of any type increases glucose transporter levels (GLUT-4) in the cell membrane of skeletal muscle, and resistance training seems to increase fat-free mass. There may be added benefits for patients who adopt a programme of exercise that combines aerobic activity with resistance training.

In type 1 diabetes, short-term glycaemic changes during exercise depend largely on circulating insulin levels, which in turn depend on the type of insulin used and the interval between insulin injection and exercise. For example, hyperinsulinaemia that occurs when exercise is taken shortly after the injection of short-acting insulin (and particularly when the site of insulin injection is an exercising limb) causes blood glucose levels to fall. Other factors that determine the effects of exercise are the intensity of the exercise and the intake of food (Box 26.1).

Most studies have not found that exercise improves the long-term glycaemic control in patients with type 1 diabetes, perhaps because patients tend to consume extra carbohydrate to prevent hypoglycaemia. However, as with type 2 diabetes, patients with type 1 diabetes who exercise regularly have lower long-term morbidity and mortality compared with their sedentary counterparts, so regular exercise carries benefits that may not be reflected in short-term markers of glycaemic control (Figure 26.3).

Handbook of Diabetes, 4th edition. By © Rudy Bilous & Richard Donnelly. Published 2010 by Blackwell Publishing Ltd.

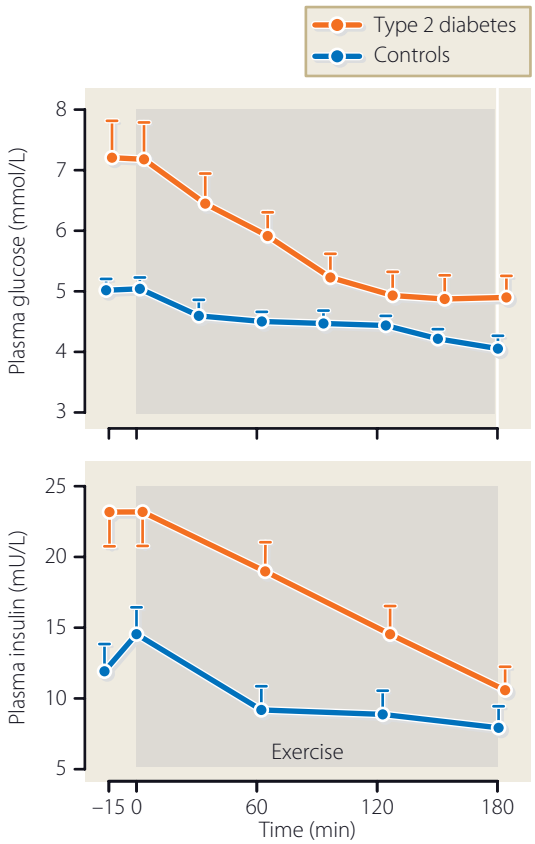

Figure 26.1 Changes in plasma glucose and insulin concentrations during prolonged low-intensity exercise in non-obese patients with type 2 diabetes. The exercise (30–35% of maximal) was performed after an overnight fast. The fall in endogenous insulin secretion diminishes the risk of hypoglycaemia during exercise in type 2 diabetes. From Devlin et al. Diabetes 1987; 36: 434–439.

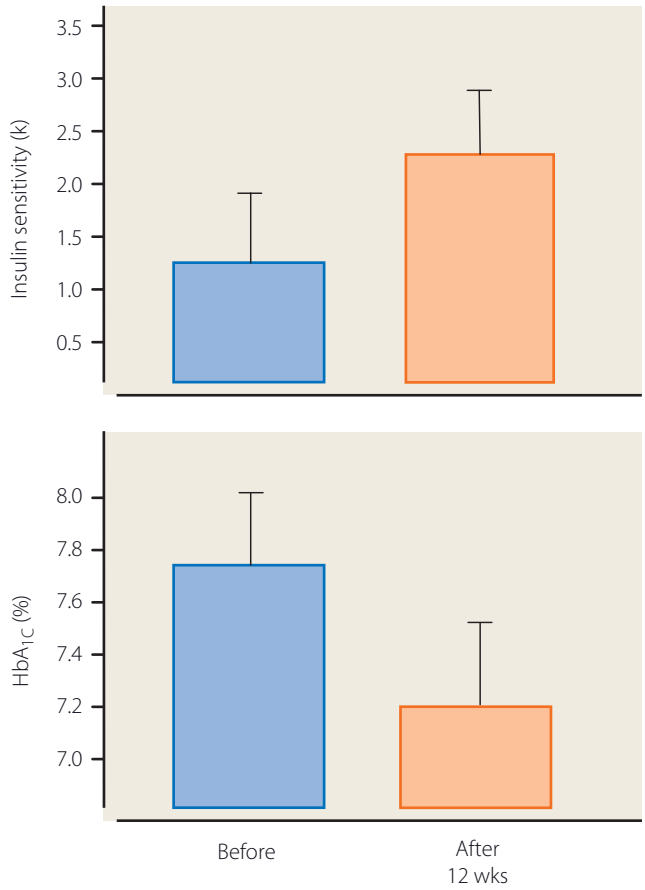

Figure 26.2 Progressive resistance exercise training, supervised over 12 weeks (three sessions per week), leads to increases in insulin sensitivity and decreased HbA_{1c} in patients with type 2 diabetes. Adapted from Misra et al. Diabetes Care 2008; 1282–1287.

CASE HISTORY

A 84-year-old woman, who lives in a nursing home, has long-standing type 2 diabetes. She is managed with metformin and gliclazide, and has some early dementia. The staff have reported that she has developed urinary incontinence. On review by her family doctor, there is limited history from the patient, but the doctor also notes an area of cellulitis affecting the lower leg, spreading from a superficial abrasion. HbA_{1c} is 9.1%.

Comment: Infections are common in patients with diabetes, especially if glycaemic control is poor. It is likely that this woman has both a urinary tract infection (though collection of a sample may be difficult) and a spreading cellulitis that require antibiotic therapy. If recurrent infections occur, she would merit further investigation of the urinary tract. Incontinence in elderly patients should prompt suspicion of a urinary tract infection.

Box 26.1 Factors that determine the glycaemic response to acute exercise in type 1 diabetes

In type 1 diabetes, blood glucose decreases if:
- Hyperinsulinaemia exists during exercise
- Exercise is prolonged (>30–60 min) or intensive
- Less than 3 h have elapsed since the preceding meal
- No extra snacks are taken before or during the exercise

Blood glucose generally remains unchanged if:
- Exercise is brief
- Plasma insulin concentration is normal
- Appropriate snacks are taken before and during exercise

Blood glucose increases if:
- Hypoinsulinaemia exists during exercise
- Exercise is strenuous
- Excessive carbohydrate is taken before or during exercise

Patients with type 1 diabetes can reduce the risk of hypoglycaemia during exercise by following specific guidelines, which include close blood glucose monitoring, extra carbohydrate taken before and hourly during exercise, avoiding exercising muscle territories used for injection (such as the legs) and reducing the pre-exercise insulin dose by 30–50% if necessary (Box 26.2).

Drugs

Numerous drugs can affect diabetic control and cause hyper- or hypoglycaemia by interfering with insulin secretion or action, or both, or by interacting with antidiabetic agents (Table 26.1). Hyperglycaemia can be caused or worsened by many drugs. Corticosteroids, which are widely prescribed for numerous medical conditions, have an especially potent diabetogenic effect and act by inducing insulin resistance. Dosages equivalent to 30 mg/day of prednisolone are especially likely to raise blood glucose in diabetic patients, and may cause glucose intolerance or overt diabetes in previously normoglycaemic individuals. Oral contraceptives rarely worsen diabetic control; the risks of hyperglycaemia are highest with the now obsolete high-dose oestrogen pills, combined pills that contain the progestogen levonorgestrel and in women with a history of gestational diabetes. High-dose thiazide diuretics (e.g. 5 mg/day of bendroflumethiazide) cause insulin resistance and impair insulin secretion, whereas lower dosages (2.5 mg/day bendroflumethiazide), which are still effective in controlling blood pressure, do not. Diabetogenic drugs that damage the β cell include pentamidine (an antiprotozoal agent) and cyclosporin.

Several drugs can cause or exacerbate hypoglycaemia (Box 26.3). Important examples are alcohol, sulphamethoxazole (combined with trimethoprim in co-trimoxazole), quinine, aspirin and paracetamol (acetaminophen) in overdosage, and the numerous drugs that enhance the action of sulphonylureas (e.g. probenecid, sulphonamides, monoamine oxidase inhibitors, chloramphenicol, fluconazole).

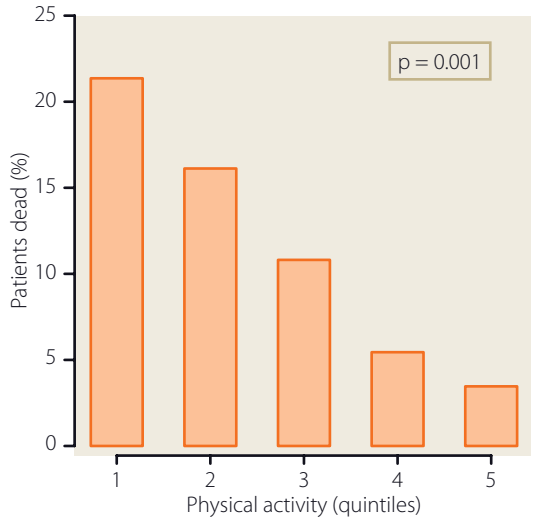

Figure 26.3 Proportion of men who died during a 7-year follow-up period among 548 patients with type 1 diabetes, stratified according to their physical activity quintile. Quintile cut-offs were 398, 398–1000, 1000–2230, 2230–4228 and more than 4228 kcal/week. From Moy et al. Am J Epidemiol 1993; 137: 74–81.

Box 26.2 Guidelines for exercise in patients with type 1 diabetes

Monitor glycaemia before, during and after exercise as necessary

Avoid hypoglycaemia during exercise by:

- Taking 20–40 g extra carbohydrate before and hourly during exercise
- Avoiding heavy exercise during peak insulin injection
- Using non-exercising sites for insulin injection
- Reducing preinjection insulin dosages by 30–50% if necessary

After prolonged exercise, monitor glycaemia and take extra carbohydrate to avoid delayed hypoglycaemia

Table 26.1 Drugs that may exacerbate hyperglycaemia

Potentially potent effects	Minor or no effects
Glucocorticoids	Oral contraceptives • Progestogen-only pills • High-dose oestrogen
Thiazides*	• Levonorgestrel in combination pills
Loop diuretics	
Thiazide diuretics (high dosages)*	ACE inhibitors
β-adrenoceptor antagonists	Calcium channel blockers
β2-adrenoceptor agonists • Salbutamol • Ritodrine	α1-adrenoceptor antagonists
	Growth hormone (physiological doses)
Atypical antipsychotics • Clozapine • Olanzapine	Somatostatin analogues†
	Selective serotonin reuptake inhibitors
HIV protease inhibitors • Indinavir, nelfinavir and others	
Others • Pentamidine • Streptozocin • Diazoxide • Cyclosporin • Tacrolimus	

ACE, angiotensin-converting enzyme; HIV, human immunodeficiency virus.
*'High' and 'low' dosages of thiazides correspond to 5 mg/day and 2.5 mg/day of bendroflumethiazide, respectively.
†Somatostatin analogues may induce hyperglycaemia in type 2 but not type 1 diabetes.

Box 26.3 Drugs that can cause or exacerbate hypoglycaemia

Antidiabetic drugs
- Insulins
- Sulphonylureas (e.g. glimepiride)
- Repaglinide

Drugs that interact to enhance the actions of sulphonylureas

Other drugs:
- Quinine
- Quinidine
- Mefloquine
- Sulphamethoxazole (in co-trimoxazole)
- Pentamidine
- Disopyramide
- Cibenzoline
- Non-selective β-adrenoceptor antagonists
- Paracetamol (in overdosage)
- Aspirin (in overdosage)
- Ethanol

Box 26.4 Classification of infections in diabetes mellitus

Common infections with increased incidence in patients with diabetes
- Urinary tract infections
- Respiratory tract infections
- Soft tissue infections

Infections predominantly occurring in patients with diabetes
- Malignant otitis externa
- Necrotizing fasciitis
- Fournier's gangrene
- Emphysematous infections
- Cholecystitis
- Pyelonephritis and cystitis
- Infections in the diabetic foot

Infections

Diabetes is associated with a wide range of infections (Box 26.4), which are more frequent than in the general population (e.g. urinary tract infections, UTI), occur almost exclusively in subjects with diabetes (e.g. malignant otitis externa) or run a different or more aggressive course in the host with diabetes (e.g. respiratory tract infections). The multiple defects in immunity in diabetes may explain the susceptibility to infection, including impaired polymorphonuclear leukocyte function. Other contributory causes in some patients include frequent hospitilisation, delayed wound healing and chronic renal failure. Common infections include UTI, respiratory tract infections and soft tissue infections.

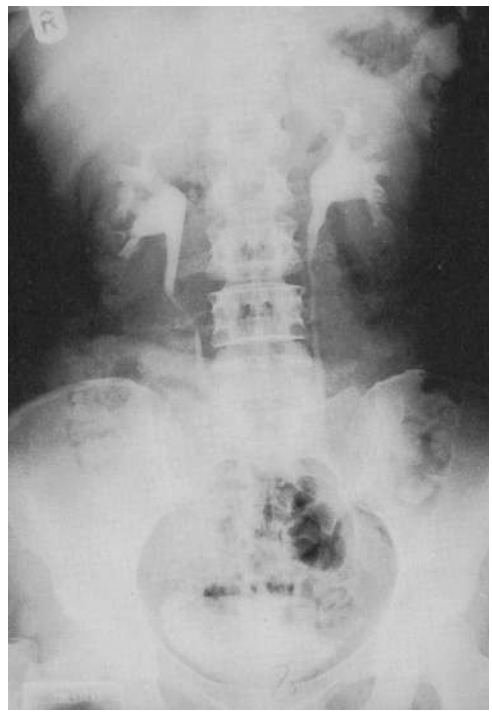

Figure 26.4 Acute papillary necrosis showing loss of papilla and a calyceal ring shadow in the left kidney. Courtesy of Dr I MacFarlane, Walton Hospital, Liverpool, UK.

About 25% of women with diabetes have asymptomatic bacteriuria (this is four times more common than in the population without diabetes). *Escherichia coli* is the most common pathogen. UTI may be asymptomatic or present with dysuria, frequency or urgency (lower UTI), or flank pain, fever and vomiting (upper UTI). Perinephric abscess and papillary necrosis are rare complications (Figure 26.4).

With respiratory tract infections in diabetes, bacteraemia, delayed resolution and recurrence are more common than in the general population, though the overall frequency is probably no greater. Respiratory infection caused by certain micro-organisms, including *Staphylococcus aureus*, gram-negative bacteria, *Mycobacterium tuberculosis* and Mucor, is more common in diabetes. Respiratory infection with Streptococcus, Legionella and influenza virus is associated with more morbidity and mortality in diabetes. Cough and fever are the usual presenting complaints, although ketoacidosis can be the first manifestation. Deep soft tissue infections with bacteria (e.g. pyomyositis, a muscle abscess that occurs after trauma and haematoma and is caused by *Staph. aureus*) and fungi (e.g. cutaneous mucormycosis) are more common in diabetes.

Some rare infections occur predominantly in patients with diabetes. Malignant otitis externa is a life-threatening

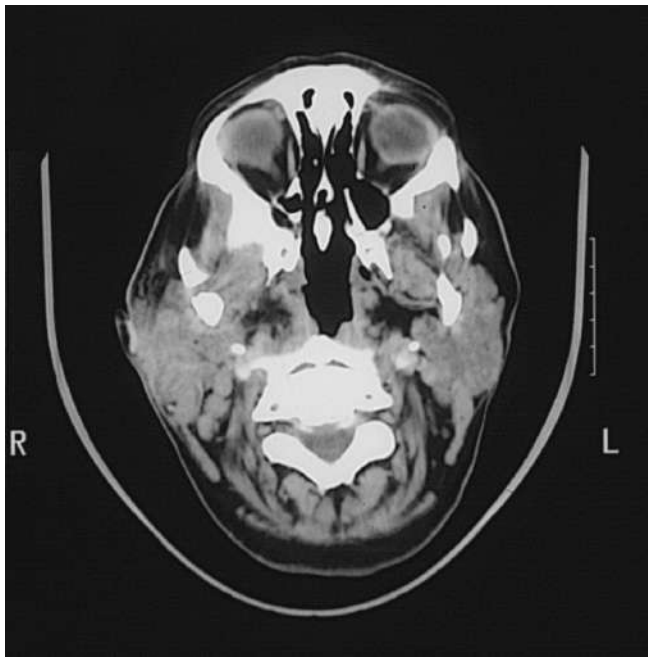

Figure 26.5 Necrotizing ('malignant') otitis externa. This magnetic resonance scan shows extensive soft tissue necrosis and swelling, with early involvement of the underlying bone. The patient was a 28-year-old woman with long-standing diabetes. Courtesy of Professor G Williams, University of Bristol, Bristol, UK.

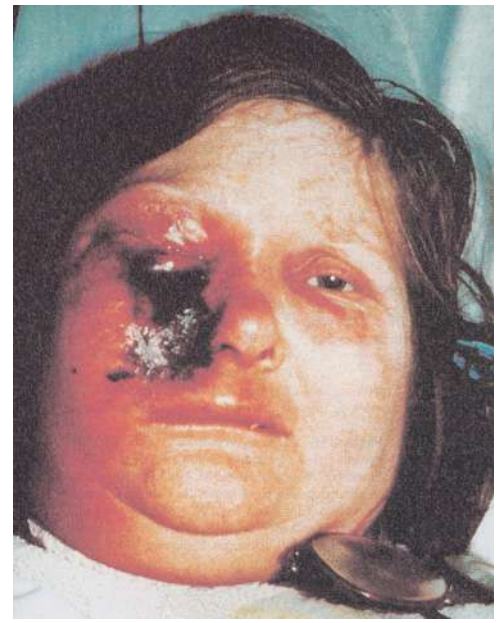

Figure 26.6 Rhinocerebral mucomycosis. Typical appearance, in a 45-year-old woman with poorly controlled type 1 diabetes. Periorbital and facial swelling had been present 3–4 days before admission. Major reconstructive surgery was required. From Rupp. N Engl J Med 1995; 333: 564.

condition in elderly patients with diabetes, usually due to *Pseudomonas aeruginosa* (Figure 26.5). Patients present with ear discharge, severe pain and hearing impairment, with oedema, cellulitis and polypoid granulation of the auditory canal. Cranial osteomyelitis and intracranial spread of infection may occur.

Rhinocerebral mucormycosis is a rare infection caused by fungi of the Rhizopus or Mucor species, which grow best in acid media; ketoacidosis is a predisposing factor. About 50% of cases are in diabetic patients. The fungi have a predilection to invade blood vessels. Onset may be with nasal stuffiness, epistaxis and facial and ocular pain. A characteristic black necrotic eschar (scab) occurs on the nasal turbinates or palate (Figure 26.6). Complications include cavernous sinus thrombosis, cranial palsies, visual loss, frontal lobe abscesses and carotid artery or jugular vein thrombosis, which causes hemiparesis.

LANDMARK CLINICAL TRIALS

Eriksson MK, Franks P, Eliasson M, et al. A 3-year randomised trial of lifestyle intervention for cardiovascular risk reduction in the primary care setting: The Swedish Bjorknas Study. PLoS ONE 2009; 4: e5195.

Johnson NP, Wu E, Bonow R, Holly T. Relation of exercise capacity and body mass index to mortality in patients with intermediate to high risk of coronary artery disease. Am J Cardiol 2008; 102: 1028–1033.

Kao LS, Meeks D, Moyer V, Lally K. Peri-operative glycaemic control regimens for preventing surgical site infections in adults. Cochrane Database Syst Rev 2009; 3: CD006806.

Surgery

Surgical stress stimulates secretion of counter-regulatory hormones, such as cortisol and catecholamines, which decrease insulin sensitivity and inhibit insulin release. In insulin-deficient diabetic patients, this may cause dangerous hyperglycaemia and ketosis. In general, metabolic disturbance caused by surgery is more pronounced in patients with type 1 diabetes. Hypoglycaemia is the other major risk of surgery. After preoperative assessment to confirm fitness for anaesthesia, optimisation of control and liaison with the surgical and anaesthetic teams, management plans depend on whether or not the patient is insulin treated and the nature and duration of surgery (Boxes 26.5, 26.6).

Management of diabetes throughout the perioperative period depends upon the patient's background therapy and glycaemic control; the nature, timing and duration of the procedure, and the likely speed of recovery in terms of regaining normal dietary intake (Box 26.7, Figure 26.7). A sliding scale insulin infusion is only necessary for 'high risk' patients.

Box 26.5 Patients with diabetes undergoing surgery, endoscopy or interventional radiological procedure: general principles of management

- Good glycaemic control before and after the procedure reduces risk of complications
- The main risk to anaesthetised or sedated patients is unrecognised hypoglycaemia
- Put patients first on morning, or first on afternoon, list where possible
- Anaesthetic and procedural management should minimise risks of vomiting, anorexia and sedation, which can destabilise diabetes following procedure
- When emergency procedures are required, resuscitation, fluid replacement and correction of hyper- or hypoglycaemia should be addressed preoperatively
- Careful selection of cases for day-case or elective procedures

Box 26.6 Risk stratification of patients with diabetes undergoing a surgical procedure

Low risk
- Well-controlled patients on 'diet alone' or oral hypoglycaemics
- Minor procedures or procedures where anaesthesia, sedation and procedure itself lasts no longer than 45 mins, and not likely to need IV fluids postoperatively

Medium risk
- Well-controlled insulin-treated patients (HbA_{1C} <9%)
- Not ketotic
- Likely to need IV fluids for <24 hours
- Postoperative problems unlikely

High risk
- Any patient with diabetes undergoing major surgery and/or likely to need IV fluids for >24 hours postoperatively
- Patient ill, septic or ketotic
- Patients with chronic poor glycaemic control (e.g. HbA_{1C} >9%)
- Potential to become unstable due to condition or as a result of special preparations, procedure or anaesthesia

KEY WEBSITES

- www.nhs.uk/Diabetes
- www.rch.org.au/clinicalguide/cpg.cfm?doc_id=5190
- www.ich.ucl.ac.uk/clinical_information/clinical_guidelines/cmg_guideline_00000
- SIGN Guidelines: www.SIGN.ac.uk

Box 26.7 Management of diabetes during the perioperative period

Low-risk patients (no need for sliding-scale insulin)
- Omit oral hypoglycaemic drugs on the day of the procedure, or on the day of fasting for special preparations if this is before the day of the actual procedure.
- If patient is on the afternoon list and allowed to eat, give a light breakfast (tea and toast).
- Restart usual medication as soon as patient starts eating normally.
- However, patients due to receive IV contrast medium must omit metformin on the day of the procedure, or from fasting, and must not resume until 2 days afterwards.

Well-controlled medium-risk patients (sliding-scale insulin not usually needed)

Morning surgery
- Omit the morning dose of insulin and record blood glucose.
- Post procedure: immediately prior to eating **normal** meal, give SC insulin (generally the usual dose).

Afternoon surgery patients
- If patient is not allowed to eat, omit the morning insulin.
- If they are allowed to eat, give patient ½ of their usual insulin dose before eating a light breakfast (tea and toast). Monitor blood glucose.
- Post procedure, once able to eat **normally**, resume usual insulin dose.

High-risk patients

Morning surgery patients
- At 07.30 record blood glucose and commence continuous insulin infusion via a syringe driver, with a separate drip of 4% dextrose/0.18% saline and 20 mmol potassium, via a volumetric pump. 1 litre/8 hours (less for elderly).

Afternoon surgery patients
- If they are allowed to eat, give patients ½ their usual insulin dose before a light breakfast.
- 1 hour before procedure, record blood glucose and commence continuous insulin and IV fluid infusion, as above.

Both morning and afternoon patients
- Prescribe sliding-scale insulin on the 'variable dose' section of the drug chart.
- As soon as they are eating **normally**, resume usual SC insulin, then **1 hour later** discontinue the continuous insulin and IV infusion.

NB: Patients on insulin undergoing extended fasting due to condition, or special preparations, will omit insulin at time of fasting and commence continuous IV insulin with separate drip of 4% dextrose/0.18% saline and 20 mmol potassium, 1litre/8 hours (less in the elderly) as above.

Date chart commenced:

DIABETIC TREATMENT PRESCRIPTION (for subcutaneous insulin)

PRESCRIPTION						**ADMINISTRATION**		
Drug name	Dose	Route	Date for administration	Time for administration	Prescribers signature	Date administered	Time administered	Given by

CONTINUOUS INTRAVENOUS INSULIN INFUSION
SLIDING SCALE DOSE AND RATE PRESCRIPTION GUIDE
***Only* for *high risk* patients**

ACTRAPID INSULIN INFUSION 1 UNIT/PER ML SALINE (delivered by variable rate syringe driver)

All prescriptions for insulin and fluids or change to this regime must be signed.

Use a new column each time insulin dose is changed

Date			
Start time			
Blood glucose levels	Insulin rate (units per hour)		
Up to 4.0 mmol/L	0		
4.0 mmol/L or higher	1 (usual maintenance dose)		
7.0 mmol/L or higher	2		
11.0 mmol/L or higher	3		
17.0 mmol/L or higher	4		
Prescriber's signature			

Dose alterations must also be recorded on blood glucose monitoring section and on IV infusion device checklist

If BG levels persistently higher than 17mmol/L, obtain medical advice

INTRAVENOUS FLUIDS

Prescribe 4% dextrose/ 0.18% saline & 20mmol/L potassium, 1litre/8hrs (*less for elderly*) on standard fluid balance chart and deliver by a volumetric pump.

BLOOD GLUCOSE MONITORING

Qualified practitioner should sign changes to frequency of recordings

Figure 26.7 An example of a diabetes chart for prescription of subcutaneous insulin and prescription of a sliding-scale variable-rate insulin infusion.

FURTHER READING

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Chapter

27 Pregnancy and diabetes

KEY POINTS

- Diabetes is the most common medical problem that complicates pregnancy, affecting 1 in 264 births in the UK.
- Pregestational diabetes is associated with a twofold increase in major congenital malformations, fourfold increased perinatal mortality and fivefold increase in stillbirth rate compared to age- and parity-matched non-diabetic women. These complications are related to glycaemic control in early pregnancy.
- Women with type 2 diabetes have a similar complication rate to those with type 1.
- Preconception and antenatal strict glycaemic control reduces the risk of congenital malformation.
- Macrosomia (large-for-dates fetus) is at least twice as common in women with pre- and gestational diabetes and can lead to complications during delivery.
- Gestational diabetes affects 3–5% of pregnancies in the UK and is more common in women from ethnic minorities.
- Glycaemic control can reduce complications for both mother and child.

Pregestational diabetes is the most common medical problem that complicates pregnancy, affecting 1 in 264 births (0.38%) in the UK in 2002–3, with over 25% occurring in women with type 2 diabetes. The Kaiser Permanente database recorded an average rate of 1.3% in California from 1999 to 2005, increasing from 0.81% to 1.82% of all pregnancies over this time. Diabetes can cause problems for both the mother and fetus and despite recent advances in antenatal care, the outcome in terms of perinatal health and survival remains significantly less good than for pregnancy in the absence of diabetes. Gestational diabetes usually occurs in the second half of pregnancy and is becoming more common because of increasing maternal obesity and age, although absolute rates are highly dependent on the population under study and reflect the background risk of type 2 diabetes.

Box 27.1 Effects of pregnancy on the woman with diabetes

- Change in eating pattern due to nausea/vomiting in early pregnancy; delayed gastric emptying and reflux oesophagitis in later pregnancy
- Increasing insulin dose (insulin sensitivity declines by ~50%)
- Need for tight glycaemic control
- Increasing risk of hypoglycaemia
- Risk of deterioration of retinopathy
- Risk of deterioration of renal function in women with nephropathy
- Proketotic state – vulnerable to DKA
- Decreased renal threshold to glucose predisposing to urinary infection

Effects of pregnancy on the woman with diabetes

In women with pre-existing diabetes, glycaemic control can worsen and insulin requirements usually increase during pregnancy, on average by 40% after the 18th week (range 0–300%) (Box 27.1). This is because pregnancy induces insulin resistance through the diabetogenic effects of placental hormones (mainly growth hormone), cytokines such as TNF-α, and progesterone, the effects of which are maximal in the second and third trimesters. Hyperglycaemia as a result of insulin resistance and consequent enhanced lipolysis is probably favourable in the woman without diabetes as it encourages nutrient transfer to the growing fetus, but in diabetes it can be seen as a form of accelerated starvation and predisposes to ketosis. As pregnancy progresses and the

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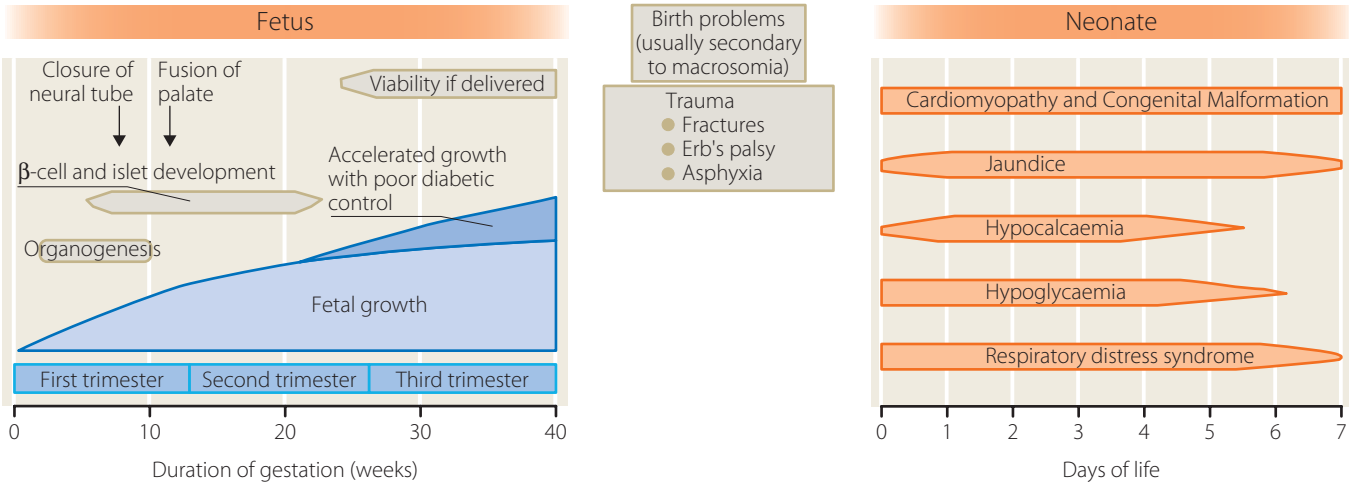

Figure 27.1 Impact of maternal diabetes on the fetus and neonate.

diaphragm is pushed upwards, there is a relative increase in alveolar ventilation with a consequent respiratory alkalosis and compensatory renal tubular loss of bicarbonate. There is a fall in serum bicarbonate and loss of acid-buffering capacity, which partly explains why DKA can occur in pregnancy at relatively modest hyperglycaemia or even normoglycaemia.

Because of the stringent glycaemic targets, there is a real risk of hypoglycaemia; 41% of 323 women with diabetes in The Netherlands who were pregnant in 1999–2000 reported at least one severe episode, and one died in a road traffic accident almost certainly as a result of hypoglycaemia. Women who are driving should be advised to follow carefully guidance on blood glucose monitoring (see Chapter 30).

Effects of maternal diabetes on the pregnancy

Maternal diabetes can affect the fetus adversely by causing developmental malformations and altered islet cell development (increased insulin secretion) and by accelerating growth (macrosomia). Pre-eclampsia is more common in pregnancies with diabetes (particularly in women with nephropathy); there was a reported >12-fold increase compared to pregnancy without diabetes in The Netherlands in 1999–2000. Perinatal mortality rate has fallen in recent years but is still 3–4 times that in non-diabetic pregnancy (32/1000 in the Confidential Enquiry into Maternal and Child Health (CEMACH) report in the UK in 2002–3). Stillbirth rates remain about five times those of the non-diabetic population and are linked to standard of glycaemic control throughout pregnancy; in the CEMACH enquiry less than 50% of women with a stillbirth ever achieved an HbA_{1c} <7.0% at any time during their pregnancy, whereas >70% of women with a normal pregnancy outcome recorded an HbA_{1c} <7.0% (53 mmol/mol) at some stage. Maternal mortality is also significantly higher than in non-diabetic pregnancies; there were two deaths in the Dutch cohort (0.6% of 323) and five within 1 year of delivery in the CEMACH cohort of 3733, but only three of these may have had a diabetes link.

Box 27.2 Effects of maternal diabetes on pregnancy

- Need for preconception care
- Increased congenital malformations
- Increased risk of miscarriage and late intrauterine death
- Need for regular surveillance and ultrasound monitoring
- Increased risk of pre-eclampsia
- Macrosomia and consequent difficult delivery
- Increased early delivery and caesarean section rate
- Increased perinatal mortality

Diabetes is teratogenic, particularly in the first 8 weeks' gestation, when the major organs are forming. Major congenital malformations occurred in 144 of the CEMACH cohort, about twice the non-diabetic rate, and there was no difference by type of diabetes; the major defects affected the heart (42%), musculoskeletal (17%) and nervous (13%) systems. Malformation rate is closely related to hyperglycaemia in early pregnancy; pre-pregnancy median HbA_{1c} was 8.35% (68 mmol/mol) (interquartile range (IQR) 7.1–10.2) in women whose babies had a major malformation, compared to 7.8% (62 mmol/mol) (IQR 6.8–9.0) in those who had a normally formed baby alive at 28 days. Although preconceptual care and tight glycaemic control are associated with lower rates (for obvious reasons, there are no ran-

LANDMARK CLINICAL TRIALS

Crowther CA, Hiller JE, Moss JR, et al, for the ACHOIS Trial Group. Effect of treatment of gestational diabetes mellitus on pregnancy outcomes. N Engl J Med 2005; 352: 2477–2486.

The ACHOIS Trial has completely revolutionized our thinking and approach to GDM. Prior to its publication, there were no data to suggest that GDM was of any clinical significance because there were no properly powered intervention studies to show that management influenced outcome. Six hundred women were randomised to routine care or an intensive programme of dietary advice, blood glucose monitoring and insulin therapy, in order to maintain pre- and post-prandial levels <5.5 and <7.0 mmol/L respectively. The postprandial target was relaxed to <8.0 mmol/L after 35 weeks' gestation. There was a relative risk of 0.33 (95% CI 0.14–0.75) for serious perinatal complications (death, shoulder dystocia, bone fracture or nerve palsy) in the intensively treated women. However, there was also an increased rate of induction of labour and more of the infants required admission to the neonatal unit. Caesarean section rates were the same between groups, but postpartum mood and quality of life were better in the intensive arm.

There has been an extensive critique of these findings and the complication rate in the routine care women seems higher than in many published series. There has also been some concern over the definition of shoulder dystocia. However, the findings have also prompted many to call for universal screening for GDM.

With the publication of HAPO and evidence from ACHOIS that glycaemic intervention is of benefit, the management of GDM will never be the same.

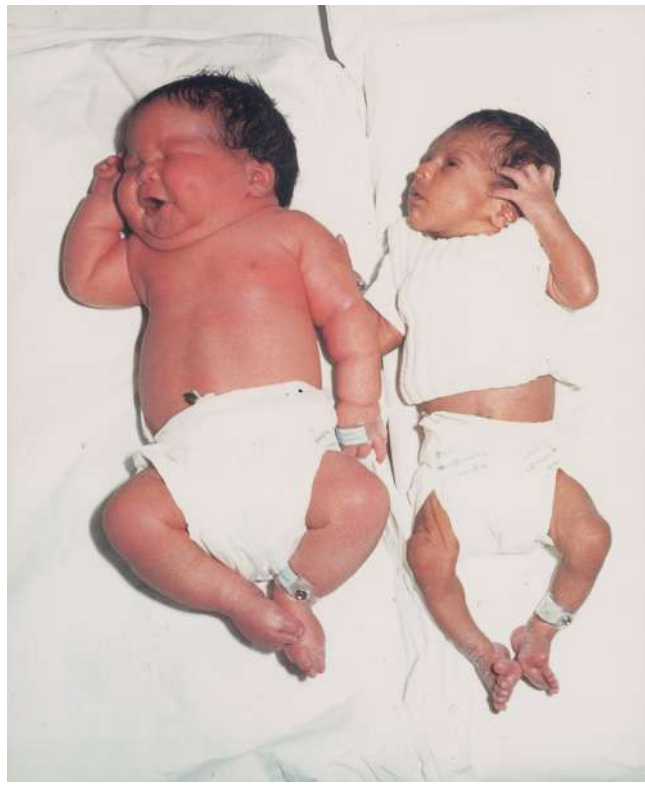

Figure 27.2 (*Left*) A macrosomic baby born to a mother with diabetes. (*Right*) A normal baby born to a mother without diabetes.

domised controlled trials in this area), 84% of the Dutch cohort pregnancies were planned and 75% achieved a first-trimester HbA_{1c} <7.0%, despite which their congenital malformation rates were over three times those seen in non-diabetic women. In the CEMACH, 25% of women whose babies had a major malformation had a first-trimester HbA_{1c} <7.0%. Part of the problem is that HbA_{1c} is only a measure of average glycaemia; peak blood glucose or variation may be more important, and very few women have complete normoglycaemia before or at conception and during embryogenesis. Nonetheless, the Dutch researchers reported an odds ratio of 0.34 (95% CI 0.13–0.88) for major malformations in women with diabetes with a planned versus an unplanned pregnancy.

Accelerated fetal growth, which leads to a macrosomic, large-for-gestational-age infant, is caused by enhanced delivery of glucose and other nutrients to the fetus. This stimulates the islets and induces fetal hyperinsulinaemia, which promotes abdominal fat deposition, skeletal growth and organomegaly. Complications for these large babies include birth trauma and neonatal hypoglycaemia and hypocalcaemia. Despite being large for gestational age, the macrosomic fetus tends to be dysmature and is prone to the respiratory distress syndrome at birth. Rates of macrosomia depend upon the definition; in the CEMACH over 50% of babies were above the 90th centile birthweight. Using a definition of 4 kg, 21% of babies were macrosomic compared to 11% in women without diabetes (Figure 27.2). Interestingly, rates are similar in type 1, type 2 and gestational diabetes and relate to glycaemia in the latter half of pregnancy.

Pre-pregnancy counselling

Management of pregnancy in women with diabetes begins with preconception advice and counselling (Box 27.3). This includes explanation of the risks of pregnancy and the requirements for successful pregnancy, including frequent clinic visits beginning as soon as possible after conception, optimised metabolic control, stopping both smoking and drinking alcohol, and a folate-rich and supplemented diet (5 mg/day – a higher dose than usually recommended for non-diabetic pregnancy). Potentially teratogenic drugs should be replaced with safer alternatives – ACE inhibitors are contraindicated, for example. Outpatient preconception care of women with diabetes is thought to reduce congenital anomalies by about two-thirds.

Box 27.3 Pre-pregnancy care. Adapted from NICE Guidance CG 63

Give advice and information on:

- the risks of diabetes in pregnancy and how to reduce them with good glycaemic control
- diet, bodyweight and exercise, including weight loss for women with a BMI over 27 kg/m^2, smoking cessation and alcohol avoidance
- hypoglycaemia and hypoglycaemia unawareness and avoidance
- pregnancy-related nausea/vomiting and glycaemic control
- retinal and renal assessment
- when to stop contraception
- taking folic acid supplements (5 mg/day) from preconception until 12 weeks of gestation
- review of, and possible changes to, medication (stop statins and any antihypertensive medication contraindicated in pregnancy), glycaemic targets and self-monitoring routine
- frequency of appointments and local support, including emergency telephone numbers

Management of diabetic pregnancy

NICE guidance for the management of pregnancy in pregestational diabetes includes optimisation of glycaemic control, aiming for a fasting plasma glucose concentration 3.5–5.9 mmol/L, a 1-hour postprandial peak <7.8 mmol/L and an HbA_{1c} <6.1% (44 mmol/mol). Virtually all women with type 1 diabetes require a basal-bolus insulin injection regimen to achieve strict glycaemic control, with at least four times daily blood glucose self-monitoring. The choice of insulin is controversial. There are no prospective trials that establish the safety of the new long-acting analogues, but neither are there many for older insulins. Current guidance suggests that long-acting analogues should not be started in pregnancy but may be continued after discussion with the pregnant woman. Neutral protamine Hagedorn (NPH) should be used if a change is requested or a new longer acting preparation is started. The short-acting analogues aspart and lispro are safe to continue. Continuous subcutaneous insulin infusion (CSII – insulin pump therapy) is an alternative option in those who have difficulty achieving good control on multiple injections without unacceptable hypoglycaemia, although a meta-analysis of six studies showed no advantage over multiple injection therapy. Suitably powered prospective trials are required in order to determine optimum management of glycaemia in pregnancy.

Screening for complications is necessary, since pregnancy can worsen renal function in women with established nephropathy (serum creatinine >124 µmol/L or estimated GFR (eGFR), <45 mL/min/1.73 m^2); consequently, blood pressure

CASE HISTORY

A 28-year-old woman with type 1 diabetes of 20 years' standing and poor overall control was commenced upon CSII prior to planning a pregnancy. Her HbA_{1c} gradually improved over 6 months from 9.8% to 7.1%. During this time she had careful retinal surveillance and there was no change in her mild background retinopathy. Her urine ACR was normal at <2 mg/mmol and she was normotensive (BP 118/78 mmHg). Shortly thereafter she conceived a singleton pregnancy and her control further improved to an HbA_{1c} of 6.5%. Her progress was uneventful until the 32nd week when she developed increasing proteinuria of over 2 g/day. Her blood pressure rose to 138/96 mmHg and she reported blurred vision. Fetal growth was satisfactory. Ophthalmological exam revealed ischaemic changes with multiple cotton wool spots but no new vessels. Her discs appeared normal. Over the next week, she developed headache and sickness with photophobia and worsening blurred vision. An MRI scan was normal, a lumbar puncture revealed normal pressures and CSF. Over the next week BP rose further to 144/102 mmHg, proteinuria increased to >4 g/d and she developed significant peripheral oedema. She was commenced on methyldopa and labetalol. The next fetal scan showed a diminished growth velocity so she was admitted for antepartum corticosteroids. Following these, her BP settled but her proteinuria continued to worsen, creatinine clearance declined and her visual symptoms deteriorated. Because of this she was delivered at just over 35 weeks' gestation of a live girl who spent 3 weeks on the neonatal unit but then did very well with no adverse sequelae.

The woman's visual symptoms and headache rapidly resolved. Her ischaemic retinopathy improved without the need for photocoagulation. She remained significantly proteinuric, however. Because of this and her completely normal renal function before pregnancy, she underwent a renal biopsy 6 months later. This showed classic features of diffuse diabetic glomeruloscerosis only. She is now managed with an ARB (she developed a cough on lisinopril) and still has microalbuminuria (ACR 8 mg/mmol). BP is 130/78 mmHg.

Comment: There are several learning points arising from this case. Firstly, although pregnancy can worsen established nephropathy, it is unusual for it to appear *de novo* antenatally. Secondly, she developed pre-eclampsia and this might have been responsible for both the retinal changes (secondary to vasoconstriction and hypertension) and the development of nephropathy. It is interesting that the eye changes resolved almost immediately after delivery but she remained albuminuric. Transient retinal ischaemia is described in diabetic pregnancy but is unusual; early delivery is strongly recommended in this situation. Pre-eclampsia is more common in diabetic pregnancy, particularly in women with nephropathy. Monitoring renal function is difficult where pre-eclampsia is superimposed on nephropathy and requires repeated, timed urine collections to estimate creatinine clearance. Lastly, the temporary improvement in blood pressure with steroids is a well-recognised feature of pre-eclampsia and should be a prompt to consider the diagnosis.

Box 27.4 Suggested antenatal care for women with pre-gestational diabetes. Adapted from NICE Guidance CG 63

First appointment (joint diabetes and antenatal clinic)

- Offer information, advice and support on glycaemic control.
- Set blood glucose targets:
  - HbA_{1c} <6.1% (44 mmol/mol)
  - Fasting glucose 3.5–5.9 mmol/L
  - 1-hour postprandial blood glucose <7.8 mmol/L
- Give urine or blood ketone monitoring equipment and education on its use
- Warn of risks of hypoglycaemia, give advice on treatment, give glucagon injection kit and education on its use
- Dietary assessment
- Commence or continue folic acid 5 mg/day
- Smoking cessation and advise alcohol avoidance
- Consider switch to CSII
- Take a clinical history.
- Check blood pressure and assess cardiovascular risk (especially type 2 diabetes)
- Review medications – stop contraindicated drugs (e.g. RAS-blocking agents, statins). Switch antihypertensive therapy to methyldopa/nifedipine/labetalol
- Offer retinal screening and renal assessment (serum creatinine and urine albumin:creatinine ratio) if these have not been performed in the previous 12 months

Specific antenatal care for women with diabetes

7–9 weeks

- Confirm viability of pregnancy and gestational age.

Booking appointment (ideally by 10 weeks)

- Discuss information, education and advice about how diabetes will affect pregnancy, birth and early parenting (such as breastfeeding and initial care of the baby).

16 weeks

- Offer extra retinal assessment to women with pre-existing diabetes who had signs of diabetic retinopathy at the first antenatal appointment.

18–20 weeks

- Offer fetal ultrasound four-chamber view of the heart and outflow tracts.
- Offer scans that would be offered at 18–20 weeks in routine antenatal care.

25 weeks

- Offer routine care only (appointment for nulliparous women).

28 weeks

- Offer ultrasound monitoring of fetal growth and amniotic fluid volume.
- Offer retinal assessment.

31 weeks

- No appointment (routine care offered to nulliparous women at 32 weeks).

32 weeks

- Offer ultrasound monitoring of fetal growth and amniotic fluid volume.
- Offer investigations that would be offered to nulliparous women at 31 weeks in routine antenatal care.

34 weeks

- Offer routine care only.

36 weeks

- Offer ultrasound monitoring of fetal growth and amniotic fluid volume.
- Offer information and advice about:
  - timing, mode and management of birth
  - analgesia and anaesthesia (including anaesthetic assessment for women with co-morbidities, such as obesity or autonomic neuropathy)
  - changes to hypoglycaemic therapy during and after birth
  - initial care of the baby
  - initiation of breastfeeding and the effect of breastfeeding on glycaemic control
  - advice on contraception and arrange follow-up.

38 weeks

- Offer induction of labour or caesarean section if indicated.
- Offer tests of fetal well-being for women waiting for spontaneous labour.

39 weeks

- Offer tests of fetal well-being for women waiting for spontaneous labour.

40 weeks

- Offer tests of fetal well-being for women waiting for spontaneous labour.

41 weeks

- Offer tests of fetal well-being for women waiting for spontaneous labour.

American Diabetes Association glycaemic targets are:
HbA_{1c} <6.0% (42 mmol/mol)
Fasting blood glucose 60–99 mg/dL (3.3–5.5 mmol/L)
Peak postprandial blood glucose 100–129 mg/dL (5.5–7.2 mmol/L)

should be controlled carefully (e.g. with nifedipine, methyldopa or labetalol). Increasing proteinuria and hypertension are common in worsening nephropathy, but can be difficult to distinguish from pre-eclampsia in later pregnancy (see below). eGFR is not valid in pregnancy so timed creatinine clearances are necessary to monitor declining renal function. Retinopathy may also deteriorate rapidly during diabetic pregnancy, especially when glycaemic control is improved suddenly. Increased frequency of surveillance and early photocoagulation should be considered in high-risk patients in early pregnancy or even before conception.

Obstetric assessment includes regular ultrasound scans for gestational age, detecting major malformations, monitoring fetal growth and assessing the volume of amniotic fluid. The maternal complications of diabetic pregnancy include pre-eclampsia (hypertension, proteinuria, oedema and fetal compromise), polyhydramnios, urinary tract infections, vaginal candidiasis, carpal tunnel syndrome, reflux oesophagitis and preterm labour. The odds ratio for pre-eclampsia is 1.65 for each increase of 1% (11 mmol/mol) in HbA_{1c} level.

Insulin requirements usually increase gradually through the second trimester, coinciding with increasing insulin resistance and food intake, and may continue to increase until 34–36 weeks' gestation. HbA_{1c} is less precise as an estimate of glycaemic control in later pregnancy because of altered red cell survival, possible iron deficiency and increased circulating volume leading to a dilutional fall in haemoglobin concentration. Serum fructosamine is considered by some to be more useful in this situation (see Chapter 9).

In the UK most women with diabetes are delivered at 38, and at the latest 40 weeks, because of the risk of late stillbirth; 35.8% of the CEMACH cohort were delivered before 37 weeks' gestation. In terms of mode of delivery, for the whole group only 18% had a spontaneous labour, 38.9% were induced and 42.7% had a caesarean section; one-quarter, twice and nearly four times respectively the rates in women without diabetes.

If an early delivery is anticipated then antenatal corticosteroids in high dose are often given in order to facilitate fetal lung maturation. This will inevitably cause hyperglycaemia and may even provoke DKA. For these reasons careful monitoring, preferably in hospital, is required and insulin doses increased by 50% or more for 48 hours in order to prevent metabolic decompensation.

During labour, diabetes should be controlled by continuous intravenous infusions of insulin (typically 2–4 U/h) and glucose. Women on CSII can often be managed with adjustments in their infusion rates without the need for intravenous dextrose. After delivery, insulin requirements return almost immediately to pre-pregnancy values or less, and doses should be reduced in order to avoid hypoglycaemia. Elective caesarean section is indicated if mechanical problems with vaginal delivery are anticipated (e.g. malpresentation or disproportion), for fetal compromise and severe pre-eclampsia. Breastfeeding requires a further 10–20% reduction in insulin dose.

Type 2 diabetes

The numbers of pregnant women with type 2 diabetes are increasing, especially in the developing world where this type of diabetes predominates, but they also comprised 27.6% (n = 1041) of the CEMACH cohort in the UK. As a group, these UK women were older and much more likely to be of Afro-Caribbean, Asian or other ethnic minority background than those with type 1 diabetes (48.5% versus 8.5%). Women with type 2 diabetes more often present later in pregnancy and have other risk factors for poor outcome, such as obesity, hypertension and greater age and parity. However, outcome in the CEMACH cohort was no different from type 1 women.

Management of pregnancy in type 2 diabetes is the same as that for type 1 diabetes. In general, women should change to insulin before conception or early in the first trimester. Oral hypoglycaemic agents may not achieve sufficiently good glycaemic control; moreover, some cross the placenta, may aggravate fetal hyperinsulinaemia and are potentially teratogenic (although evidence is conflicting). Glibenclamide (glyburide) does not cross the placenta and although metformin does cross the placenta, there is increasing experience of its use (particularly in gestational diabetes) such that it is currently supported by NICE and so far there have been no safety concerns.

Gestational diabetes

Gestational diabetes mellitus (GDM) is glucose intolerance first recognised in pregnancy. It will therefore include women with impaired glucose tolerance, those with previously unrecognised type 2 diabetes and those who develop type 1 diabetes when pregnant. The earlier in pregnancy it is diagnosed, the more likely it is to be type 1 or 2 diabetes. The pathophysiology is a combination of pregnancy-induced insulin resistance and diminished insulin secretory capacity. Some studies suggest that women who develop GDM have demonstrable deficiencies in β cell function prior to pregnancy. There are no universally agreed diagnostic criteria, but the World Health Organization definition (which is similar to IGT outside pregnancy, i.e. plasma glucose >7.8 mmol/L 2 hours after a 75 g oral glucose load) is used widely and forms the basis of NICE guidance in the UK. However, this definition is likely to change as a result of the Hyperglycaemia and Adverse Pregnancy Outcomes (HAPO) Study which has shown a linear relationship between fasting and postglucose load plasma glucose for birthweight (OR for birthweight >90th centile is 1.32 for each 0.4 mmol/L

Table 27.1 Diagnostic values for the diagnosis of gestational or overt diabetes in pregnancy

		Plasma glucose threshold*	
GDM	Fasting	5.1 mmol/L	92 mg/dL
	1 hr post 75 g OGTT	10.0 mmol/L	180 mg/dL
	2 hr post 75 g OGTT	8.5 mmol/L	153 mg/dL
		Diagnostic threshold†	
Overt diabetes	Fasting	≥7.0 mmol/L	≥126 mg/dL
	HbA_{1c}	≥6.5%	≥48 mmol/mol
	Random plasma glucose	≥11.1 mmol/L	≥200 mg/dL + one of above

*One or more of glucose threshold values must be exceeded for a diagnosis of GDM.
†If random glucose is used then diagnosis must be confirmed with a fasting value and/or HbA_{1c}.
Adapted from International Association of Diabetes and Pregnancy Study Groups consensus Panel. Diabetes Care 2010; 33: 676–682.

increase in fasting plasma glucose and 1.38 for each 1.3 mmol/L increase in 2-hour post 75 g oral glucose load) (Table 27.1). There was no cut-off point. An expert panel has reviewed the data and produced an international consensus on diagnostic plasma glucose levels (Table 27.1). The implication of these new criteria is that up to 18% of women may now meet the diagnostic criteria for GDM (based on the HAPO study).

Because of the lack of agreed diagnostic criteria, true prevalence is hard to ascertain but it is said to affect 1–14% of all pregnancies in the USA and 3–5% in the UK, although this varies considerably by ethnicity (white Europid ~0.4%; Asian 7.3%).

The publication of the Australian Carbohydrate Intolerance Study in Pregnant Women (ACHOIS) demonstrated for the first time that intervention with intensive glucose control could reduce complications for the mother and child. As a result, there is now an intensive debate about the benefit of screening, its timing, diagnostic criteria and treatment. Neither NICE nor the US Preventive Services Task Force currently recommends population screening, but most national guidelines suggest a targeted approach even though there are data to suggest that this will miss a significant number of cases. A meta-analysis of 20 studies has shown an increasing OR for GDM for increasing maternal weight (2.14, 3.56 and 8.56 for the overweight, obese [BMI >30 kg/m^2] and severely obese [BMI >40 kg/m^2] respectively).

Treatment is controversial, but the glycaemic targets are similar to those for established diabetes. Dietary assessment and carbohydrate reduction to 35–40% of total daily calorie

Box 27.5 Screening strategy for detection of gestational diabetes based upon risk factor assessment. Adapted from Metzger et al. Diabetes Care 2007; 30(Suppl 2): S259

Risk assessment of gestational diabetes should be ascertained at the first prenatal visit.

Low risk: blood glucose testing not routinely required if all the following characteristics are present
- Member of an ethnic group with a low prevalence of gestational diabetes
- No known diabetes in first-degree relatives
- Age <25 years old
- Weight normal before pregnancy
- Weight normal at birth
- No history of abnormal glucose metabolism
- No history of poor obstetric outcome

Average risk: do blood glucose testing at 24–28 weeks' gestation using either:
- Two-step procedure: 50 g glucose challenge test followed by a diagnostic oral glucose tolerance test in those meeting the threshold value in the glucose challenge test
- One-step procedure: diagnostic oral glucose tolerance test done in all individuals

High risk: do blood glucose testing as soon as possible, using the procedures described above if one or more of these are present
- Severe obesity
- Strong family history of type 2 diabetes
- Previous history of gestational diabetes, impaired glucose metabolism or glycosuria

If gestational diabetes is not diagnosed, blood glucose testing should be repeated at 24–28 weeks' gestation or whenever a patient has symptoms or signs that are suggestive of hyperglycaemia.

Box 27.6 NICE guidance (CG 63) on risk factors for screening for gestational diabetes

- BMI >30 kg/m^2
- Previous macrosomic infant >4.5 kg birthweight
- Previous GDM
- First-degree relative with diabetes
- Family origin with a high prevalence of diabetes (South Asian, black Caribbean or Middle Eastern)
- Screen at 16–18 weeks if previous GDM
- 75 g OGTT at 24–28 weeks if any other risk factors, or first test normal

intake (30% if obese) is recommended by the ADA although there is little firm supportive evidence. Other lifestyle advice in terms of increasing exercise should be given and a 2-week trial of both with home blood glucose monitoring is recommended. If glycaemic targets are not achieved then treatment with glibenclamide (up to 20 mg/day, and dosage up to 3 times daily 30–60 mins before meals), metformin (up to 2500 mg/d but starting at 500 mg/d) or acarbose (50 mg tds) should be considered. There are no trial data for combination therapy. If targets are still not reached then insulin should be started.

There is no evidence-based guidance on preferred mode of delivery but because many of the babies are large there is a risk of birth trauma and inevitably the caesarean section rate is high. Neonates have a similar risk for the same medical problems as for the offspring of mothers with pregestational diabetes. Moreover, macrosomic infants have a twofold risk for childhood obesity and an increased odds for developing diabetes and cardiovascular disease in adulthood. It is not known if prevention of macrosomia will reduce these risks; prospective and long-term studies will be required to settle this question.

Diabetes usually resolves after delivery (except in those with type 1 or 2 diabetes) but is very likely to recur in subsequent pregnancies, and the lifetime risk of developing type 2 diabetes over the subsequent 10 years is linear at 35–60%, depending on the background risk of the population. Women who have had GDM therefore need health education about reducing weight, increasing exercise and improving their cardiovascular risk profile.

KEY WEBSITES

- NICE Guidance on Diabetes in Pregnancy CG 63: www.nice.org.uk/nicemedia/pdf/DiabetesFullGuidelineRevisedJULY2008.pdf
- American Diabetes Association Standards of Care: http://care.diabetesjournals.org/ content/32/Supplement_1/S6.full
- CEMACH: www.cemach.org.uk
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Chapter

28

Diabetes in childhood and adolescence

KEY POINTS

- The incidence of type 1 diabetes is rising, especially among children <4 years. For example, the prevalence of type 1 diabetes in Europe among those <15 years old will increase from 94,000 in 2005 to 160,000 in 2020.
- There is considerable unexplained geographic variation in the incidence of type 1 diabetes within Europe.
- Type 1 diabetes usually presents acutely with diabetic ketoacidosis which can be life-threatening due to cerebral oedema, especially if pH <7.0.
- Significant associations are found between the HLA region on chromosome 6p21 and the most common form of type 1 diabetes (type 1A). HLA-DR and HLA-DQ genes also affect genetic susceptibility.
- A partial remission ('honeymoon phase') may occur soon after the diagnosis of type 1 diabetes, resulting in much reduced insulin requirements for up to 2 years.
- Continuous subcutaneous insulin infusion (CSII, insulin pump therapy) is a treatment option when multiple injections are failing to achieve glycaemic control and/or disabling hypoglycaemia is problematic.

The vast majority of cases of diabetes in children are type 1, caused by autoimmune destruction of β cells in the pancreatic islets. A steady increase in the incidence of type 1 diabetes has been reported worldwide (average increase 2.5–3% per year worldwide with significant geographical variations), especially in children aged <4 years. This suggests changes in environmental factors that operate early in life. The incidence of type 1 diabetes varies considerably between countries; for example, the lowest incidence is in China and the highest in Finland and Sardinia (Figure 28.1). Rarer causes of diabetes in childhood include cystic fibrosis (which usually requires insulin), the rare transient and permanent neonatal forms of diabetes, maturity-onset diabetes of the young (MODY, see Chapter 8) and various other genetic syndromes such as Down's syndrome, Wolfram or DIDMOAD (diabetes insipidus, diabetes mellitus, optic atrophy and deafness) syndrome, lipoatrophic diabetes and diabetes associated with mitochondrial mutations (see Chapter 8). Type 2 diabetes is also increasing in childhood.

Among children aged <14 years of age, the number of new cases of type 1 diabetes in Europe in 2005 is estimated at 15,000. The predicted number of new cases in 2020 is >24,000 with a doubling in numbers diagnosed among children below 5 years. The prevalence of type 1 diabetes in

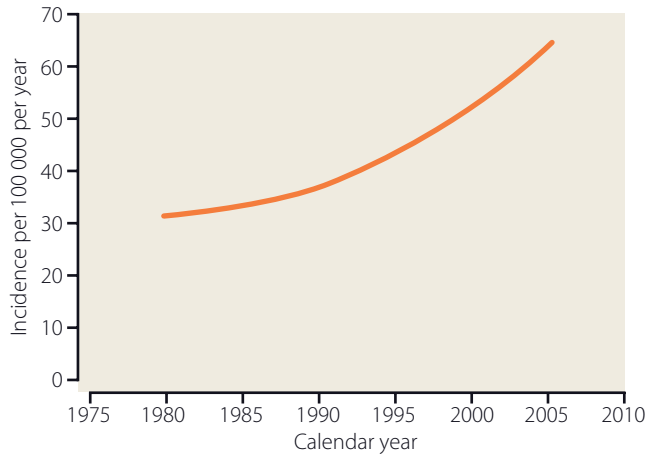

Figure 28.1 Finland has one of the highest rates of type 1 diabetes in Europe. This graph shows the rising incidence of type 1 diabetes in Finland diagnosed at or before 14 years of age. Adapted from Harjutsalo et al. Lancet 2008; 371: 1777-1782.

Handbook of Diabetes, 4th edition. By © Rudy Bilous & Richard Donnelly. Published 2010 by Blackwell Publishing Ltd.

Europe among those under 15 years is predicted to increase from 94,000 in 2005 to 160,000 in 2020 (Figure 28.2).

There is considerable geographical variation in the incidence of type 1 diabetes within Europe (up to 10-fold), but the explanation for these differences and the increasing trend towards younger age at diagnosis is unclear (Figure 28.3). The maternal and infant environment, as well as dietary factors, may be important. Data are inconsistent with respect to breastfeeding, and the introduction of cow's milk and cereals. An emerging dietary risk factor may be the early consumption of root vegetables (potatoes, carrots, etc.) between 3–4 months of age, and it is interesting that per-capita consumption of potatoes correlates with the incidence of type 1 diabetes in different countries. Other possible triggers for type 1 diabetes in early life include placental transmission of enteroviruses, food toxins and cereals which could activate autoimmune pathways during pregnancy.

Childhood diabetes usually presents acutely with polyuria (including nocturia and incontinence), thirst and polydipsia; about 40% have diabetic ketoacidosis (DKA) (Table 28.1). Other symptoms are weight loss, fatigue and abdominal pain. A simultaneous febrile illness is noted in about 20% of cases, particularly in younger children. Other possible presenting features include muscle cramps, infections (e.g. boils, urinary tract infections), behaviour disturbance and poor school performance.

As with adults, DKA in children is a medical emergency that requires urgent admission to hospital, intravenous

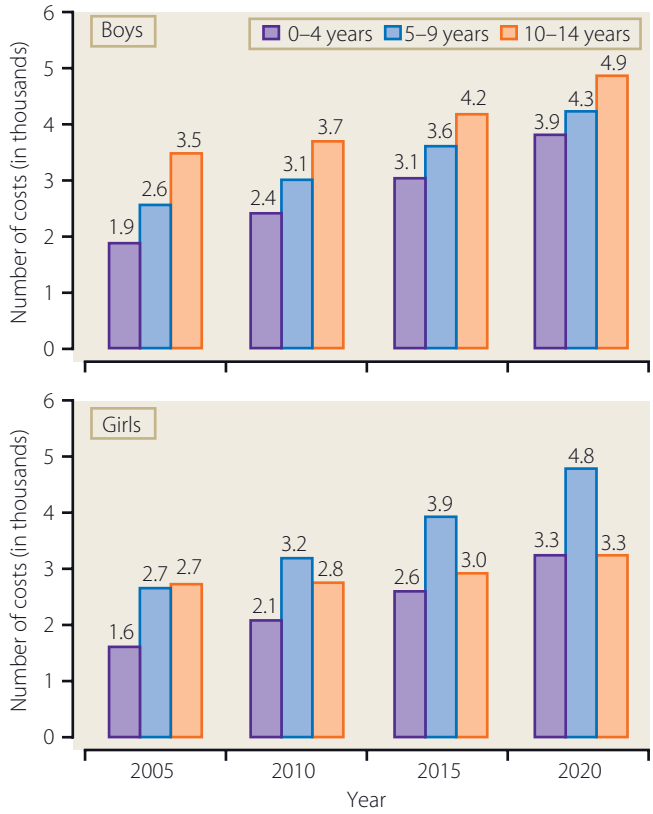

Figure 28.2 Actual and predicted numbers of new diagnoses of childhood-onset type 1 diabetes in Europe for boys and girls in three age bands: 0–4 years, 5–9 years and 10–14 years. Adapted from Patterson et al. Lancet 2009; 373: 2027-2033.

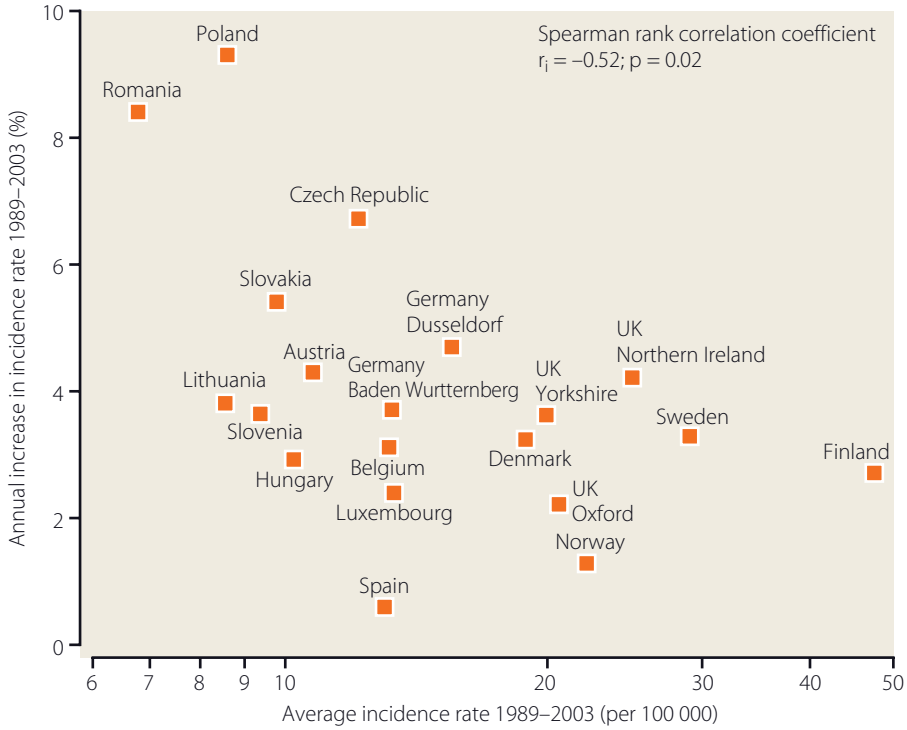

Figure 28.3 There seems to be an inverse relationship, across Europe, between the average incidence rate of type 1 diabetes (1989–2003), per 100,000 population and the annual increase in incidence (%), i.e. those countries with the lower incidence (e.g. Eastern European countries like Poland and Romania) are showing the highest rate of increase. Adapted from Patterson et al. Lancet 2009; 373: 2027-2033.

CASE HISTORY

A 14-year-old girl has a 5-year history of type 1 diabetes treated with twice-daily mixed insulin. She has had three hospital admissions with diabetic ketoacidosis over the last 2 years, and her glycaemic control is poor (HbA_{1c} range 8.6–10.3%). In addition, there have been frequent episodes of severe hypoglycaemia requiring third-party assistance. These have been more frequent during puberty. At her last retinal screening visit, there were signs of background retinopathy in both eyes. She has missed a lot of schooling as a result of her diabetes, and she admits to frequently missing her insulin injections and/or missing meals.

Comment: This case history is typical of the challenges faced by young patients, their parents and the healthcare team in managing type 1 diabetes, particularly during adolescence. There is good evidence from the DCCT/EDIC study that early tight glycaemic control has long-lasting benefits in terms of fewer complications, but balancing insulin therapy with the lifestyle of a teenager and motivating them to self-manage their disease can be extremely difficult. This girl could be considered for insulin pump therapy, which can be very effective. She has had disabling hypoglycaemia and failed to achieve adequate glycaemic control using two or three injections per day.

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rehydration and insulin infusion. Severe acidosis (pH <7.0) is life-threatening. Unless there is initial hyperkalaemia, potassium is added early, at the rate of 20 mmol/L of saline, because the serum K^+ concentration is likely to fall during insulin replacement. The usual rate of insulin infusion is 0.1 U/kg/h or 0.05 U/kg/h in the child <5 years of age. The initial saline infusion should be replaced by 5% glucose (dextrose) when the plasma glucose reaches about 14 mmol/L (Figure 28.4).

The most common cause of death during DKA in children is cerebral oedema, which leads to herniation of the brainstem, extension of the cerebellar tonsils into the foramen magnum and respiratory arrest (Figure 28.5). It is diagnosed by magnetic resonance imaging or computed tomography of the brain. Clinically, there is headache, depressed consciousness and sometimes papilloedema. Cerebral oedema is unpredictable but more common in younger children, and carries a mortality of 25%. Risk factors include low arterial PCO_2, elevated blood urea and treatment with bicarbonate. Over-rapid delivery of fluid and insulin might be involved also. The treatment involves intravenous mannitol (20% mannitol, 2.5 mL/kg over 15 minutes, repeated if necessary) or use of hypertonic saline. Other causes of death include aspiration pneumonia and hypokalaemia.

Table 28.1 Symptoms before diagnosis in 1260 children with type 1 diabetes

	Symptom noted *n* (%)	**First symptom noted by the family *n* (%)**
Polyuria	1159 (96%)	854 (71%)
Weight loss	731 (61%)	104 (9%)
Fatigue	630 (52%)	82 (7%)
Abdominal pain	277 (23%)	31 (3%)
Changes in character	137 (11%)	22 (2%)
Others	238 (19%)	36 (3%)
No symptom/unspecified	16 (1%)	78 (6%)

Type 1 diabetes has two subtypes: type 1A includes the common, immune-mediated forms of the disease, and type 1B includes the non-immune forms. The common form of type 1A diabetes is probably caused by multiple actions, and

Confirm the diagnosis of DKA: investigations

- High blood sugar on fingerprick test (> 11 mmol/L)
- Blood pH < 7.3 and/or HCO_3 < 15 mmol/L
- Fingerprick blood ketones > 3.0 mmol/L
- Blood gases – venous blood gives very similar pH and pCO_2 to arterial
- Near-patient blood ketones superior to urine ketones

Clinical assessment

- Degree of dehydration:
  - Mild, 3% - barely clinically detectable
  - Moderate, 5% - dry mucous membranes
  - Severe, 8% - sunken eyes, poor capillary return + shock – severely ill, thready pulse
- Conscious level ?
- Cerebral oedema ?
- Infection ?
- Ileus ?
- Weigh the child

Fluid replacement

- Once circulating volume restored, calculate fluid requirements as:

  Fluid reqd = maintenance + deficit – fluid already given

  deficit (L) = % dehydration x body wt (kg)

- For most children, use 5–8% dehydration to calculate fluids
- Maintenance requirements by wt:

  0–12.9 kg — 80mL/kg/24 hrs
  13–19.9 kg — 65mL/kg/24 hrs
  20–34.9 kg — 55mL/kg/24 hrs
  35–55.9 kg — 45mL/kg/24 hrs
  > 60kg — 35mL/kg/24 hrs

- Neonates may need larger volumes, e.g. 100–150 mL/kg/24 hrs
- N saline + 20 mmol KCL in 500 mL, continued for first 12hr of rehydration

Management

- Insulin by continuous low-dose IV infusion, started 1 hr after fluid replacement begins
- Insulin infusion made-up as 1 unit/mL (e.g. Actrapid)
- Insulin infusion: 0.1 units per kg per hour. No need for initial bolus
- HCO_3 is rarely, if ever, needed except in profound acidosis (pH < 6.9) and/or circulatory collapse
- Long-acting insulin therapy (e.g. Glargine) may be continued during DKA treatment
- Femoral lines may risk venous thrombosis: consider prophylaxis
- Stop insulin pump treatment during DKA treatment (if patient using pump therapy)
- Use fingerprick blood ketone levels

Figure 28.4 Key learning points in the assessment and management of DKA in children. Extracts adapted from the updated (2009) guidelines of the British Society of Paediatric Endocrinology and Diabetes.

interactions, of genetic and environmental factors. Genetic linkage studies have shown significant associations between the HLA region on chromosome 6p21 and type 1A diabetes. In addition, class II genes encoding HLA-DR and HLA-DQ, as well as some other HLA foci, seem to account for most of the genetic risk for type 1A diabetes. Thus, children who carry both of the highest risk HLA haplotypes (DR3-DQ2 and DR4-DQ8) have a risk of approximately 1 in 20 for developing type 1 diabetes by the age of 15 years. Current approaches for the prediction of type 1 diabetes rely on the major genetic risk factors, genotyping for HLA-DR and HLA-DQ loci, and screening for autoantibodies directed against islet cell antigens (Figure 28.6).

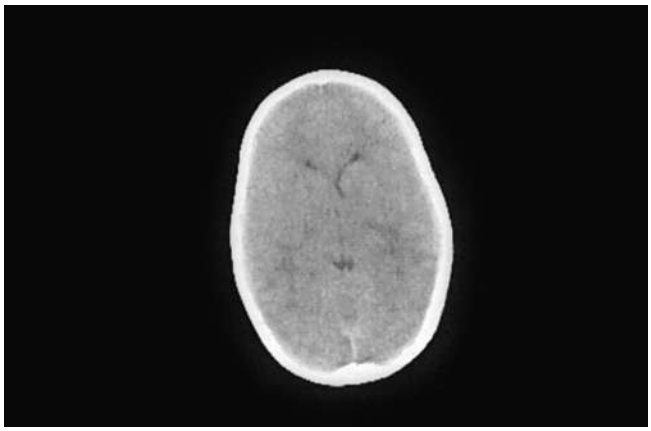

Figure 28.5 CT scan of the brain of a child with diabetic ketoacidosis complicated by cerebral oedema. There is marked swelling of the brain substance with compression of the lateral ventricles.

Twice-daily injections of short- and intermediate-acting insulins are most common in paediatric practice. Monomeric insulins, such as lispro or aspart, which can be injected with or even after meals, are helpful in toddlers with their erratic appetites. These insulin analogues may also reduce nocturnal hypoglycaemia. After the diagnosis of diabetes, there is sometimes a partial remission (the 'honeymoon period'), lasting from a few months to 2 years, during which the insulin dose is <0.5 U/kg. This is due to a transient improvement in residual β cell function. It is usual to maintain low-dose insulin treatment during the honeymoon period. Use of multiple daily injections, or long-acting analogues, has no effect on the duration of this honeymoon phase. Children and young adults with type 1 diabetes should be screened regularly for complications (Box 28.1).

Hypoglycaemia is common in children with diabetes, particularly in younger children who cannot communicate and in whom signs of hypoglycaemia (pallor, drowsiness, lethargy) are often detected by the parents (Figure 28.7, Table 28.2). Moreover, young children are at risk of later neuropsychological impairment from severe, recurrent hypoglycaemia. Presumably, this relates to the effect of hypoglycaemia on the developing brain. Even older children

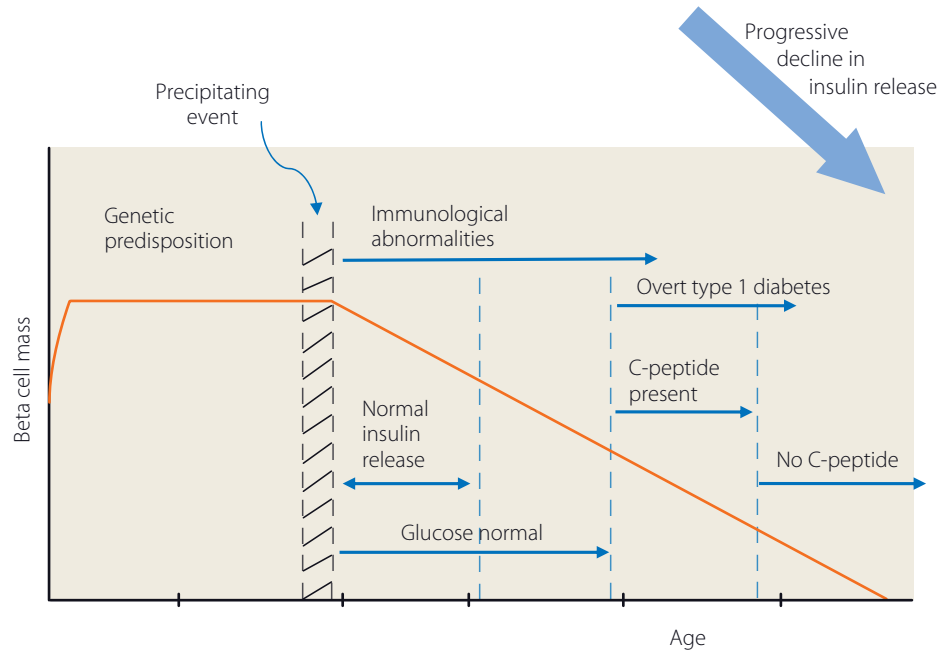

Figure 28.6 Type 1 diabetes has a preclinical phase of varying duration when autoimmune destruction of β cells reduces β cell mass in the pancreatic islets. This probably follows a precipitating event. Gradually, β cell mass is reduced to a point when glucose levels can no longer be maintained within normal limits. This schematic illustrates stages in the development of type 1A diabetes. It also illustrates a potential window for therapeutic intervention during the preclinical phase to prevent the onset of overt diabetes. Trials of immunosuppressive therapies in high-risk indiviuduals are ongoing.

Box 28.1 According to the NICE guideline, children and young people with type 1 diabetes should be offered screening for:

- Coeliac disease – at diagnosis and every 3 years thereafter
- Thyroid disease – at diagnosis and annually thereafter
- Retinopathy – annually from age 12 years
- Microalbuminuria – annually from age 12 years
- Blood pressure – annually from age 12 years

Clinicians should also be aware of the rarer complications: juvenile cataracts and Addison's disease

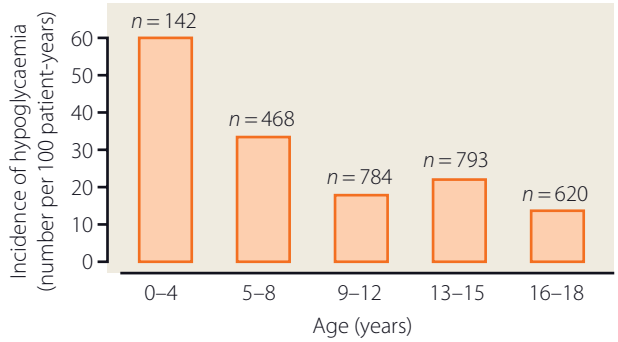

Figure 28.7 Incidence of hypoglycaemia (unconsciousness or seizures) in different age groups with type 1 diabetes.

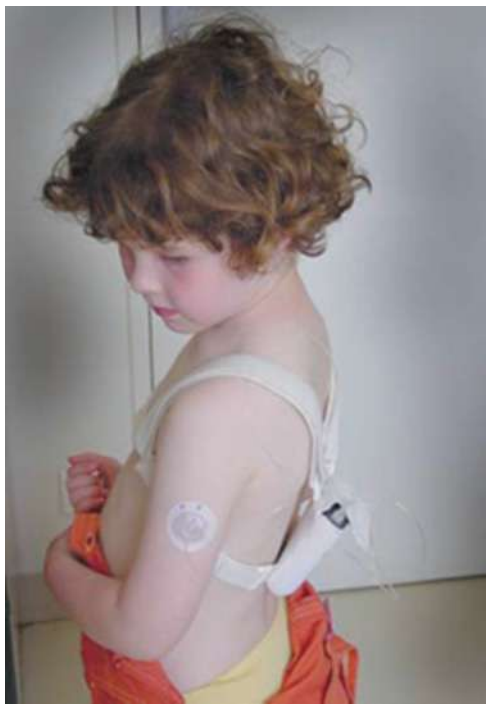

Figure 28.8 Insulin pump treatment for a child with type 1 diabetes.

Table 28.2 Clinical features of hypoglycaemia in children

Neuroglycopenic and autonomic	Behavioural
Reported by the children	
Weakness	Headache
Trembling	Argumentative
Dizziness	Aggressive
Poor concentration	Irritability
Hunger	Naughty
Sweating	
Confusion	
Blurred vision	
Slurred speech	Nausea
Double vision	Nightmares
Observed by the parents	
As above, plus:	
Pallor	
Sleepiness	
Convulsions	

From Mortensen et al. Diabetes Care 1997; 20: 714–720.

are less able to detect hypoglycaemia than adults. Behavioural manifestations of hypoglycaemia include aggression, irritability, sadness, fatigue and naughtiness.

Continuous subcutaneous insulin infusion (CSII, insulin pump therapy) is an alternative option for achieving strict metabolic control in selected patients, particularly in children who have been unable to maintain adequate glycaemic control with multiple-dose injections without frequent, unpredictable and disabling hypoglycaemia (Figure 28.8). Experience of CSII in children is less extensive than in adults but it is rapidly gaining in popularity. As with adults, careful selection of patients and a healthcare team experienced in insulin pump therapy are essential.

The prevalence of impaired glucose tolerance and type 2 diabetes in children is increasing in parallel with the increase in childhood obesity. When type 2 diabetes is diagnosed in young people, most are undergoing puberty, so perhaps the increased insulin resistance of puberty triggers or unmasks the type 2 diabetes (Box 28.2). Most of these children also belong to a high-risk ethnic group, i.e. African, Caribbean, Asian or Latino descent. There may be clinical signs of insulin resistance apart from obesity, such as acanthosis nigricans or the polycystic ovary syndrome. The pathophysiology of type 2 diabetes in childhood is probably similar to that in adults (see Chapter 7).

KEY WEBSITES

- www.nice.org.uk/nicemedia/pdf/CG015NICEguideline.pdf
- www.ispad.org/FileCenter/10-Wolfsdorf_Ped_Diab_2007,8.28-43.pdf
- SIGN Guidelines: www.SIGN.ac.uk

Box 28.2 Diagnostic features of type 2 diabetes in children

- Family history of type 2 diabetes
- High-risk ethnic groups: African-American, Asian, Caribbean, Latino
- Obesity
- Female sex
- Pubertal period
- Clinical signs of insulin resistance: acanthosis nigricans, polycystic ovary signs
- Biological signs of insulin resistance: detectable, high or normal insulin or C-peptide level
- No insulin therapy necessary for survival

Negative facts in favour of type 2 diabetes

- No HLA haplotypes associated with type 1 diabetes
- No signs of autoimmunity: no anti-islet cell antibodies

FURTHER READING

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Chapter

29

Diabetes in old age

KEY POINTS

- There is a steep age-related increase in the risk of type 2 diabetes. By 2030 there will be >82 million people with diabetes over the age of 64 years in developing countries alone.
- Type 2 diabetes often presents late, insidiously and/or is undetected in older patients. Subtle symptoms affecting mental state may not be recognised.
- The fosus of management in older patients is on symptom control, in particular avoiding recurrent infections, thirst, incontinence and fatigue.
- Hypoglycaemia may be more common, and carry greater risks, in elderly patients with an inconsistent dietary intake, impaired renal function and/or frailty with autonomic imbalance.
- DPP-4 inhibitors, rather than sulphonylureas, may be safer in elderly patients because of less risk of hypoglycaemia.
- Metformin may be difficult to use in elderly patients because of renal impairment and the risk of lactic acidosis, and in elderly patients the GI side effects may be more troublesome.

There is a steep age-related increase in the prevalence of diabetes and impaired glucose tolerance which applies equally to both sexes. Overall, diabetes prevalence is higher in men but there are more women with diabetes. In developing countries, most people with diabetes are in the 45–64 year age band, whereas in developed countries the majority of people with diabetes are aged >64 years (Figure 29.1). There is a particularly high frequency of type 2 diabetes in certain susceptible ethnic groups such as black Americans and Mexican Americans (about 30% of the elderly).

By the year 2030, it is estimated that the number of people with diabetes over 64 years of age will be >82 million in developing countries and >48 million in developed countries (Figure 29.2). In future years, a bigger proportion of the diabetes population will be elderly. This will have a

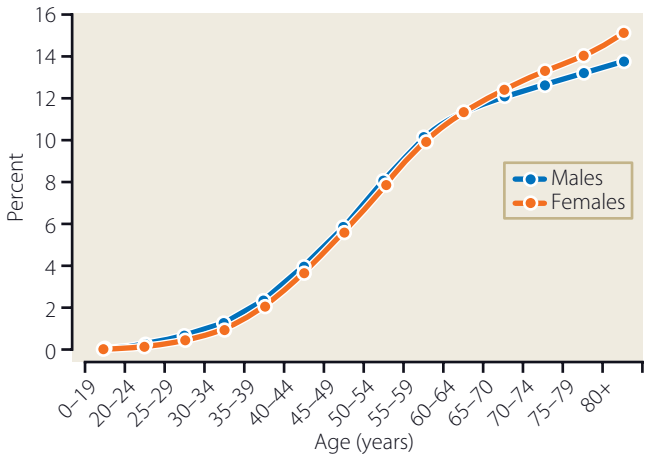

Figure 29.1 Global diabetes prevalence by age and sex (data from 2000). Adapted from Wild et al. Diabetes Care 2004; 27: 1047–1053.

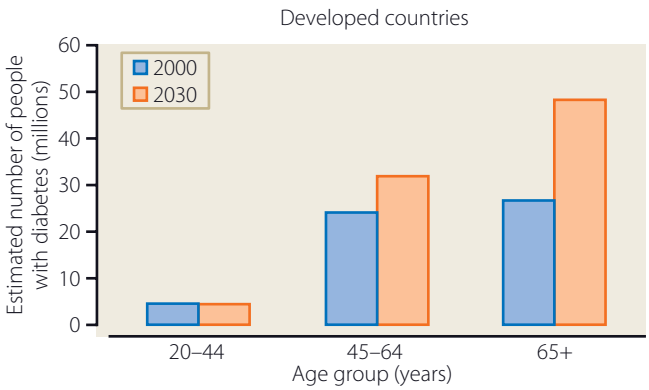

Figure 29.2 Estimated number of adults with diabetes in developed countries by age in 2030 compared with 2000. Adapted from Wild et al. Diabetes Care 2004; 27: 1047–1053.

CASE HISTORY

A family doctor was asked to review an 86-year-old lady living in a nursing home. She was confused, febrile and incontinent of urine. Normally, she mobilises with a frame and has short-term memory difficulties, but for several days she has been unwell, more confused and off her feet. The GP notes an episode of left leg cellulitis, treated with antibiotics, 1 month ago. On examination, she is obese, febrile, confused and clinically dehydrated. The GP suspects a urinary tract infection. It has been impossible to dipstick her urine; blood tests are sent off. These confirm a raised white cell count (neutrophilia), impaired renal function and elevated random serum glucose (23 mmol/L). HbA_{1c} 9.1%.

Comment: Infections, dehydration and urinary incontinence can often reflect undiagnosed diabetes in the elderly. In turn, these metabolic disturbances can affect cognitive function. The emphasis should be on symptom control. This lady needs rehydration and treatment. With renal impairment, a glitazone may be preferred or, for practical reasons, it may be easier to start once-daily basal insulin therapy instead of an oral agent, especially if her intake is limited.

LANDMARK CLINICAL TRIALS

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Box 29.1 The various ways in which diabetes may present in the elderly

- Non-specific symptoms (lassitude, confusion, incontinence, falls, etc.)
- Presentation with co-morbidity (coincidental hyperglycaemia)
  - cardiovascular disease (NB: myocardial infarction may be silent in the elderly)
  - delayed recovery from illness (e.g. stroke)
  - repeated infections
- Classic osmotic symptoms
- Acute metabolic disturbance (mostly HONK, rarely DKA)

number of effects on clinical practice. The presentation, management and outcomes of diabetes are different in older patients, especially if diabetes occurs in the context of other co-morbidities, frailty, physical and cognitive impairment and multiple drug therapies.

The presentation of diabetes in older people is often insidious and the diagnosis is often delayed. The symptoms can be non-specific and vague, such as fatigue, urinary incontinence or change in mental state (e.g. depression, confusion and apathy) (Box 29.1). Many cases are detected by finding incidental hyperglycaemia during the investigation of co-morbidities, such as a delayed recovery from specific illnesses, repeated infections or cardiovascular disease; the latter may present with atypical features, such as painless myocardial infarction, manifested as breathlessness, lassitude or falls. Acute metabolic disturbance is a further, rarer presentation: about 25% of cases of hyperosmolar non-ketotic hyperglycaemic coma (HONK, see Chapter 12) occur in people with previously undiagnosed type 2 diabetes. The tendency to hyperosmolarity may be worse in elderly people, who may not perceive thirst or drink enough to compensate for the osmotic diuresis of diabetes, and who are often taking diuretics.

Elderly patients with diabetes require treatment mainly to alleviate symptoms, to reduce the risk of hyperglycaemic crises, to prevent and manage vascular and other complications and to achieve a normal life expectancy whenever possible (Box 29.2). Strict glycaemic control may not always be appropriate. Diets rarely produce weight loss in the elderly and may be unjustifiably burdensome in the frail. Short-acting sulphonylureas such as gliclazide, or DPP-4 inhibitors, are preferred because of the likelihood in the elderly of impaired renal function, poor nutrition, impaired counter-regulatory responses and cognition, and other factors that increase the risk of hypoglycaemia. Metformin is best avoided in many elderly subjects because of its

Table 29.1 General guidelines for treatment in older people

	Indications	Advantages	Disadvantages
Once-daily insulin	• Frail subjects • Very old (>80 y) • Symptomatic control	• Single injection • Can be given by carer or district nurse	• Control usually poor • Hypoglycaemia common
Twice-daily insulin	• Preferred if good glycaemic control • Suitable for type 1 diabetes	• Low risk of hypoglycaemia • Easily managed by most older people with diabetes	• Normoglycaemia difficult to achieve • Fixed meal times reduce flexibility
Basal/bolus insulin	• Well-motivated individuals • Can reduce microvascular complications	• Enables tight control • For acute illness in hospital • Flexible meal times	• Frequest monitoring required to avoid hypoglycaemia
Insulin plus oral agents	• If glycaemic control is unsatisfactory with oral agents alone • To limit weight gain in obese subjects	• Limits weight gain by reducing total daily insulin • Increased flexibility	• May delay conversion to insulin in thin or patients with type 1 diabetes

Box 29.2 Diabetes in the elderly: key points with respect to treatment approach

- The risks versus benefits of tight glycaemic control merit careful consideration
- Hypoglycaemia can be life-threatening
- DPP-4 inhibitors may be safer than sulphonylureas
- Avoid metformin
- Use simple insulin regimens

KEY WEBSITES

- www.diabetes.co.uk/diabetes-and-the-elderly.html
- www.diabetes-healthnet.ac.uk/HandBook/DiabetesSpecialCircumstancesElderly.aspx
- SIGN Guidelines: www.SIGN.ac.uk

increased tendency to cause lactic acidosis with renal impairment and hepatic or cardiac failure.

Simple insulin regimens are usually the most appropriate in diabetes of old age. Twice-daily injections of premixed insulins for type 1 diabetes or NPH insulin in type 2 patients are preferred. However, the practical difficulties of administration can limit their use in some patients and once-daily insulin, though unlikely to produce good control, may be more suitable for the very old and frail. The use of once- or twice-daily injections of the long-acting insulin analogues glargine or detemir may be advantageous and practical. The traditional multiple-dose, basal-bolus regimen for achieving near normoglycaemia is probably only suitable for the comparatively few well-motivated, mobile and mentally alert patients who are independent in self-care and have no other medical disorders.

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Chapter

30 Diabetes and lifestyle

KEY POINTS

- Most countries issue driving guidance for people with diabetes, particularly for those on insulin or other therapies with a risk of hypoglycaemia. Many countries apply restrictions with regard to the type of vehicle that can be driven by people on insulin therapy.
- Disability discrimination legislation makes it illegal to impose restrictions on people with diabetes with regard to employment but there are exceptions which vary between and within countries.
- Smoking confers a risk both for the development of diabetes and for its complications.
- Diabetes is not a bar to long distance travel but planning is necessary beforehand and individual identification is essential, particularly if transporting insulin and injecting devices.

Driving

In many countries, drivers with diabetes are legally required to declare the diagnosis to the national licensing authority and to the vehicle insurer. The main problems for drivers with diabetes are hypoglycaemia and visual impairment from cataract or retinopathy. Rarely, disability from severe neuropathy, peripheral vascular disease or leg amputation can present mechanical difficulties, but usually these can be overcome by adapting the vehicle or using automatic transmission.

Different countries apply different restrictions on the type of vehicle that can be driven by people with diabetes who are on insulin treatment. In the UK and most of the European Union, people taking insulin cannot drive large goods or passenger carrying (including minibuses with more than 9 passengers) vehicles (Box 30.1). In the USA there is now a relaxation of restrictions for large goods vehicle drivers providing they have satisfactory glycaemic control and are not subject to hypoglycaemia.

General advice to the driver with diabetes includes the requirement in most countries to declare diabetes to the relevant authorities (Box 30.2). Drivers with diabetes must actively avoid hypoglycaemia – motor skills and judgement can be reduced at blood glucose levels of 3–4 mmol/L (54–72 mg/dL), without obvious hypoglycaemic symptoms. Impaired awareness of hypoglycaemia is therefore a relative contraindication to driving. If hypoglycaemia occurs while driving, subjects should stop, leave the driver's seat and wait 45–60 minutes before driving again. Hypoglycaemia can resemble alcohol intoxication and people with diabetes can be arrested on the assumption that they are drunk – they should therefore carry an identity card or bracelet that states they have diabetes. Worryingly, a recent survey in the UK found that no more than a third of drivers adhere to these recommendations and many do no blood glucose tests at all prior to driving.

Box 30.1 UK regulations on the need for patients to inform the licensing authority (DVLA) of their diabetes

- Requirement for insulin treatment
- Laser treatment to both eyes (or in the remaining eye if you have sight in one eye only)
- Visual problems (need to read a car registration plate in good light at 20.5 m)
- Circulation or sensation problems in feet
- One or more disabling hypoglycaemic episodes in last year (or patients and/or their carer feel they are at risk)
- Hypoglycaemic unawareness
- Any episode of disabling hypoglycaemia while driving

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Box 30.2 Current recommendations from UK DVLA for people with diabetes on insulin who drive

Drivers with insulin-treated diabetes are advised to take the following precautions

- Do not drive if you feel hypoglycaemic or if your blood glucose is less than 4.0 mmol/L.
- If hypoglycaemia develops while driving, stop the vehicle as soon as possible in a safe location, switch off the engine, remove the keys from the ignition and move from the driver's seat.
- Do not resume driving until 45 minutes after blood glucose has returned to normal. It takes up to 45 minutes for the brain to fully recover.
- Always keep an emergency supply of fast-acting carbohydrate such as glucose tablets or sweets within easy reach in the vehicle.
- Carry your glucose meter and blood glucose strips with you. Check blood glucose before driving (even on short journeys) and test regularly (every 2 hours) on long journeys. If blood glucose is 5.0 mmol/L or less, take a snack before driving.
- Carry personal identification indicating that you have diabetes in case of injury in a road traffic accident.
- Particular care should be taken during changes of insulin regimens, changes of lifestyle, exercise, travel and pregnancy.
- Take regular meals, snacks and rest periods on long journeys. Always avoid alcohol.

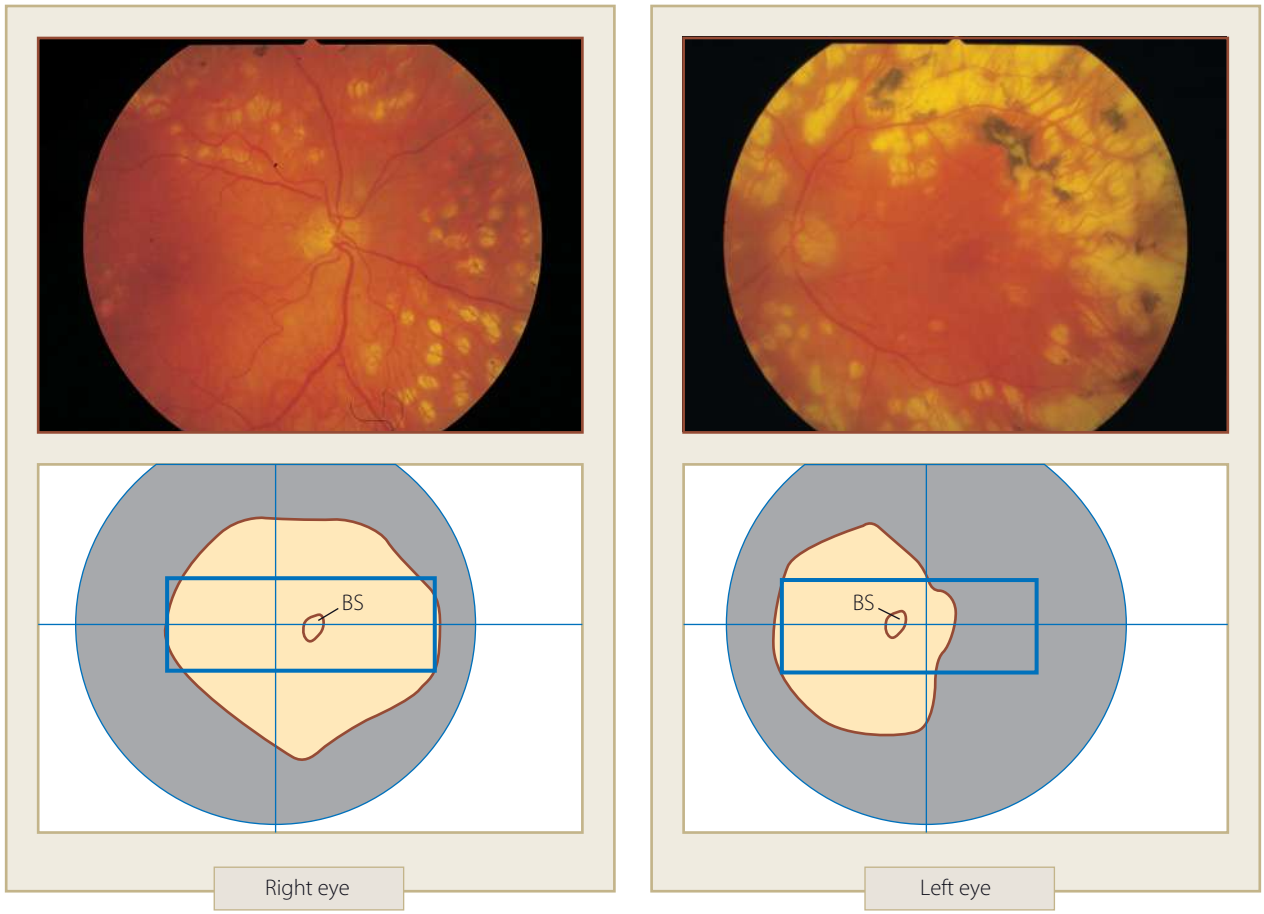

Figure 30.1 Visual field loss due to photocoagulation. This 60-year-old man with diabetes needed heavy laser photocoagulation to the temporal retina of the left eye, which caused nasal visual field loss such that this eye failed the standard test for driving. The right eye required less intensive laser treatment and the visual field was adequate for driving. He was allowed to drive. BS, blind spot. Blue rectangle: minimum area recommended for safe driving.

Whether diabetes *per se* is associated with an increased risk of accident remains controversial. However, data from the UK suggest that there are five fatal accidents per year and at least 45 serious incidents per month where one of the drivers has diabetes and there is a possibility of hypoglycaemia.

Corrected visual acuity worse than about 6/12 in the better eye precludes driving in the general population in many countries (e.g. in the UK), but subjects with diabetes with better acuity than this may still have visual field loss, poor night vision and impaired perception of movement because of retinopathy, laser treatment or cataracts (Figure 30.1).

Employment

People with diabetes can and should be encouraged to undertake a wide range of employment and, in the UK, diabetes is covered by the Disability Discrimination Act which means that it is now possible for individuals to work in almost any area (except the armed forces). Employment is generally restricted where hypoglycaemia poses a risk to the worker with diabetes or to his or her colleagues (Box 30.3). In most countries, employment is disbarred in the armed forces, civil aviation, emergency services such as fire fighting, in many forms of commercial driving and in dangerous areas such as off-shore and overhead working. Sometimes restrictions have been established by individual firms or industries, rather than by legislation. Individual assessment is desirable to take account of the type and method of treatment of diabetes.

Box 30.3 Forms of employment from which insulin-treated people with diabetes are excluded or will need to obtain individual assessment in order to continue employment in the UK

- Vocational (professional) driving
- Large goods vehicles (LGV)
- Passenger-carrying vehicles (PCV)
- Locomotives and underground trains
- Professional drivers (chauffeurs)
- Taxi drivers (variable; depends on local authority)
- National and emergency services
- Armed forces
- Police force
- Fire brigade or rescue services
- Merchant navy
- Prison and security services
- Civil aviation
- Commercial pilots and flight engineers
- Aircrew
- Air-traffic controllers
- Dangerous working areas
- Offshore: oil rigs, gas platforms
- Moving machinery
- Incinerators and hot-metal areas
- Work on railway tracks
- Coal mining
- Heights: overhead lines, cranes, scaffolding

Smoking

Smoking is one of the major avoidable causes of ill health and death. Smoking is a powerful independent risk factor for macrovascular disease and enhances the cardiovascular risk and mortality associated with diabetes (Figure 30.2). Smoking is also a risk factor for the development of type 2 diabetes (relative risk 1.44 but higher in those who smoke more), predisposes to microvascular and other complications and is associated with poorer glycaemic control (Box 30.4).

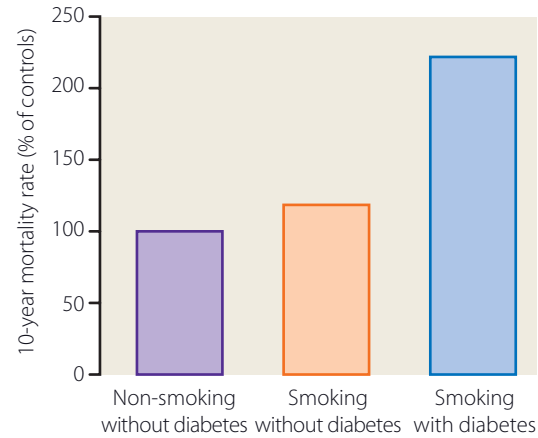

Figure 30.2 Deleterious effects of smoking and disease on 10-year mortality. Death rate is expressed as a percentage of age- and sex-matched, non-smoking populations without diabetes. From Suarez & Barrett-Connor. Am J Epidemiol 1984;120:670–675.

Box 30.4 Suggested deleterious effects of smoking on diabetes

Potentially diabetogenic
- Impairs glucose tolerance and insulin sensitivity
- Independent risk factor for type 2 diabetes

Atherogenic
- Independent risk factor: enhances atherogenic effect of diabetes
- Coagulation and haemorheological changes (increase viscosity, fibrinogen, free radicals and endothelial damage)

Risk factors for diabetic complications
- Retinopathy
- Nephropathy
- Limited joint mobility and necrobiosis lipoidica

Increases mortality

Strenuous efforts should be made to discourage smoking in patients with diabetes, but anti-smoking policies often fail. Fear of weight gain is a major reason for not giving up smoking. Measures to aid cessation of smoking include special 'stop smoking clinics', nicotine replacement (chewing gum or nasal sprays are probably better than dermal patches) and oral bupropion (a catecholamine reuptake inhibitor that may reduce craving and withdrawal symptoms; it can provoke seizures and is therefore contraindicated in those at risk of severe hypoglycaemia). A Cochrane review found an increased rate of stopping smoking of 50–70% with all types of nicotine replacement therapy (although people with diabetes were not specifically mentioned).

Travel

Diabetes is not a bar to travelling but planning is needed for extra supplies, insurance, medical identification, and changes in meals, fluid intake, physical activity and antidiabetic treatment en route and after arrival. It is not necessary to store insulin in a refrigerator in hot countries provided supplies are kept cool and out of direct sunlight (Box 30.5).

Box 30.5 Checklist of essential items for travellers with insulin-treated diabetes

- Documents
- Diabetes identity card or bracelet
- Document stating diagnosis and treatment
- Blood glucose monitoring diary
- Equipment
- Insulin vials or cartridges
- Syringes and needles (or pens and spare pen needles)
- Flask or cool bag for insulin storage
- Blood glucose meter; spare meter and batteries
- Finger pricker and spare lancets; container for used needles
- Blood glucose test strips (visual reading)
- Fluids
- Glucose-free drinks (screw-top container)
- Bottled water (plastic container)
- Hypoglycaemia treatment
- Quick-acting carbohydrate
  - Glucose drinks (screw-top container)
  - Glucose tablets/confectionery
- Slow-acting carbohydrate
  - Biscuits or cereal bars

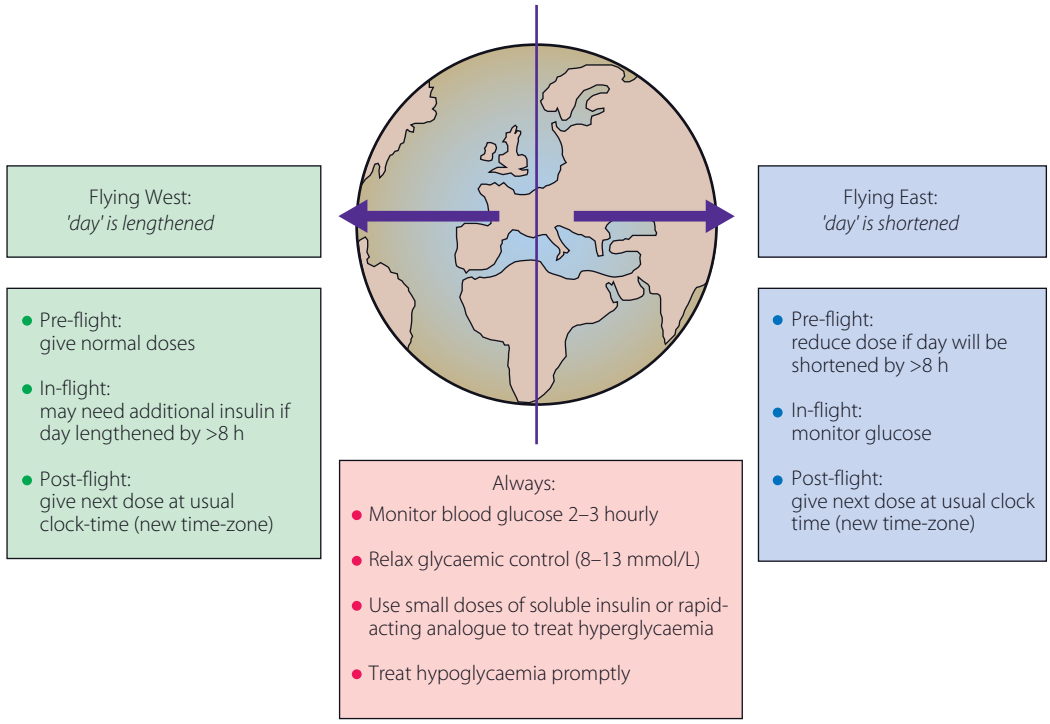

Figure 30.3 Scheme for adjusting insulin doses during flights that cross time zones.

During long flights, blood glucose should be monitored frequently (every 2–3 hours) and glycaemic control may need to be relaxed to avoid hypoglycaemia: a few hours of moderate hyperglycaemia, say 10–13 mmol/L (180–234 mg/dL), is acceptable. Time changes of less than 4 hours in either direction require no major adjustments to the usual insulin schedule – simply give the next insulin at its usual clock time, using the destination's time zone. Westward flights effectively extend the day, and if this delay is long (>6–8 hours), extra insulin may be needed – small doses of rapid-acting insulin injected 3–4 hourly. Long-acting insulin doses before eastward flights, which shorten the day, may need to be reduced if shortened by >6–8 hours (Figure 30.3).

KEY WEBSITES

Each country has its own regulations (these are fairly standard across the European Union) and most have their own websites.

- Diabetes UK Guidance: www.diabetes.co.uk/driving-with-diabetes.html
- Driver and Vehicle Licensing Authority (DVLA) (UK): www.dvla.gov.uk/medical/ataglance.aspx
- DVLA guidance for healthcare professionals (UK): www.direct.gov.uk/en/Motoring/DriverLicensing/MedicalRulesForDrivers/DG_10030957
- American Diabetes Association and Department for Transportation Guidelines (USA): www.nhtsa.dot.gov/people/injury/olddrive/Diabetes%20Web/#Anchor-40100
- Travel advice (UK): www.diabetes.org.uk/Guide-to-diabetes/Living_with_diabetes/Everyday_life/Travelling_with_diabetes/Air_travel_and_insulin/
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Chapter

31

Organisation of diabetes care: diabetes specialist nursing, diabetes education and general practice

KEY POINTS

- A well co-ordinated multiprofessional diabetes team, and patients who are well informed and empowered, are the keys to success. The diabetes specialist nurse (DSN) is central to the delivery of high-quality care.
- The UK National Service Framework (NSF) is an example of a national action plan to improve the organisation and quality of diabetes services over a 10-year period (2003–2013). It includes 12 key standards.
- Empowering patients and facilitating their greater involvement in decision making is an essential element in the management of any long-term condition, especially diabetes.
- The 'commissioning windmill' illustrates key steps in the organisation of services to deliver the 'year of care' approach developed in the UK.
- Care planning with patients engages them in thinking about their own priorities, expectations and goals, so that patients feel a greater sense of ownership.
- Structured education programmes (e.g. DAFNE for type 1 diabetes and DESMOND for type 2 diabetes) have had a major impact, but organisation and delivery of these programmes are a challenge.

Providing effective, high-quality diabetes care requires a co-ordinated, multiprofessional team of specialists, as well as patients who are well informed and empowered (Figure 31.1). Patient-centred care is a priority in all healthcare systems, but the organisational and logistical challenges should not be underestimated. The role of the diabetes specialist nurse (DSN) has become crucial in providing education, advocacy, psychological support and counselling, and as a central co-ordinator of individualised patient care. Many DSNs also prescribe and provide dietary advice.

In the UK, a government pledge to improve diabetes, called the Diabetes National Service Framework (NSF), was launched in 2001. The NSF outlined a 10-year plan (2003–2013) to change and improve diabetes services, focused around a set of 12 national standards which cover all aspects of diabetes care and prevention (Box 31.1). A National Diabetes Support Team (now called NHS Diabetes) was established to develop sustainable service improvements through multiagency and multiprofessional partnership working. A number of current priorities include: (a) improving diabetes care for hospitalised patients; (b) improving preconception care for women with diabetes of childbearing age; (c) improving the knowledge base around the

Box 31.1 The 12 standards outlined in the NSF

1. Prevention of diabetes
2. Identification of people with diabetes
3. Empowering people with diabetes
4. Clinical care of adults with diabetes
5. Clinical care of children and young people with diabetes
6. Ensuring a smooth transition of care from paediatric to adult diabetes services
7. Management of diabetic emergencies
8. Care of people with diabetes during admission to hospital
9. Diabetes and pregnancy
10. Regular surveillance for long-term complications of diabetes
11. Effective investigation and management of cardiovascular complications
12. Integrated multiagency health and social care

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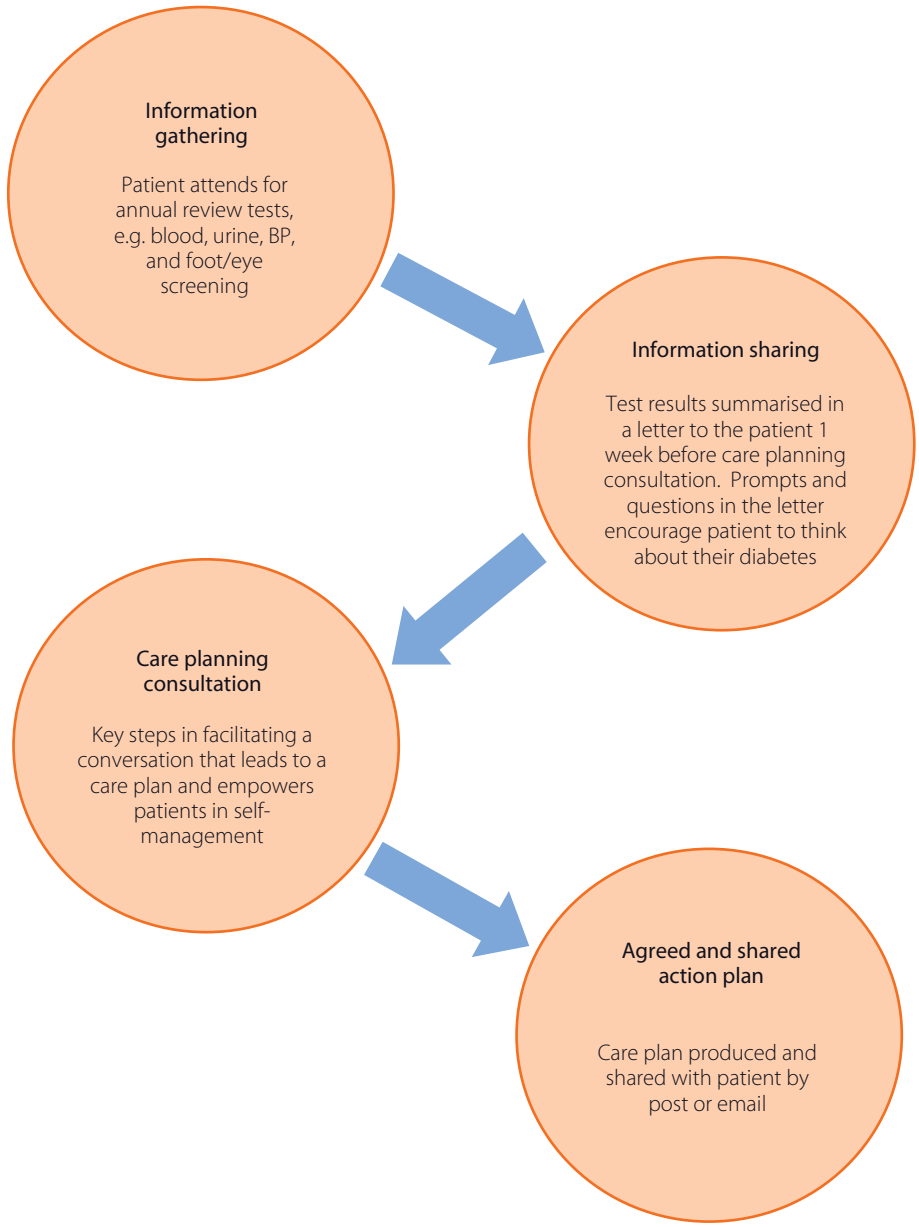

Figure 31.1 There are many different dimensions to effective diabetes services.

CASE HISTORY

A 71-year-old man with type 2 diabetes, coronary heart disease and frailty is reviewed by the diabetes team. A care planning approach is adopted, replacing the traditional 'annual review' with a conversation about his priorities, fears, wishes and goals. It is clear during these conversations that he does not want to take more than five medications, he is fearful of hypoglycaemia and symptom control is more of a priority. He also thinks it would be helpful to get his wife (who does the cooking) to see the dietitian. He does not want to pursue aggressive HbA_{1c} or BP targets if this means an excessive number of tablets and/or a risk of side effects. These discussions result in some simple goals, action points and targets as part of a 'year of care' plan.

Comment: Care planning is a new approach that is more likely to result in better self-management. This man's priorities and goals may be different from those of the health professional, but his perceptions of medication and his aim to avoid hypoglycaemia result in a negotiated, simplified drug regimen (no doubt resulting in better compliance).

LANDMARK CLINICAL TRIALS

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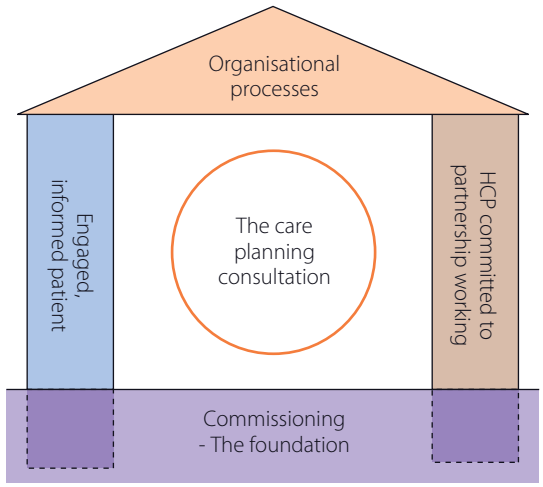

Figure 31.2 The care planning house model. This model was developed to illustrate the bigger picture: an engaged, informed patient and a healthcare professional committed to partnership working can achieve the best results if they are brought together in an appropriate environment with good organisational processes to facilitate their effective interaction. Robust commissioning therefore underpins the care planning 'house'. HCP, healthcare professional.

effectiveness of fingerprick self-monitoring; and (d) improving the delivery of care planning.

Facilitating greater involvement of people with long-term conditions in planning their own care and choosing how to manage their own condition has become a major priority. This is seen as a key step in achieving better health outcomes and overall improvements in service quality. In 2007, a UK Healthcare Commission survey of 70,000 people with diabetes found that although 95% of people had diabetes checks at least once per year, less than 50% had discussed their goals in managing their condition. Thus, more recently there has been a greater emphasis on 'care planning' and commissioning of services to enable patients to be more informed and engaged with their treatment (Figure 31.2).

The 'year of care' approach has been developed in the UK in order to put the person with diabetes at the centre of decision making and to support them in self-management. It represents care planning in action. The rationale is that each individual will have different priorities and goals, and greater opportunity to select from a range of services those that will best support and empower them in making decisions and achieving their desired outcomes. The challenge is to link each individual's needs and goals, choices and service use into the commissioning decisions that take place at a population level. Thus, care planning and effective commissioning are key interlinked components of a service (Figure 31.3).

The traditional annual review for patients with diabetes has sometimes become little more than a tick box exercise. Increasingly, this may be replaced by the care planning consultation in which the patient's priorities, goals, needs and expectations contribute to a conversation leading to an action plan. There is true partnership working to develop a set of goals and action points that the patient feels

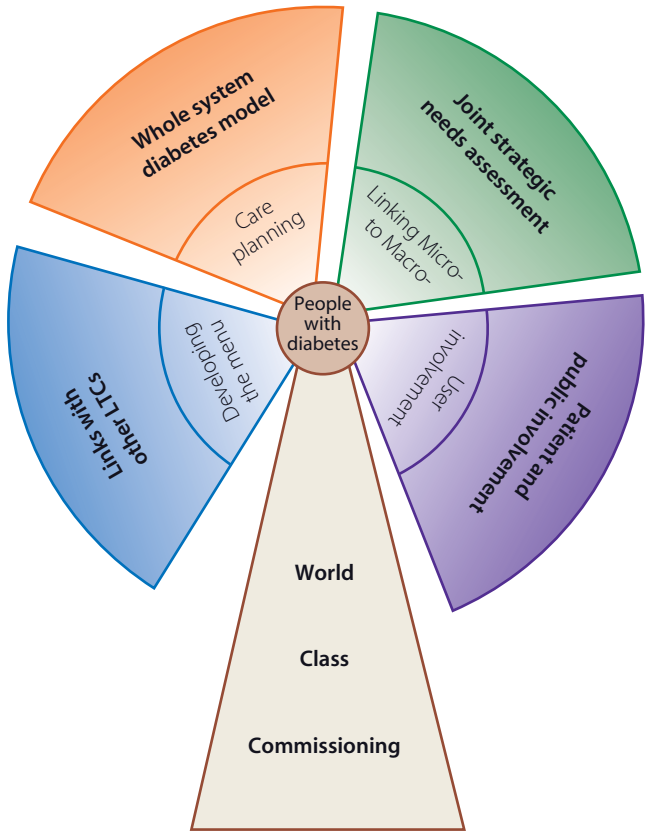

Figure 31.3 The 'commissioning windmill'. A model that illustrates key elements of service organisation to underpin care planning and the 'year of care' approach. LTC, long term conditions.

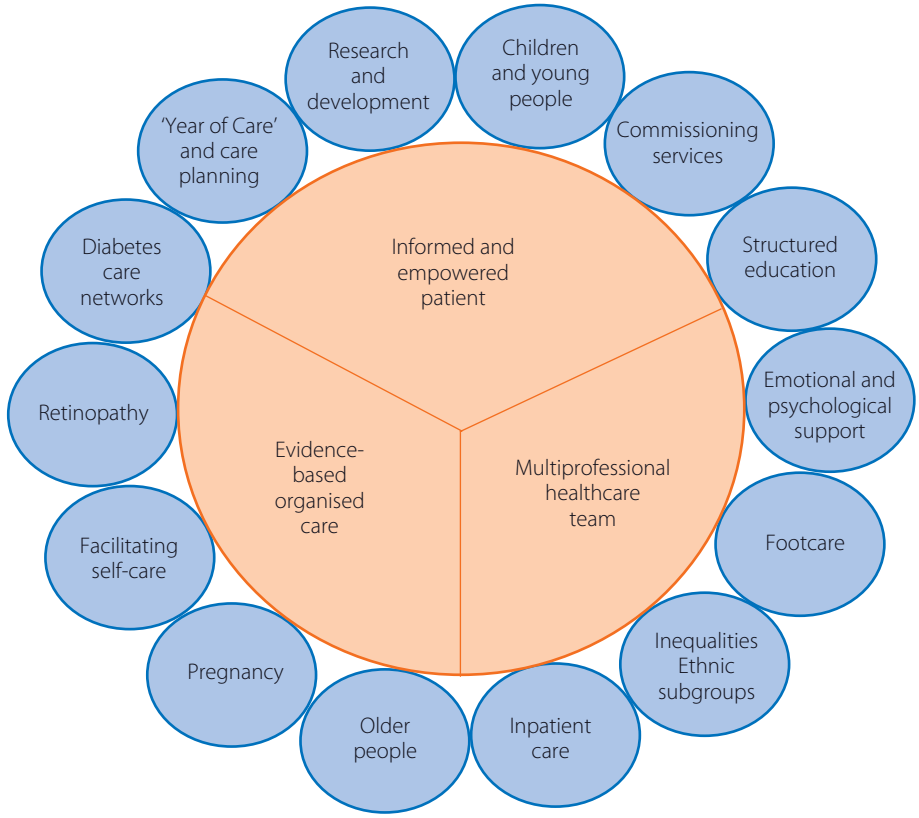

Figure 31.4 Key elements of the care planning consultation.

ownership of. Instead of imposing management decisions and expectations, the health professional seeks to facilitate greater ownership and engagement by the patient in setting their own aims and targets (Figure 31.4). Care planning for the year ahead will increasingly replace the current model of annual review.

In order to self-manage their diabetes effectively and participate fully in decision making, individuals need a good understanding of their condition and an awareness of how to access information (Figure 31.5). Thus, structured education courses have become a key component of diabetes services. An engaged, informed patient is the key to successful self-management, but it requires an individualised approach by the health professional team. As part of the NSF, many centres in the UK (>100) are now running Dose Adjustment for Normal Eating (DAFNE) courses for people with type 1 diabetes, and a similar number have established Diabetes Education and Self-Management for Ongoing and Newly Diagnosed (DESMOND) courses for people with type 2 diabetes. But there is still much to be done: in 2006, only 11% of respondents to a Healthcare Commission survey said they had participated in an educational course to help them manage their diabetes.

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- www.diabetes.nhs.uk/tools_and_resources/reports_and_guidance/
- www.desg.org/
- www.diabetes.nhs.uk/work-areas/year-of-care
- www.dh.gov.uk/en/Publicationsandstatistics/Publications/PublicationsPolicyAndGuidance/DH_4140284
- Skills for Health/Skills for Care, Common Core Principles to Support Self Care: A Guide to Support Implementation: www.dh.gov.uk/en/publicationsandstatistics/publications/publicationspolicyandguidance/DH_084505
- Department of Health, Raising the Profile of Long Term Conditions Care: A Compendium of Information: www.dh.gov.uk/en/publicationsandstatistics/publications/publicationspolicyandguidance/DH_082069
- Department of Health, Care Planning in Diabetes: www.dh.gov.uk/en/publicationsandstatistics/publications/publicationspolicyandguidance/DH_063081
- Department of Health, Supporting People with Long Term Conditions to Self Care: A Guide to Developing Local Strategies and Good Practice: www.dh.gov.uk/en/publicationsandstatistics/publications/publicationspolicyandguidance/DH_4130725
- National Diabetes Support Team, Partners in Care: A Guide to Implementing a Care Planning Approach to Diabetes Care: www.diabetes.nhs.uk/news-1/partners%20in%20care.pdf
- SIGN Guidelines: www.SIGN.ac.uk

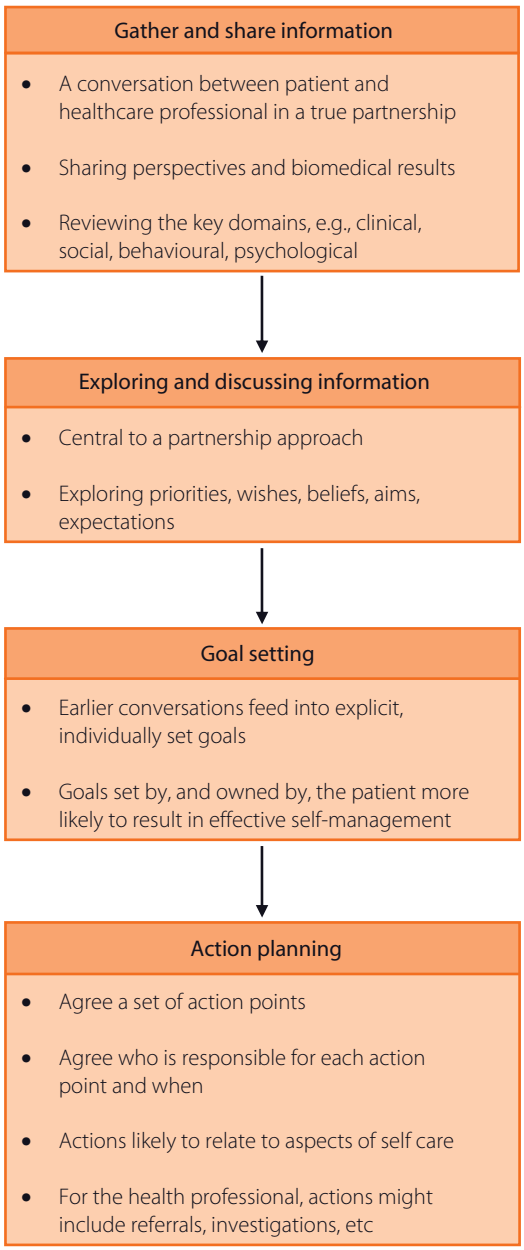

Figure 31.5 A framework for increasing the effectiveness of self-management.

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Chapter

32 Future directions in diabetes management and research

KEY POINTS

- Whole-organ pancreas transplantation still offers the most consistent method of achieving long-term normoglycaemia in type 1 diabetes.
- The initially very positive clinical outcome of islet cell transplantation using the Edmonton protocol has not been reproduced in multicentre trials, with only 44% insulin independent at 1 year and 23% at 3 years.
- Closed loop infusion pumps are under trial but have problems with time lag sensing of blood glucose levels and trends.
- Insulin-producing cells have been derived from stem cells obtained from a variety of tissues and been shown to function in animals. To date, only one trial in human diabetes has been reported using haematopoietic stem cells with some success but with significant complications.
- Reprogramming cells to produce insulin using gene therapy has yet to be proven in human diabetes.

Pancreas and islet cell transplantation

Until recent advances in islet cell transplantation, whole or segmental pancreas transplantation was the only treatment for type 1 diabetes able to restore endogenous insulin secretion. Currently, about 1200 whole-pancreas transplants take place every year worldwide, with nearly 200 in the UK in 2007 (Figure 32.1). Functioning graft survival is generally better with simultaneous pancreas–kidney grafts than with a pancreas alone transplant, probably because it is easier to detect early rejection by monitoring kidney function using serum creatinine. Even so, graft survival is only ~80% at 3 years and <25% at 10 years.

One of the problems of whole-organ transplantation is how to deal with the exocrine secretions. Many different techniques have been developed, including enteric exocrine drainage by graft-duodenojejunal anastomosis or drainage into the bladder (Figure 32.2). Venous drainage of endocrine secretions into the peripheral circulation via the internal iliac vein or by primary portal venous drainage are other options. Although some of these innovations offer theoretical advantages, there are few survival data to suggest that any one gives better long-term results. Newer immunosuppressive regimens have helped increase graft survival. The progression of diabetic complications can be halted or even reversed by pancreas transplantation if there is a sufficient period of post-transplant normoglycaemia, although up to 10 years is necessary in the case of glomerular pathology.

The clinical outcome for islet cell transplantation was transformed from the year 2000, with the introduction of the Edmonton protocol (named for the group at the University of Edmonton, Canada). The protocol is based on transplanting an adequate mass of freshly isolated islet cells, providing a potent, steroid-free and less diabetogenic immunosuppression regimen, and careful selection of patients without renal failure. The immunosuppression involved pre- and post-transplant daclizumab (anti-interleukin 2 receptor monoclonal antibody), maintenance sirolimus and low-dose tacrolimus. Unfortunately, this combination is potentially nephrotoxic and only patients with well-preserved renal function can tolerate it. There is research into encapsulating the islets in material that would resist both rejection and autoimmune attack in order to get around this problem. Xenotransplantation using porcine islets is a potential solution to the shortage of human tissue but there remain potential problems with inadvertent transfer of donor viral pathogens.

The procedure for islet isolation is labour intensive and involves enzymatic fragmentation of the pancreas in a semi-automatic dissociation chamber. Islets are injected or infused through the percutaneous intraportal route with embolisation into the liver. In most cases, two sequential donors are used – approximately 850,000 islet equivalents per recipient. In the initial report of 32 consecutive type 1 diabetic patients treated in Edmonton, there was 85% sustained insulin

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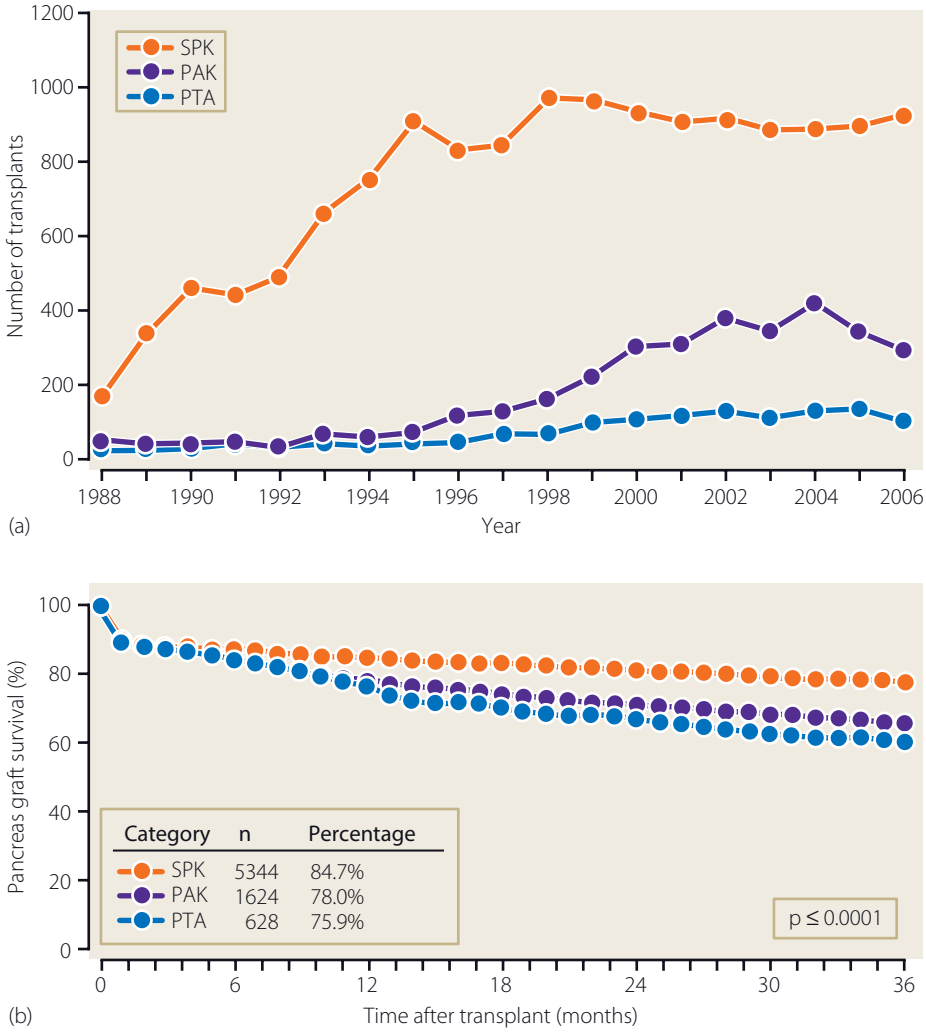

Figure 32.1 (a) Numbers of simultaneous pancreas kidney (SPK), pancreas after kidney (PAK) and pancreas alone (PTA) transplants worldwide from 1988 to 2006. (b) Percentage graft survival for the SPK, PAK, and PTA over 36 months. From White et al. Lancet 2009; 373: 1808–1801.

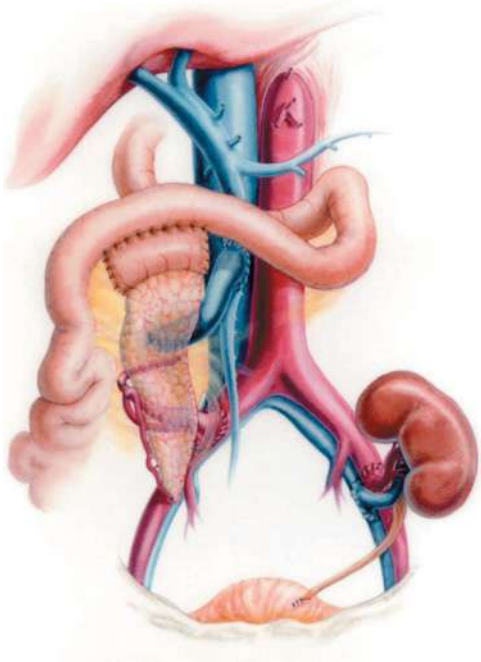

Figure 32.2 Simultaneous kidney and whole-organ pancreas transplantation showing exocrine drainage via a duodenojejunal anastomosis and venous drainage via the portal vein. The kidney transplant is shown with anastomosis to the internal iliac vessels and with ureteric implantation into the bladder. Courtesy of Dr S Bartlett, University of Maryland, MD, USA.

independence and return to normoglycaemia at 1 year. However, a multicentre trial (nine sites worldwide) in 36 recipients of 10,000 islet equivalents per kg bodyweight reported only 44% (n=16) insulin independent at 1 year, with 10 having a complete loss of islet function. In the 9 years since 1999, the Collaborative Islet Transplant Registry reported that of 325 recipients, only 23% were insulin independent 3 years after transplant, with a further 29% with partial function. The main indication remains hypoglycaemic unawareness and it is interesting that symptoms are much improved even in those with only partial function. In the UK, NICE has approved islet transplantation for this purpose.

Box 32.1 Potential stem cells that can be induced to produce insulin experimentally. Only haematopoietic stem cells have been used in humans

Adult stem cells	**Others**
Pancreatic (from ducts)	Embryonic
Haematopoietic and myelopoietic	Fetal
Hepatic oval cells	Umbilical cord blood
Neural	Placenta
Adipose tissue	Amniotic epithelium

Closed-loop devices

The development of continuous glucose monitoring systems has led to their linkage with insulin infusion pumps, although a truly automatic closed loop device has yet to be realised. This is partly because the current systems monitor interstitial, not blood, glucose and the insulin delivery is also subcutaneous. There is thus an inevitable lag both in the sensing of changes in glycaemia and in the insulin response. Algorithms have been devised to circumvent these problems by using 'front loading' of insulin infusion at meals anticipating the postprandial rise in blood glucose for example, but major problems still remain as long as both glucose sensing and insulin delivery remain subcutaneous. There are major research efforts in the areas of glucose sensors and infusion pumps (both internal and external) largely sponsored by industry so there will be undoubted advances in the next few years.

Stem cell therapy

The aim of stem cell research in diabetes is to provide a source of cells nearly identical to the pancreatic β cell for treatment of type 1 diabetes by transplantation. Stem cells are self-renewing cells that produce large numbers of differentiated progeny; the two main categories are embryonic and adult stem cells (Box 32.1). Embryonic stem cells are derived from the inner cell mass of mammalian blastocysts; they can be cultured *in vitro* and when allowed to aggregate (as an 'embryoid body'), they can differentiate into all of the tissues of the embryo, including β cells. The numerous growth and transcription factors that guide embryonic stem cells to transform into endoderm and β cells are being discovered. One of the key signals is pancreatic and duodenal homeobox factor 1 (PDX-1, also known as IPF-1) and its deficiency in humans leads to pancreatic agenesis and diabetes (MODY 4, see Chapter 8).

Many of these factors have been discovered in studies of adult stem cells from the pancreas and other tissues which offer less controversial and a more differentiated cell line to work with. Many different cell types have been manipulated to produce insulin in culture and many have been shown to reduce blood glucose in diabetic animals. The first clinical trial of autologous adult haematopoietic stem cell therapy in human type 1 diabetes has reported a mean follow-up of 29.8 (range 7–58) months in a cohort of 23 newly diagnosed patients; 12 remained insulin independent and eight were on low-dose (0.1–0.3 units/kg bodyweight) insulin at follow-up; three always required insulin. There were serious side effects, mostly related to immunosuppression, and the long-term safety and cost benefit need to be established by further trials.

Gene therapy

Gene therapy for diabetes is still at the stage of animal experimentation, but the aim is to transfer DNA to somatic cells to treat or prevent diabetes or its complications. Several strategies are envisaged, including prevention of β cell destruction through autoimmune attack by manipulating β cells to produce a survival factor (e.g. interleukin-1 receptor antagonist or antiapoptotic factors). This requires a vector to transform the remaining β cells *in vivo* in newly diagnosed type 1 diabetic patients. Immunomodulation might be achieved by DNA vaccination in high-risk individuals, such as vaccination with glutamic acid decarboxylase (GAD) DNA to induce tolerance to this key autoantigen. The first randomised controlled trial in 70 type 1 adolescent patients found that there was a small but statistically significantly increased C peptide concentration in the treated subjects, but no effect on insulin dose requirement. Stimulation of β cell differentiation and regeneration might involve gene therapy with transcription factors that control development (e.g. PDX-1). Other approaches have used islets which have had genes inserted that will express proteins (such as IL-10) that help resist immune attack when transplanted and avoid the need for immunosuppression. Ectopic production of insulin by several substitute cells has already been achieved, including in fibroblasts, hepatocytes and pituitary cells, with glucose responsiveness achieved by placing the insulin gene under the control of glucose-sensitive gene transcription (e.g. glucose-6-phosphatase, carbohydrate responsive element binding protein). Another approach is to reduce morbidity and mortality from complications by transferring genes that can modify the causative processes or that can

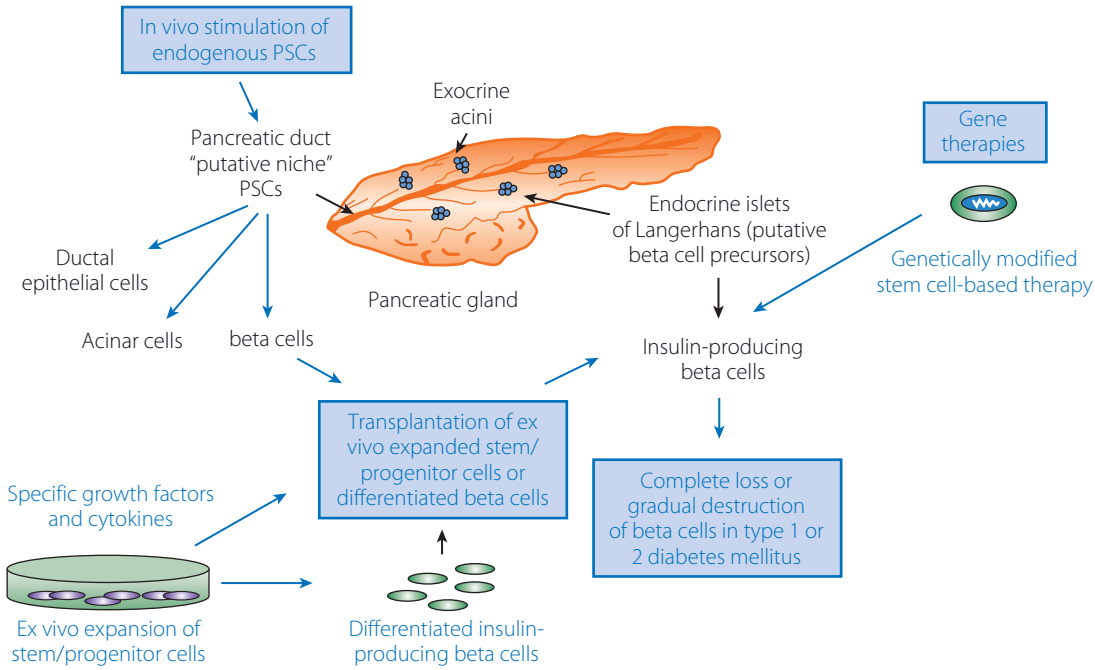

Figure 32.3 Schematic representation of the pancreatic gland showing the anatomical localisation of pancreatic stem/progenitor cells (PSCs) and β cell precursors, and stem cell-based therapies for diabetes mellitus. Pancreatic stem/progenitor cells exist within the ductal structure and exocrine acini; putative β cell precursors are found near or within the islets of Langerhans. From Mimeault & Batra. Gut 2008; 57: 1456–1468.

stimulate repair. Finally, conditionally transformed β cell lines may produce cells in quantity for transplantation. Most of these techniques have been tested in animal models. Gene therapy trials in other (mainly monogenic) diseases have had serious complications and there remain daunting problems to solve before they become practicable and safe for people with diabetes.

Oral medication

Animal studies suggest that the GLP-1 analogues may increase β cell mass as a part of the efficacy in treating diabetes. This potential is being explored as an adjunct to islet transplantation to see if it helps preserve or enhance function. The haematopoietic stem cell trial reported the use of sitagliptin in patients who were losing insulin secretion and found a restoration of insulin independence. Newer agents which affect mechanisms responsible for insulin resistance, orally effective insulin and therapies directed at tissue complications (such as drugs that prevent or reverse glycation) are in development or early human trials.

KEY WEBSITES

- NICE Interventional Procedure Guidance 257. Allogeneic pancreatic islet transplantation for type 1 diabetes mellitus: www.nice.org.uk/nicemedia/pdf/IPG257Guidance/pdf
- Collaborative Islet Transplant Registry: www2.niddk.nih.gov/Research/ScientificAreas/Pancreas/EndocrinePancreas/CITT.htm

FURTHER READING

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