10-20 Diabetes mellitus

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720 • DIABETES MELLITUS Clinical examination of the patient with diabetes Insets (Acanthosis nigricans) From Lim E (ed.). Medicine and surgery: an integrated textbook. Edinburgh: Elsevier Ltd; 2007. (Exudative maculopathy) Courtesy of Dr A.W. Patrick and Dr I.W. Campbell. Blood pressure Skin Bullae Pigmentation Granuloma annulare Vitiligo Axillae Neck Carotid pulse Bruits Thyroid enlargement Eyes (see opposite) Visual acuity Cataract/lens opacity Fundoscopy Insulin injection sites (see opposite) Hands (see opposite) Feet (see opposite) Inspection Peripheral pulses Sensation Abdomen Hepatomegaly (fatty infiltration of liver) Legs Muscle-wasting Sensory abnormality Hair loss Tendon reflexes Exudative maculopathy Necrobiosis lipoidica Charcot neuroarthropathy Neuropathic foot ulcer Head Xanthelasma Cranial nerve palsy/eye movements/ptosis Observation • Weight loss in insulin deficiency • Obesity in type 2 diabetes • Mucosal candidiasis • Dehydration– dry mouth, ↓tissue turgor • Air hunger– Kussmaul breathing in ketoacidosis

Acanthosis nigricans in insulin resistance ‘Prayer sign’

Clinical examination of the patient with diabetes • 721

Diabetes can affect every system in the body. In routine clinical practice, examination of the patient with diabetes is focused on hands, blood pressure, axillae, neck, eyes, insulin injection sites and feet. 1 Examination of the hands Several abnormalities are more common in diabetes: • Limited joint mobility (‘cheiroarthropathy’) causes painless stiffness. The inability to extend (to 180°) the metacarpophalangeal or interphalangeal joints of at least one finger bilaterally can be demonstrated in the ‘prayer sign’ • Dupuytren’s contracture (p. 1059) causes nodules or thickening of the skin and knuckle pads • Carpal tunnel syndrome (p. 1139) presents with wrist pain radiating into the hand • Trigger finger (flexor tenosynovitis) may be present • Muscle-wasting/sensory

changes may be present in peripheral sensorimotor neuropathy, although this is more common in the lower limbs Background retinopathy. Courtesy of Dr A.W. Patrick and Dr I.W. Campbell. Proliferative retinopathy. Courtesy of Dr A.W. Patrick and Dr I.W. Campbell. 7 Examination of the eyes Visual acuity • Check distance vision using Snellen chart at 6 m • Check near vision using standard reading chart • Note that visual acuity can alter reversibly with acute hyperglycaemia due to osmotic changes affecting the lens. Most patients with retinopathy do not have altered visual acuity, except after a vitreous haemorrhage or in some cases of maculopathy Lens opacification • Look for the red reflex using the ophthalmoscope held 30 cm from the eye Fundal examination • Either use a three-field retinal camera or dilate pupils with a mydriatic (e.g. tropicamide) and examine with an ophthalmoscope in a darkened room • Note features of diabetic retinopathy (p. 1174), including photocoagulation scars from previous laser treatment 8 Insulin injection sites Main areas used • Anterior abdominal wall • Upper thighs/buttocks • Upper outer arms Inspection • Bruising • Subcutaneous fat deposition (lipohypertrophy) • Subcutaneous fat loss (lipoatrophy; associated with injection of unpurified animal insulins – now rare) • Erythema, infection (rare) Lipohypertrophy of the upper arm. 11 Examination of the feet Inspection • Look for evidence of callus formation on weight-bearing areas, clawing of the toes (in neuropathy), loss of the plantar arch, discoloration of the skin (ischaemia), localised infection and ulcers • Deformity may be present, especially in Charcot neuroarthropathy • Fungal infection may affect skin between toes, and nails Circulation • Peripheral pulses, skin temperature and capillary refill may be abnormal Sensation • This is abnormal in stocking distribution in typical peripheral sensorimotor neuropathy • Testing light touch with monofilaments is sufficient for risk assessment; test other sensation modalities (vibration, pain, proprioception) only when neuropathy is being evaluated Reflexes • Ankle reflexes are lost in typical sensorimotor neuropathy • Test plantar and ankle reflexes Monofilaments. The monofilament is applied gently until slightly deformed at five points on each foot. Callus should be avoided as sensation is reduced. If the patient feels fewer than 8 out of 10 touches, the risk of foot ulceration is increased 5–10-fold.

722 • DIABETES MELLITUS The incidence of diabetes is rising. Globally, it is estimated that 415 million people had diabetes in 2015 (10% of the world adult population), and this figure is expected to reach 642 million by 2040. This global pandemic principally involves type 2 diabetes; prevalence varies considerably around the world (Fig. 20.1), being associated with differences in genetic factors, as well as environmental ones such as greater longevity, obesity, unsatisfactory diet, sedentary lifestyle, increasing urbanisation and economic development. A pronounced rise in the prevalence of type 2 diabetes occurs in migrant populations to industrialised countries, as in Asian and Afro-Caribbean immigrants to the UK or USA. Type 2 diabetes is now seen in children and adolescents, particularly in some ethnic groups such as Hispanics, non-Hispanic blacks and Asian Indians. The incidence of type 1 diabetes is also increasing: between 1960 and 1996, 3% more children were diagnosed worldwide each year. It is generally more common in countries closer to the polar regions. Finland, for instance, has the highest rate of type 1 diagnosis per year at > 60 per 100 000 of the population, whereas in China, India and Venezuela the incidence is only 0.1 per 100 000. Type 1 diabetes is most common in Caucasians, and more people are diagnosed in the winter months. Diabetes is a major burden on health-care facilities in all countries. Globally, in 2015, diabetes caused 5 million deaths in those aged 20–79 years, and health-care expenditure attributed to diabetes was estimated to be at least 673 billion US dollars, or 12% of total health-care expenditure. Fig. 20.1 Prevalence (%) of diabetes in those aged 20–79 years, 2015. Based on estimates from the International Diabetes Federation. IDF Diabetes Atlas, 7th edn. Brussels,

Belgium: International Diabetes Federation, 2015. http://www.diabetesatlas.org. <4% 4–5% 5–7% 7–9% 9–12%

> 12% Diabetes mellitus is a clinical syndrome characterised by an increase in plasma blood glucose (hyperglycaemia). It has many causes (see Box 20.9), most commonly type 1 or type 2 diabetes. Type 1 diabetes is generally considered to result from autoimmune destruction of insulin-producing cells (β cells) in the pancreas, leading to marked insulin deficiency, whereas type 2 diabetes is characterised by reduced sensitivity to the action of insulin and an inability to produce sufficient insulin to overcome this 'insulin resistance'. Hyperglycaemia causes both acute and long-term problems. Acutely, high glucose and lack of insulin can result in marked symptoms, metabolic decompensation and hospitalisation. Chronic hyperglycaemia is responsible for diabetes-specific 'microvascular' complications affecting the eyes (retinopathy), kidneys (nephropathy) and feet (neuropathy). There is a continuous distribution of blood glucose in the population, with no clear division between people with normal values and those with abnormal ones. The diagnostic criteria for diabetes (a fasting plasma glucose of ≥ 7.0 mmol/L (126 mg/ dL) or glucose 2 hours after an oral glucose challenge of ≥ 11.1 mmol/L (200 mg/dL); p. 726) have been selected to identify a degree of hyperglycaemia that, if untreated, carries a significant risk of microvascular disease, and in particular diabetic retinopathy. Less severe hyperglycaemia is called 'impaired glucose tolerance'. This is not associated with a substantial risk of microvascular disease, but is connected with an increased risk of large-vessel disease (e.g. atheroma leading to myocardial infarction) and with a greater risk of developing diabetes in future.

down its concentration gradient through cell membrane glucose transporters (GLUTs). Glucose is then metabolised by glycolysis and oxidative phosphorylation. The first step of the glycolytic pathway, the conversion of glucose to glucose-6-phosphate, is catalysed by the enzyme glucokinase (GK). Glucokinase has a low affinity for glucose and so its activity under normal physiological conditions varies markedly, according to the concentration of glucose. This makes it a very effective glucose sensor in the β cell. In what is considered a classical direct or triggering pathway, glucose metabolism results in increased intracellular adenosine triphosphate (ATP) and reduced adenosine diphosphate Functional anatomy and physiology Regulation of insulin secretion Insulin is the primary regulator of glucose metabolism and storage (Box 20.1), and is secreted from pancreatic β cells into the portal circulation (Fig. 20.2). The pancreatic β cell is designed to regulate blood glucose concentrations tightly by coupling glucose and other nutrient stimulus with insulin secretion (Fig. 20.2). Entry of glucose into the pancreatic β cell is by facilitated diffusion 20.1 Metabolic actions of insulin Increase Decrease Carbohydrate metabolism Glucose transport (muscle, adipose tissue) Glucose phosphorylation Glycogen synthesis Glycolysis Pyruvate dehydrogenase activity Pentose phosphate shunt Gluconeogenesis Glycogenolysis Lipid metabolism Triglyceride synthesis Fatty acid synthesis (liver) Lipoprotein lipase activity (adipose

tissue) Lipolysis Lipoprotein lipase (muscle) Ketogenesis Fatty acid oxidation (liver) Protein metabolism Amino acid transport Protein synthesis Protein degradation Fig. 20.2 Pancreatic structure and endocrine function. A The normal adult pancreas contains about 1 million islets, which are scattered throughout the exocrine parenchyma. Histology is shown in Figure 20.6. B The core of each islet consists of β cells that produce insulin, and is surrounded by a cortex of endocrine cells that produce other hormones, including glucagon (α cells), somatostatin (δ cells) and pancreatic polypeptide (PP cells). C Schematic representation of the pancreatic β cell. (1) Glucose enters the cell via a glucose transporter (GLUT1 or GLUT2). (2) Glucose then enters glycolysis, and subsequent oxidative phosphorylation in the mitochondria results in a rise in intracellular adenosine triphosphate (ATP). (3) This ATP acts to close the KATP channel (which consists of four KIR6.2 subunits and four SUR1 subunits). This leads to membrane depolarisation. (4) The rise in membrane potential results in calcium influx due to opening of a voltage-gated calcium channel. This rise in intracellular calcium causes insulin secretory vesicles to fuse with the cell membrane, leading to insulin secretion. (5) Other stimuli, such as glucagon-like peptide-1 (GLP-1) or gastric inhibitory polypeptide (GIP), act on G-protein-coupled receptors to increase cyclic adenosine monophosphate (cAMP) and amplify the insulin secretion. Genetic defects in the β cell result in diabetes. The primary genes are glucokinase (the initial step in glycolysis) and HNF1α, HNF4α and HNF1β (nuclear transcription factors). Two groups of drugs act on the β cell to promote insulin secretion. Sulphonylureas act to close the KATP channel, causing membrane depolarisation, calcium influx and insulin secretion. Incretin-acting drugs either increase the concentration of endogenous GLP-1 and GIP (the dipeptidyl peptidase 4, or DPP-4, inhibitors) or act as directly on the GLP-1 receptor (GLP-1 receptor agonists). Both of these drug groups act to augment insulin secretion but only following an initial stimulus to insulin secretion through closure of β cell KATP channels by glucose (or sulphonylureas). Accessory ampulla Ampulla of Vater Duodenum Islet core (β cells) Arteriole Other islet cells Venule Glucose GLUT

Glucose Nucleus HNF1α HNF4α HNF1β Glucokinase Glycolysis Incretin-acting drugs Insulin KIR6.2 SUR1 ATP GLP-1 Ca2+ K+ Mitochondria Sulphonylureas A B C Oxidative phosphorylation

724 • DIABETES MELLITUS classically occurs in two phases (see Fig. 20.3). The rapid first phase represents the secretion of pre-formed insulin from granules within the β cells, while the more prolonged second phase is a consequence of newly synthesised insulin. Regulation of glucagon secretion Pancreatic islets also contain other endocrine cells such as α cells that secrete the peptide hormone glucagon, and δ cells that produce somatostatin (see Fig. 20.2B). Alpha cells make up about 20% of the human islet cell population. Glucagon has opposite effects to insulin and acts on the liver (and kidney) to stimulate glycogenolysis, leading to increased hepatic glucose production. Regulation of glucagon secretion by the α cell is complex, but β-cell insulin secretion, co-secreted zinc and γ-aminobutyric acid (GABA), as well as somatostatin from δ cells, are thought to have major regulatory roles. This means that insulin and glucagon are tightly, and reciprocally, regulated, such that the ratio of insulin to glucagon in the portal vein is a major determinant of hepatic glucose production. Glucagon is also critically important to the body’s defence against hypoglycaemia (p. 738). Blood glucose homeostasis Blood glucose is tightly regulated and maintained within a narrow range. This is essential for ensuring a continuous supply of glucose to the central nervous system. The brain has little capacity to store energy in the form of glycogen or triglyceride, and the blood–brain barrier is largely impermeable to fatty acids, so the brain depends on the liver for a constant supply of glucose for oxidation and hence generation of ATP. Glucose

homeostasis is achieved through the coordinated actions of multiple organs, but mainly reflects a balance between the entry of glucose into the circulation from the liver, supplemented by intestinal absorption of glucose after meals, and the uptake of glucose by peripheral tissues, particularly skeletal muscle and brain. After ingestion of a meal containing carbohydrate, normal blood glucose levels are maintained by: • suppression of hepatic glucose production • stimulation of hepatic glucose uptake • stimulation of glucose uptake by peripheral tissues (Fig. 20.5). The post-prandial rise in portal vein insulin and glucose, together with a fall in portal glucagon concentrations, suppresses hepatic glucose production and results in net hepatic glucose uptake. Depending on the size of the carbohydrate load, around one-quarter to one-third of ingested glucose is taken up in the liver. In addition, insulin stimulates glucose uptake in skeletal muscle and fat, mediated by the glucose transporter GLUT4. Fig. 20.3 Insulin secretion in response to intravenous or oral glucose. A An acute first phase of insulin secretion occurs in response to an elevated blood glucose, followed by a sustained second phase. B The incretin effect describes the observation that insulin secretion is greater when glucose is given by mouth than when glucose is administered intravenously to achieve the same rise in blood glucose concentrations. The additional stimulus to insulin secretion is mediated by release of peptides from the gut and these actions are exploited in incretin-based therapies (p. 747). 1st phase 2nd phase Basal secretion Insulin secretion The incretin effect Glucose stimulus 0–5 mins Time Time After oral glucose After intravenous glucose Insulin A B Fig. 20.4 Processing of pro-insulin into insulin and C-peptide. Pro-insulin in the pancreatic β cell is cleaved to release insulin and equimolar amounts of inert C-peptide (connecting peptide). Measurement of C-peptide can be used to assess endogenous insulin secretory capacity. Pro-insulin Pancreatic β cell C-peptide Insulin (ADP), which causes closure of an ATP-sensitive potassium channel (KATP). The resulting membrane depolarisation of the β cell results in insulin secretion due to triggering of calcium release by voltage-sensitive calcium channels. In addition to this pathway, the amount of insulin released can be amplified or potentiated by the background blood glucose, other nutrients and peptides, and by neuronal control via the sympathetic and parasympathetic nervous system. A good example of this potentiation of insulin release is seen with the secretion of two gut peptides following ingestion of food. Glucagon-like peptide-1 (GLP-1) and gastric inhibitory polypeptide (GIP) are released from gastrointestinal L cells and K cells, respectively, following a meal, and act via receptors on the pancreatic β cells to augment insulin secretion. Thus, for a given glucose stimulus to the β cell, there is greater insulin secretion with oral glucose administration (where the gut peptides are released) compared to intravenous glucose administration (which does not stimulate gut peptide release). This enhanced insulin secretion following oral administration of glucose is termed the ‘incretin’ effect (Fig. 20.3), and GLP-1 and GIP are known as incretin hormones. Insulin is synthesised as a pro-hormone (pro-insulin) that consists of an α and a β chain, which are linked by C-peptide (Fig. 20.4). The C-peptide is cleaved by β-cell peptidases to create insulin (which now consists of the α and β chains) and free C-peptide. Insulin secretion in response to a glucose stimulus

utilisation of ketone bodies by peripheral tissues is limited, and when the rate of production by the liver exceeds their removal, hyperketonaemia results. This occurs physiologically during starvation, when low insulin levels and high catecholamine levels increase lipolysis and delivery of FFAs to the liver. Investigations Urine glucose Testing the urine for glucose with dipsticks is a common screening procedure for detecting diabetes. If possible, testing should be performed on urine

passed 1–2 hours after a meal to maximise sensitivity. Glycosuria always warrants further assessment by blood testing (see below). The greatest disadvantage of urine glucose measurement is the individual variation in renal threshold for glucose. The most frequent cause of glycosuria is a low renal threshold, which is common during pregnancy and in young people; the resulting ‘renal glycosuria’ is a benign condition unrelated to diabetes. Another disadvantage is that some drugs (such as β-lactam antibiotics, levodopa and salicylates) may interfere with urine glucose tests. When intestinal glucose absorption declines between meals, portal vein insulin and glucose concentrations fall while glucagon levels rise. This leads to increased hepatic glucose output via gluconeogenesis and glycogen breakdown. The liver now resumes net glucose production and glucose homeostasis is maintained. The main substrates for gluconeogenesis are glycerol and amino acids, as shown in Figure 20.5. Fat metabolism Adipocytes (and the liver) synthesise triglyceride from nonesterified (‘free’) fatty acids (FFAs) and glycerol. Insulin is the major regulator not only of glucose metabolism but also of fatty acid metabolism. High insulin levels after meals promote triglyceride accumulation. In contrast, in the fasting state, low insulin levels permit lipolysis and the release into the circulation of FFAs (and glycerol), which can be oxidised by many tissues. Their partial oxidation in the liver provides energy to drive gluconeogenesis and also produces ketone bodies (acetoacetate, which can be reduced to 3-hydroxybutyrate or decarboxylated to acetone), which are generated in hepatocyte mitochondria. Ketone bodies are organic acids that, when formed in small amounts, are oxidised and utilised as metabolic fuel. However, the rate of Fig. 20.5 Major metabolic pathways of fuel metabolism and the actions of insulin. Ⴖ indicates stimulation and Ω indicates suppression by insulin. In response to a rise in blood glucose, e.g. after a meal, insulin is released, suppressing gluconeogenesis and promoting glycogen synthesis and storage. Insulin promotes the peripheral uptake of glucose, particularly in skeletal muscle, and encourages storage (as muscle glycogen). It also promotes protein synthesis and lipogenesis, and suppresses lipolysis. The release of intermediate metabolites, including amino acids (glutamine, alanine), 3-carbon intermediates in oxidation (lactate, pyruvate) and free fatty acids (FFAs), is controlled by insulin. In the absence of insulin, e.g. during fasting, these processes are reversed and favour gluconeogenesis in liver from glycogen, glycerol, amino acids and other 3-carbon precursors. Liver Adipose tissue Muscle Gut Gluconeogenesis FFAs Amino acids Lactate Pyruvate Proteolysis Glucose GLUT4 GLUT4 Ketone bodies Oxidation Glucose Glycogen Oxidation FFAs Triglycerides Food Glucose Glycogen Ketogenesis Oxidation Glycerol FFAs Glucose Glycerol +

 Interstitial glucose A relatively new approach to measuring glucose levels in diabetes is through the use of interstitial continuous glucose monitoring (CGM). CGM systems use a tiny sensor inserted under the skin to check glucose levels in interstitial fluid. The sensor can stay in place for up to 2 weeks before being replaced and provides real-time measurements of glucose levels every 1 or 5 minutes (see Fig. 20.16, p. 751). These devices are not as accurate as blood glucose testing, particularly when levels are low or changing rapidly, so users must still check blood glucose with a glucose meter before driving or changing therapy. CGM provides useful information on daily glucose profiles and, in particular, night-time glucose levels. In addition, alarms can be incorporated into the CGM device to warn individuals about hypoglycaemia. Urine and blood ketones Acetoacetate can be identified in urine by the nitroprusside reaction, using either tablets or dipsticks. Ketonuria may be found in normal people who have been fasting or exercising strenuously for long periods, vomiting repeatedly, or eating a diet high in fat and low in carbohydrate. Ketonuria is therefore not pathognomonic of diabetes but,

if it is associated with glycosuria, the diagnosis of diabetes is highly likely. Urine ketone measurements are semi-quantitative, awkward to perform and retrospective (i.e. the urine has accumulated over several hours). Also, they do not measure the major ketone found in blood during diabetic ketoacidosis (DKA), beta-hydroxybutyrate (β-OHB). Beta-OHB can be measured in blood in the laboratory and also in a fingerprick specimen of capillary blood with a test stick and electronic meter. Whole-blood β-OHB monitoring is useful in assisting with insulin adjustment during intercurrent illness or sustained hyperglycaemia to prevent or detect DKA. Blood β-OHB monitoring is also useful in monitoring resolution of DKA in hospitalised patients (Box 20.4). Glycated haemoglobin Glycated haemoglobin provides an accurate and objective measure of glycaemic control over a period of weeks to months. In diabetes, the slow non-enzymatic covalent attachment of glucose to haemoglobin (glycation) increases the amount in the HbA1 (HbA1c) fraction relative to non-glycated adult haemoglobin (HbA0). These fractions can be separated by chromatography; Blood glucose Laboratory glucose testing in blood relies on an enzymatic reaction (glucose oxidase) and is cheap, usually automated and highly reliable. However, blood glucose levels depend on whether the patient has eaten recently, so it is important to consider the circumstances in which the blood sample was taken. Blood glucose can also be measured with testing sticks that are read with a portable electronic meter. These are used for capillary (fingerprick) testing to monitor diabetes treatment (p. 742). There is some debate as to whether self-monitoring in people with type 2 diabetes improves glycaemic control. Many countries now offer self-monitoring only to people with type 2 diabetes taking sulphonylurea or insulin therapy because of the risk of hypoglycaemia. To make the diagnosis of diabetes, the blood glucose concentration should be estimated using an accurate laboratory method rather than a portable technique. Glucose concentrations are lower in venous than arterial or capillary (fingerprick) blood. Whole-blood glucose concentrations are lower than plasma concentrations because red blood cells contain relatively little glucose. Venous plasma values are usually the most reliable for diagnostic purposes (Boxes 20.2 and 20.3). 20.4 Interpretation of capillary blood ketone measurements Measurement* Interpretation < 0.6 mmol/L Normal; no action required 0.6–1.5 mmol/L Suggests metabolic control may be deteriorating; the patient should continue to monitor and seek medical advice if sustained/progressive 1.5–3.0 mmol/L With high blood glucose (> 10 mmol/L), there is a high risk of diabetic ketoacidosis; seek medical advice

> 3.0 mmol/L Severe ketosis; in the presence of high glucose (> 10 mmol/L) suggests presence of diabetic ketoacidosis; seek urgent medical help *To convert to mg/dL, multiply values by 18. 20.3 How to perform an oral glucose tolerance test (OGTT) Preparation before the test • Unrestricted carbohydrate diet for 3 days • Fasted overnight for at least 8 hrs • Rest for 30 mins • Remain seated for the duration of the test, with no smoking Sampling • Measure plasma glucose before and 2 hrs after a 75 g oral glucose drink 20.2 Diagnosis of diabetes and pre-diabetes Diabetes is confirmed by: • either plasma glucose in random sample or 2 hrs after a 75 g glucose load ≥ 11.1 mmol/L (200 mg/dL) or • fasting plasma glucose ≥ 7.0 mmol/L (126 mg/dL) or • HbA1c ≥ 48 mmol/mol In asymptomatic patients, two diagnostic tests are required to confirm diabetes; the second test should be the same as the first test to avoid confusion ‘Pre-diabetes’ is classified as: • impaired fasting glucose = fasting plasma glucose ≥

> 6.1 mmol/L (110 mg/dL) and < 7.0 mmol/L (126 mg/dL) • impaired glucose tolerance = fasting plasma glucose < 7.0 mmol/L (126 mg/dL) and 2-hr glucose after 75 g oral glucose drink 7.8–11.1 mmol/L (140–200 mg/dL) HbA1c criteria for pre-diabetes vary. The National Institute for Health and Care Excellence (NICE) guidelines (UK) recommend considering an HbA1c range of 42–47 mmol/mol to be indicative of pre-diabetes; the American Diabetes Association (ADA) guidelines suggest a range of 39–47 mmol/mol. The ADA also suggests a lower fasting plasma glucose limit of ≥ 5.6 mmol/L (100 mg/dL) for impaired fasting glucose.

approximately 85% of newly diagnosed type 1 diabetes. Some laboratories now include anti-ZnT8 antibodies in their panel of tests, which increases sensitivity for type 1 diabetes to 92%. C-peptide C-peptide is the connecting peptide that is cleaved in the production of insulin from pro-insulin (see Fig. 20.4). It can be readily measured in blood and urine by sensitive immunoassays. Serum C-peptide is a marker of endogenous insulin secretion (a synthetic insulin does not contain C-peptide) and is particularly useful if a patient is on exogenous (injected) insulin treatment, when insulin assays would simply detect the injected insulin. Serum C-peptide can help clarify the differential diagnosis of diabetes, as it is usually very low in long-standing type 1 diabetes and very high in severe insulin resistance. It is also useful in the diagnosis of spontaneous hypoglycaemia (p. 676). Urine protein Standard urine dipstick testing for albumin detects urinary albumin at concentrations above 300 mg/L, but smaller amounts (microalbuminuria; see Box 15.9, p. 394) can only be measured using specific albumin dipsticks or quantitative biochemical laboratory tests. Microalbuminuria or proteinuria, in the absence of urinary tract infection, is an important indicator of diabetic nephropathy and/or increased risk of macrovascular disease (p. 757). Establishing the diagnosis of diabetes Glycaemia can be classified into three categories: normal, impaired (pre-diabetes) and diabetes (see Box 20.2). The glycaemia cut-off that defines diabetes is based on the level above which there is a significant risk of microvascular complications (retinopathy, nephropathy and neuropathy). People categorised as having pre-diabetes have blood glucose levels that carry a negligible risk of microvascular complications but are at increased risk of developing diabetes. Also, because there is a continuous risk of macrovascular disease (atheroma of large conduit blood vessels) with increasing glycaemia in the population, people with pre-diabetes have an increased risk of cardiovascular disease (myocardial infarction, stroke and peripheral vascular disease). The traditional way to diagnose diabetes or pre-diabetes has been by using random or fasting plasma glucose and/or an oral glucose tolerance test (OGTT). In 2011, the World Health Organisation (WHO) advocated the use of glycated haemoglobin (HbA1c, see above) to diagnose diabetes and this has been adopted in some regions. When a person has symptoms of diabetes, the diagnosis can be confirmed with either a fasting glucose of ≥ 7.0 mmol/L (126 mg/dL) or a random glucose of ≥ 11.1 mmol/L (200 mg/dL) (see Box 20.2). Asymptomatic individuals should have a second confirmatory test. Diabetes should not be diagnosed on capillary blood glucose results. Alternatively, an HbA1c of ≥ 48 mmol/mol is also diagnostic of diabetes. As HbA1c reflects the last 2–3 months of glycaemia, it should not be used to diagnose diabetes where the duration of onset is short, i.e. in someone with suspected type 1 diabetes or severe symptomatic

hyperglycaemia (p. 734). If there is a high clinical suspicion of diabetes with an HbA1c of less than 48 mmol/ mol, then a fasting glucose measurement is required to rule out diabetes. It should be noted that the two populations identified using blood glucose and using HbA1c will not be identical, some laboratories may report glycated haemoglobin as total glycated haemoglobin (GHb), HbA1 or HbA1c. In most countries, HbA1c is the preferred measurement. The rate of formation of HbA1c is directly proportional to the ambient blood glucose concentration; a rise of 11 mmol/mol in HbA1c corresponds to an approximate average increase of 2 mmol/L (36 mg/dL) in blood glucose. Although HbA1c concentration reflects the integrated blood glucose control over the lifespan of erythrocytes (120 days), HbA1c is most sensitive to changes in glycaemic control occurring in the month before measurement. Various assay methods are used to measure HbA1c, but most laboratories have been reporting HbA1c values (as %) aligned with the reference range that was used in the Diabetes Control and Complications Trial (DCCT). To allow worldwide comparisons of HbA1c values, the International Federation of Clinical Chemistry and Laboratory Medicine (IFCC) has developed a standard method; IFCC-standardised HbA1c values are reported in mmol/mol. In 2011, many countries adopted the IFCC reference method (Box 20.5) and this is used throughout this textbook. HbA1c estimates may be erroneously diminished in anaemia or during pregnancy, and may be difficult to interpret with some assay methods in patients who have uraemia or a haemoglobinopathy. It is particularly important to be aware of this in some developing countries where nutritional deficiency is common, especially when an absolute cut-off point is used, e.g. in the diagnosis of diabetes. Islet autoantibodies As type 1 diabetes is a characterised by autoimmune destruction of the pancreatic β cells, it can be useful in the differential diagnosis of diabetes (see below) to establish evidence of such an autoimmune process. If islet autoantibodies are present at high titre, this can be supportive of a diagnosis of type 1 diabetes. The antibodies that are measured are directed against components of the islet and consist of antibodies to insulin, glutamic acid decarboxylase (GAD), protein tyrosine phosphatase-related proteins (IA-2) and the zinc transporter ZnT8. These antibodies can be detected in the general population; the level at which they are called positive does vary by laboratory but is usually at concentrations greater than the 95th centile or 97.5th centile of the general population. This means that pancreatic autoantibodies can be weakly positive in people who do not have type 1 diabetes. However, if anti-GAD and anti-IA-2 antibodies are measured together, they will be ‘positive’ (alone or in combination) in 20.5 Conversion between DCCT and IFCC units for HbA1c DCCT units (%) IFCC units (mmol/mol)

IFCC HbA1c (mmol/mol) = [DCCT HbA1c(%)−2.15] × 10.929 (DCCT = Diabetes Control and Complications Trial; IFCC = International Federation of Clinical Chemistry and Laboratory Medicine)

 insulin-secreting β cells in the pancreatic islets. The natural history of type 1 diabetes is based on the model proposed by Eisenbarth in 1986, which proposed that genetically susceptible individuals with a given β-cell mass who were subsequently exposed to an environmental trigger then developed β-cell autoimmunity that led to progressive loss of β cells. This process was seen to take place over a prolonged period (months to years). Marked hyperglycaemia, accompanied by the classical symptoms of diabetes, occurs only when 80–90% of the functional capacity of β cells has been lost. More recent data have led to modifications of this model. For example, it is now recognised that pancreatic β cells can persist in some individuals with very long-standing diabetes and may never reach zero. On the contrary, some individuals present with much higher levels of β-cell viability (40–50%) and that may reflect lower levels of

physical activity or increased body mass. Despite this uncertainty, in the natural history of type 1 diabetes there is initially a loss of first-phase insulin secretion, followed by a period of glucose intolerance and clinically undiagnosed diabetes. The pathology in the pre-diabetic pancreas is characterised by an inflammatory lesion within islets, ‘insulitis’ (Fig. 20.6), with infiltration of the islets by mononuclear cells containing activated macrophages, helper cytotoxic and suppressor T lymphocytes, natural killer cells and B lymphocytes. Initially, these lesions are patchy and, until a very late stage, lobules containing heavily infiltrated islets are seen adjacent to unaffected lobules. The destructive process is β-cell-specific. It is unclear why other hormone-secreting cells in the islets, such as α and δ cells, remain intact. In addition, while a number of theories such as molecular mimicry, oxidative stress and viral infections have been proposed, the specific mechanisms for inducing autoimmunity in type 1 diabetes are unknown. Autoimmunity in type 1 diabetes is identified by the presence of autoantibodies to islet and/or β-cell antigens. Islet cell antibodies can be present long before the clinical presentation of type 1 diabetes, and their detection can be useful in confirming a diagnosis of type 1 diabetes, but they are poorly predictive of disease progression and disappear over time (Fig. 20.6). Autoantibodies are typically present in 70–80% of newly diagnosed type 1 diabetes, but this can vary depending on age, gender and ethnicity, as well as quality of the assay employed. Autoantibodies can also be used to predict disease with a 5-year risk of type 1 diabetes of about 20–25% in people with a single positive autoantibody, 50–60% in those with two positive autoantibodies, and 70% in those with three autoantibodies. Type 1 diabetes is associated with other autoimmune disorders (Ch. 4), including thyroid disease (p. 638), coeliac disease (p. 805), Addison’s disease (p. 671), pernicious anaemia (p. 944) and vitiligo (p. 1257). The association between type 1 diabetes and coeliac disease is particularly strong; it is estimated that around 1 in 20 people with type 1 diabetes (especially when diagnosed in childhood) will have biopsy-proven coeliac disease and so many countries advocate routine screening for this condition. Genetic predisposition Although not showing a simple pattern of inheritance, type 1 diabetes is strongly influenced by genetic factors. The relationship is complex and, as indicated, multifactorial. Monozygotic twins have a disease concordance rate of 30–50%, while dizygotic twins have a concordance of 6–10%. In the USA, the risk of developing type 1 diabetes is 1 : 20 for those with a first-degree relative, compared with a 1 : 300 risk in the general population. Children of mothers with type 1 diabetes have a 1–4% risk of being diagnosed with diabetes using one criterion but not the other. When a person is asymptomatic and repeat testing is required, the same method should be used for the confirmatory test to avoid diagnostic confusion. Pre-diabetes can be subclassified as ‘impaired fasting glucose’ (IFG), based on a fasting plasma glucose result, or ‘impaired glucose tolerance’ (IGT), based on the fasting and 2-hour OGTT results (see Box 20.3). Patients with pre-diabetes should be advised of their risk of progression to diabetes, given advice about lifestyle modification to reduce this risk (as for type 2 diabetes, p. 743), and have aggressive management of cardiovascular risk factors such as hypertension and dyslipidaemia. The HbA1c criteria for pre-diabetes are less clear. The NICE guidelines (UK) suggest a range of 42–47 mmol/mol, whereas the American Diabetes Association guidelines recommend a range of 39–47 mmol/mol. In some people (especially those with pre-existing insulin resistance or low β-cell mass/function), an abnormal blood glucose result is observed during acute severe illness, such as infection or myocardial infarction. This ‘stress hyperglycaemia’ is a consequence of hormones, such as cortisol and catecholamines, antagonising the action of insulin and thereby increasing insulin resistance. It usually disappears after the acute illness has resolved, but affected individuals have a significantly increased risk of type 2 diabetes in subsequent years. A similar mechanism explains the occurrence of diabetes in some people treated with glucocorticoids

(steroid-induced diabetes). The diagnostic criteria recommended for diabetes in pregnancy are more stringent than those for non-pregnant patients (see Box 20.31). Pregnant women with abnormal glucose tolerance should be referred urgently to a specialist unit for full evaluation. Due to the increased red cell turnover that occurs in pregnancy, an HbA1c test should not be used to diagnose diabetes in pregnancy When a diagnosis of diabetes is confirmed, other investigations should include plasma urea, creatinine and electrolytes, lipids, liver and thyroid function tests, blood or urine ketones, and urine protein. Aetiology and pathogenesis of diabetes In both of the common types of diabetes, environmental factors interact with genetic susceptibility to determine which people develop the clinical syndrome, and the timing of its onset. However, the underlying genes, precipitating environmental factors and pathophysiology differ substantially between type 1 and type 2 diabetes. Type 1 diabetes was previously termed ‘insulin-dependent diabetes mellitus’ (IDDM) and is invariably associated with insulin deficiency requiring replacement therapy. Type 2 diabetes was previously termed ‘non-insulin-dependent diabetes mellitus’ (NIDDM) because patients retain the capacity to secrete insulin, and measured insulin levels are often higher than those seen in people without diabetes. In type 2 diabetes, though, there is an impaired sensitivity to insulin (insulin resistance) and, initially, affected individuals can usually be treated without insulin replacement therapy. However, 20% or more of patients with type 2 diabetes will ultimately develop insulin deficiency requiring replacement therapy, so IDDM and NIDDM were misnomers. Type 1 diabetes Pathology Type 1 diabetes is generally considered a T-cell-mediated autoimmune disease (p. 81) involving destruction of the

Environmental predisposition The wide geographical and seasonal variations in incidence, and the rapid acquisition of local disease incidence rates in migrants from low- to high-incidence countries suggest that environmental factors have an important role in precipitating disease. Although hypotheses abound, the nature of these environmental factors is unknown. They may trigger type 1 diabetes through direct toxicity to β cells or by stimulating an autoimmune reaction directed against β cells. Potential candidates fall into three main categories: viruses, specific drugs or chemicals, and dietary constituents. Viruses implicated in the aetiology of type 1 diabetes include mumps, Coxsackie B4, retroviruses, rubella (in utero), cytomegalovirus and Epstein–Barr virus. Various dietary nitrosamines (found in smoked and cured meats) and coffee have been proposed as potentially diabetogenic toxins. Bovine serum albumin (BSA), a major constituent of cow’s milk, has been implicated, since children who are given cow’s milk early in infancy are more likely to develop type 1 diabetes than those who are breastfed. BSA may cross the neonatal gut and raise antibodies that cross-react with a heat-shock protein expressed by β cells. It has also been proposed that reduced exposure to microorganisms in early childhood limits maturation of the immune system and increases susceptibility to autoimmune disease (the ‘hygiene hypothesis’). In addition, the high incidence rates in northern Europe have led to the suggestion that low levels of vitamin D may be important, but to date no clear cause–effect relationship has been identified. Metabolic disturbances in type 1 diabetes Patients with type 1 diabetes present when progressive β-cell destruction has crossed a threshold at which adequate insulin secretion and normal blood glucose levels can no longer be sustained. Above a certain level, high glucose levels may be toxic to the remaining β cells, so that profound insulin deficiency rapidly ensues, causing the metabolic sequelae shown in Figure 20.7. Hyperglycaemia leads to glycosuria and dehydration, causing fatigue, polyuria, nocturia, thirst and polydipsia, susceptibility to urinary and genital tract

infections, and later tachycardia and hypotension. Unrestrained lipolysis and proteolysis result in developing type 1 diabetes, but children of fathers with type 1 diabetes have a 10% risk. Despite this genetic influence, 80–85% of new cases present in individuals with no known family history of the disease. The inheritance of type 1 diabetes is polygenic (Box 20.6), with over 20 different regions of the human genome showing an association with type 1 diabetes risk. Most interest has focused on the human leucocyte antigen (HLA) region within the major histocompatibility complex on the short arm of chromosome 6. The HLA haplotypes DR3 and/or DR4 are associated with increased susceptibility to type 1 diabetes in Caucasians and are in 'linkage disequilibrium', i.e. they tend to be transmitted together, with the neighbouring alleles of the HLA-DQA1 and DQB1 genes. The latter may be the main determinants of genetic susceptibility, since these HLA class II genes code for proteins on the surface of cells that present foreign and self-antigens to T lymphocytes (p. 82). Candidate gene and genome-wide association studies have also implicated other genes in type 1 diabetes, e.g. CD25, PTPN22, SH2B3, IL2RA and IL-10. Interestingly, the majority of these disease risk loci are involved in immune responsiveness, such as recognition of pancreatic islet antigens, T-cell development and immune regulation. The genes associated with type 1 diabetes overlap with those for other autoimmune disorders, such as coeliac disease and thyroid disease, consistent with clustering of these conditions in individuals or families. Fig. 20.6 Pathogenesis of type 1 diabetes. Proposed sequence of events in the development of type 1 diabetes. Environmental triggers are described in the text. Insets (normal islet, β-cell destruction) Courtesy of Dr A. Foulis, Dept of Pathology, University of Glasgow. Normal islet β-cell mass Environmental triggers Genetic susceptibility to immune dysfunction Inflammatory cell infiltration of islet Antibody-mediated β-cell destruction Autoantibodies present in blood Overt diabetes Loss of first-phase insulin secretion Impaired glucose tolerance Insulitis β-cell destruction Time 20.6 Risk of type 1 diabetes among first-degree relatives of patients with type 1 diabetes Relative with type 1 diabetes % overall risk Identical twin 30–50 Non-identical twin 6–10 HLA-identical sibling

Non-HLA-identical sibling

Father

Mother 1–4 Both parents Up to 30

 Type 2 diabetes Pathology Type 2 diabetes is a diagnosis of exclusion, i.e. it is made when type 1 diabetes and other types of diabetes (see Box 20.9) are ruled out; it is highly heterogeneous. The natural history of typical type 2 diabetes is shown in Figure 20.8. Initially, insulin resistance leads to elevated insulin secretion in order to maintain normal blood glucose levels. However, in susceptible individuals, the pancreatic β cells are unable to sustain the increased demand for insulin and a slowly progressive insulin deficiency develops. Some patients develop diabetes at a young age, usually driven by insulin resistance due to obesity and ethnicity; others, particularly older patients, develop diabetes despite being non-obese and may have more pronounced β-cell failure. The key feature is a 'relative' insulin deficiency, such that there is insufficient insulin production to overcome the resistance to insulin action. This contrasts with type 1 diabetes, in which there is rapid loss of insulin production, resulting in ketoacidosis and death if the insulin is not replaced. Insulin resistance and the metabolic syndrome Type 2 diabetes and its pre-diabetes antecedents belong to a cluster of conditions thought to be caused by resistance to insulin action. Thus, people with type 2 diabetes often have associated disorders including

hypertension, dyslipidaemia (characterised by elevated levels of small dense low-density lipoprotein (LDL) weight loss. Ketoacidosis occurs when generation of ketones exceeds the capacity for their metabolism. Elevated blood H+ ions drive K+ out of the intracellular compartment, while secondary hyperaldosteronism encourages urinary loss of K+. Thus patients usually present with a short history (typically a few weeks) of hyperglycaemic symptoms (thirst, polyuria, nocturia and fatigue), infections and weight loss, and may have developed ketoacidosis (p. 735). Type 1 diabetes in adults While type 1 diabetes is classically thought of as a disease of children and young adults (most commonly presenting between 5 and 7 years of age and at or near puberty), it can manifest at any age, with as much as half of cases thought to develop in adults. It is also possible for patients who have a more insidious onset of diabetes to have an autoimmune aetiology; these people are sometimes described as having slow-onset type 1 diabetes or latent autoimmune diabetes of adulthood (LADA). LADA is defined as the presence of islet autoantibodies in high titre (usually GAD antibodies), without rapid progression to insulin therapy (which would usually signify type 1 diabetes). Patients with LADA can often present and be managed similarly to those with type 2 diabetes, but they do progress more rapidly to requiring insulin treatment for glucose control. Not all expert committees recognise LADA as a diagnostic category, however, and consider LADA to be just a subset of autoimmune type 1 diabetes developing in adulthood. Fig. 20.7 Acute metabolic complications of insulin deficiency. (FFA = free fatty acid) ↓Glucose uptake and utilisation ↑Glycogenolysis Hyperglycaemia Glycosuria Osmotic diuresis Dehydration Hyperosmolarity Secondary hyperaldosteronism K+ deficiency ↑Gluconeogenesis ↑Lipolysis ↑Proteolysis ↑FFA and glycerol to liver ↓Renal function ↑Lactate ↑Ketogenesis Metabolic acidosis Insufficient insulin

treatment of the diabetes but, despite this, some patients progress to non-alcoholic steatohepatitis (NASH, p. 882) and cirrhosis. Pancreatic β-cell failure In the early stages of type 2 diabetes, reduction in the total mass of pancreatic islet tissue is modest. At the time of diagnosis, around 50% of β-cell function has been lost and this declines progressively (Fig. 20.8B). Some pathological changes are typical of type 2 diabetes, the most consistent of which is deposition of amyloid in the islets. In addition, elevated plasma glucose and FFAs exert toxic effects on pancreatic β cells to impair insulin secretion. However, while β-cell numbers are reduced, β-cell mass is unchanged and glucagon secretion is increased, which may contribute to hyperglycaemia. Genetic predisposition Genetic factors are important in type 2 diabetes, as shown by marked differences in susceptibility in different ethnic groups and by studies in monozygotic twins where concordance rates for type 2 diabetes approach 100%. However, many genes are involved and the chance of developing diabetes is also influenced very powerfully by environmental factors (Box 20.7). Genome-wide association studies have identified over 70 genes cholesterol and triglycerides, and a low level of high-density lipoprotein (HDL) cholesterol), non-alcoholic fatty liver disease (p. 882) and, in women, polycystic ovarian syndrome. This cluster has been termed the ‘insulin resistance syndrome’ or ‘metabolic syndrome’, and is much more common in individuals who are obese. The primary cause of insulin resistance remains unclear; it is likely that there are multiple defects in insulin signalling, affecting several tissues. One theory is centred around the adipocyte; this is particularly appealing, as obesity is a major cause of increased insulin resistance. Intra-abdominal ‘central’ adipose tissue is metabolically active and releases large quantities of FFAs, which may induce insulin resistance because they compete with glucose as a fuel supply for oxidation in peripheral tissues such as

muscle. In addition, adipose tissue releases a number of hormones (including a variety of peptides, called ‘adipokines’ because they are structurally similar to immunological ‘cytokines’) that act on specific receptors to influence sensitivity to insulin in other tissues. Because the venous drainage of visceral adipose tissue is into the portal vein, central obesity may have a particularly potent influence on insulin sensitivity in the liver, and thereby adversely affect gluconeogenesis and hepatic lipid metabolism. Physical activity is another important determinant of insulin sensitivity. Inactivity is associated with down-regulation of insulin-sensitive kinases and may promote accumulation of FFAs within skeletal muscle. Sedentary people are therefore more insulin-resistant than active people with the same degree of obesity. Moreover, physical activity allows non-insulin-dependent glucose uptake into muscle, reducing the ‘demand’ on the pancreatic β cells to produce insulin. Deposition of fat in the liver is a common association with central obesity and is exacerbated by insulin resistance and/or deficiency. Many people with type 2 diabetes have evidence of fatty infiltration of the liver (non-alcoholic fatty liver disease, NAFLD). This condition may improve with effective Fig. 20.8 Natural history of type 2 diabetes. A In the early stage of the disorder, the response to progressive insulin resistance is an increase in insulin secretion by the pancreatic cells, causing hyperinsulinaemia. Eventually, the β cells are unable to compensate adequately and blood glucose rises, producing hyperglycaemia. With further β-cell failure, glycaemic control deteriorates and treatment requirements escalate. B Progressive pancreatic β-cell failure in patients with type 2 diabetes in the United Kingdom Prospective Diabetes Study (UKPDS). Beta-cell function was estimated using the homeostasis model assessment (HOMA) and was already below 50% at the time of diagnosis. Thereafter, long-term incremental increases in fasting plasma glucose were accompanied by progressive β-cell dysfunction. If the slope of this progression is extrapolated, it appears that pancreatic dysfunction may have been developing for many years before diagnosis of diabetes. B, Adapted from Holman RR. Diabetes Res Clin Pract 1998; 40 (Suppl.):S21–S25. Impaired glucose tolerance Type 2 diabetes Hyperinsulinaemia Normal Time Plasma glucose

β-cell function (%)

−10 −8 −6 −4 −2 Start of treatment Years

Plasma insulin Deteriorating β-cell function Increasing insulin resistance with age, obesity etc. Euglycaemia Dietcontrolled Antidiabetic drugs Insulin A B 20.7 Risk of developing type 2 diabetes for siblings of individuals with type 2 diabetes Age at onset of type 2 diabetes in proband (years) Age-corrected risk of type 2 diabetes for siblings (%) 25–44

45–54

55–64

65–80

 Ethnicity Ethnic origin is a major risk factor for development of diabetes. For example, within the USA, the prevalence of diabetes is lowest in Alaskan Natives at 5.5%, moderate for non-Hispanic whites at 7.1%, high for non-Hispanic blacks at 13% and highest in Native Americans at 33%. This considerable variation in prevalence reflects a number of different

factors, including a higher BMI and lower socioeconomic class in high-risk groups in the USA; differences in health behaviour, e.g. decreased physical activity and increased smoking; and differences in genetic risk. Studies in high-risk ethnic groups largely demonstrate increased insulin resistance and more central/visceral adiposity than in the lower-risk groups. Metabolic disturbances in type 2 diabetes Patients with type 2 diabetes have a slow onset of ‘relative’ insulin deficiency. Relatively small amounts of insulin are required to suppress lipolysis, and some glucose uptake is maintained in muscle so that, in contrast to type 1 diabetes, lipolysis and proteolysis are not unrestrained and weight loss and ketoacidosis seldom occur. In type 2 diabetes, hyperglycaemia tends to develop slowly over months or years; because of this insidious onset many cases of type 2 diabetes are discovered coincidentally and a large number are undetected. At diagnosis, patients are often asymptomatic or give a long history (typically many months) of fatigue, with or without ‘osmotic symptoms’ (thirst and polyuria). However, there are some people with type 2 diabetes who present acutely with marked osmotic symptoms and weight loss. These may be presenting late, such that they have already developed β-cell failure, but more usually this decompensation reflects a vicious spiral of decline. As hyperglycaemia worsens, patients often crave sugar and will consume large volumes of sugary drinks to try to quench their thirst; worsening hyperglycaemia is also associated with increasing lipolysis, and the high circulating glucose and FFAs are toxic to the β cell, resulting in ‘glucolipotoxicity’ and reduced β-cell function. In these patients, ketosis and even DKA can occur; this is classically described in the African American population, where up to half of patients who present with DKA have type 2 diabetes and not type 1 diabetes. The presentation of DKA in type 2 diabetes is referred to as ‘ketosis-prone’ diabetes or ‘Flatbush syndrome’, named after the Flatbush neighbourhood of New York, which had a large Caribbean population and where presentation with DKA was common. Importantly in these patients, insulin treatment is required initially but, as the glucose and lipids are controlled, the β cells recover, and they can usually transfer off insulin and on to oral treatments such as metformin after 3 months of insulin treatment. Intercurrent illness, e.g. with infections, increases the production of stress hormones that oppose insulin action, such as cortisol, growth hormone and catecholamines. This can precipitate an acute exacerbation of insulin resistance and insulin deficiency, and result in more severe hyperglycaemia and dehydration (p. 738). Other forms of diabetes Other causes of diabetes are shown in Box 20.9. These can broadly be broken down into genetic disorders including monogenic diabetes (diabetes due to a mutation in or deletion of a single gene) or diabetes as part of a genetic syndrome; endocrine disorders due to excess in hormones that oppose or gene regions that are associated with type 2 diabetes, each exerting a small effect. Most of the genes known to contribute to risk of type 2 diabetes are involved in β-cell function or in regulation of cell cycling and turnover, suggesting that altered regulation of β-cell mass is a key factor. The largest population genetic effect described to date is seen with variation in TCF7L2; the 10% of the population with two copies of the risk variant for this gene have a nearly twofold increase in risk of developing type 2 diabetes. In general, other common variants explain much lower risk than this, many explaining less than a 10% increase in risk only; as only about 10% of the genetic variance in type 2 diabetes is explained by these common genetic variants, this has led some to question the relevance of finding diabetes genes. However, it should be noted that, within a population, the distribution of risk variants will vary, with some patients having inherited a high genetic burden (e.g. more than 40 risk variants) and others having inherited very few. When studies compare those in the top 20% of this risk band with the lowest 20%, those at highest risk are over 2.5 times more likely to develop diabetes. More recent insights into the genetics of type 2 diabetes have highlighted how some genetic variants may be rare and therefore affect only a small proportion of

the population, but have large clinical effects. For example, in a Greenlandic population, 3% of people carry a homozygous variant in an insulin signalling gene, TBC1D4, that results in muscle insulin resistance; these individuals are over 10 times more likely to develop type 2 diabetes. Environmental and other risk factors Diet and obesity Epidemiological studies show that type 2 diabetes is associated with overeating, especially when combined with obesity and under-activity. Middle-aged people with diabetes eat significantly more and are fatter and less active than their non-diabetic siblings. The risk of developing type 2 diabetes increases 10-fold in people with a body mass index (BMI) of more than 30 kg/m2 (p. 698). However, although the majority of individuals with type 2 diabetes are obese, only a minority of obese people develop diabetes, as most obese people are able to increase insulin secretion to compensate for the increased demand resulting from obesity and insulin resistance. Those who develop diabetes may have genetically impaired β-cell function, reduced β-cell mass, or a susceptibility of β cells to attack by toxic substances such as FFAs or inflammatory cytokines. Age Type 2 diabetes is more common in middle-aged and older individuals (Box 20.8). In the UK, it affects 10% of the population over 65, and over 70% of all cases of diabetes occur after the age of 50 years. 20.8 Diagnosis of diabetes mellitus in old age • Prevalence: increases with age, affecting ~10% of people over 65 years. Half of these are undiagnosed. Impaired β-cell function and exaggerated insulin resistance with ageing both contribute. • Glycosuria: the renal threshold for glucose rises with age, so glycosuria may not develop until the blood glucose concentration is markedly raised. • Pancreatic carcinoma: may present in old age with the development of diabetes, in association with weight loss and diminished appetite.

Monogenic diabetes Monogenic diabetes accounts for approximately 4% of diabetes in those diagnosed under the age of 30 in the UK. While there are a number of monogenic disorders of insulin action, the most common monogenic forms of diabetes are caused by defects in insulin secretion, in part because insulin resistance alone is not sufficient to cause diabetes. Monogenic disorders of the β cell cause two diabetes subtypes: maturity-onset diabetes of the young (MODY; Box 20.10) and neonatal diabetes. The common genes involved in MODY and neonatal diabetes are shown in Figure 20.2C. MODY is defined as non-insulin-requiring diabetes that develops under the age of 25 years in one family member. MODY is dominantly inherited (p. 46), which means that the diabetes runs in families, many having a family history of diabetes spanning three generations or more. MODY itself is a heterogeneous condition, with multiple subtypes. One form is caused by mutations in glucokinase (see Fig. 20.2B); this is the pancreatic glucose sensor and patients with glucokinase mutations have an altered set-point for glucose. This results in a high fasting glucose (usually

> 5.5 mmol/L (99 mg/dL)) but a normal post-prandial response. As a result, patients with glucokinase MODY have stable, mild hyperglycaemia, with only a slightly elevated HbA1c; they do not require treatment and do not develop diabetes complications. It is therefore important to identify these patients, to avoid unnecessary diabetes treatment and monitoring. The other forms of MODY are mostly caused by defective transcription factors that play a key role in

pancreatic β-cell development and function (hepatocyte nuclear factor (HNF) 1α, 1β and 4α). Patients with transcription factor MODY develop diabetes in adolescence or early adulthood and the diabetes is progressive, requiring oral diabetes treatment before eventually needing insulin. Patients with HNF1α and 4α MODY are extremely sensitive to sulphonylureas and this is the treatment of choice for these individuals. HNF1β is a critical transcription factor not only in pancreatic development but also in renal and genital tract development in utero. Patients with HNF1β mutations usually have renal abnormalities, including renal cystic disease and genital tract malformation, such as absent or bicornuate uterus or hypospadias and infertility; about 50% of individuals with the gene mutation have young-onset diabetes. 20.10 Monogenic diabetes mellitus: maturity-onset diabetes of the young (MODY) Functional defect Main type* Gene mutated* β-cell glucose sensing MODY2 GCK The set point for basal insulin release is altered, causing a high fasting glucose, but sufficient insulin is released after meals. As a result, the HbA1c is often normal and microvascular complications are rare. Treatment is rarely required β-cell transcriptional regulation MODY3 HNF1α MODY5 HNF1β MODY1 HNF4α Diabetes develops during adolescence/early adulthood and can be managed with diet and tablets for many years, but ultimately, insulin treatment is required. The HNF1α and 4α forms respond particularly well to sulphonylurea drugs. All types are associated with microvascular complications. HNF1β mutations also cause renal cysts and renal failure *Other gene mutations have been found in rare cases. For further information, see diabetesgenes.org. 20.9 Aetiological classification of diabetes mellitus Type 1 diabetes • Immune-mediated • Idiopathic Type 2 diabetes Other specific types • Genetic defects of β-cell function (see Box 20.10) • Genetic defects of insulin action (e.g. leprechaunism, lipodystrophies) • Pancreatic disease (e.g. pancreatitis, pancreatectomy, neoplastic disease, cystic fibrosis, haemochromatosis, fibrocalculous pancreatopathy) • Excess endogenous production of hormonal antagonists to insulin, e.g.: Growth hormone – acromegaly Glucocorticoids – Cushing’s syndrome Glucagon – glucagonoma Catecholamines – phaeochromocytoma Thyroid hormones – thyrotoxicosis • Drug-induced (e.g. glucocorticoids, thiazide diuretics, phenytoin) • Uncommon forms of immune-mediated diabetes (e.g. IPEX syndrome) • Associated with genetic syndromes (e.g. Down’s syndrome, Klinefelter’s syndrome, Turner’s syndrome, DIDMOAD (Wolfram’s syndrome), Friedreich’s ataxia, myotonic dystrophy) Gestational diabetes (DIDMOAD = diabetes insipidus, diabetes mellitus, optic atrophy, nerve deafness; IPEX = immunodysregulation polyendocrinopathy X) the effects of insulin (Ch. 18); and more generalised diseases of the pancreas. Pancreatic disease Pancreatic disease is a relatively common but often unrecognised cause of diabetes, largely related to alcohol excess. Alcohol excess can cause recurrent bouts of acute pancreatitis, with progressive destruction of the pancreas and subsequent diabetes. However, more commonly, chronic alcohol excess can be linked to chronic pancreatitis, which is then termed alcoholic chronic pancreatitis. Although this is associated

> with recurrent abdominal pain, it is asymptomatic in many patients, resulting in both pancreatic exocrine failure and endocrine failure. While diabetes due to pancreatic insufficiency secondary to alcohol excess can be managed with oral therapy, the insulin deficiency usually requires insulin replacement therapy. In some geographical regions, there is a form of chronic calcific pancreatitis that is not caused by alcohol excess and causes diabetes to present in adolescence or early adulthood; this condition is called fibrocalculous pancreatic diabetes (FCPD). It is characteristically a disease of the tropics, with variable prevalence across these regions. The aetiology of FCPD is poorly understood. While there is thought to be a genetic predisposition, with mutations in SPINK1 being described, it is usually seen in malnourished individuals, but it is not clear whether this is a cause or consequence of the disease. FCPD usually presents with recurrent severe abdominal pain in childhood, diabetes developing 10–20 years later; there is a 100-fold increased risk of pancreatic cancer in later life. Insulin treatment is usually required at or soon after diagnosis.

734 • DIABETES MELLITUS Presenting problems in diabetes mellitus Hyperglycaemia The diagnosis of diabetes is simple: it is based on confirmation of hyperglycaemia using either fasting or random glucose, an OGTT or HbA1c (p. 727). Diabetes, however, results from a variety of pathological processes, meaning that within this broad category are many aetiological subtypes. Following the identification of hyperglycaemia and subsequent diagnosis of diabetes, the initial management involves a careful clinical assessment of the patient to decide whether immediate treatment is required and, with appropriate investigation, to establish the aetiology of the diabetes, as this will determine subsequent diabetes treatment (Fig. 20.9). The main differential diagnosis to consider is that of type 1 or type 2 diabetes; making a diagnosis of type 1 diabetes is important, as a failure to initiate insulin treatment can result in Neonatal diabetes is variably defined as diabetes that presents in the neonatal period, although this is usually extended to the first 6 months of life. The presentation is usually that of profound insulin deficiency with marked hyperglycaemia and DKA. Approximately half of patients with neonatal diabetes have a transient form that remits by about 1 year of age, with diabetes recurring in adolescence or early adulthood; the remaining patients have permanent neonatal diabetes. In recent years, the genetics of neonatal diabetes have been unravelled, having a major positive impact for people with this condition. Approximately two-thirds of patients with permanent neonatal diabetes have an activating mutation in the genes encoding the KIR6.2 and SUR1 subunits of the KATP channel (see Fig. 20.2C). These mutations cause the KATP channel to be insensitive to the glucose-mediated rise in intracellular ATP; as a result, the pancreatic β cells do not secrete insulin and patients require insulin treatment from soon after birth. It has been shown, however, that these individuals do respond to sulphonylureas; this finding has transformed their care, over 90% being managed with oral sulphonylurea treatment. Fig. 20.9 New-onset hyperglycaemia. (DKA = diabetic ketoacidosis; GAD = glutamic acid decarboxylase; HHS = hyperosmotic hyperglycaemic state; IA-2 = islet antigen 2; IV = intravenous; SC = subcutaneous) New-onset hyperglycaemia Confirm diagnosis of diabetes (Box 20.2) Patient unwell and/or Marked symptoms of hyperglycaemia and/or Blood ketones elevated Intercurrent illness; dehydration HHS Box 20.17 DKA Box 20.16 Commence IV insulin and fluids Continue on SC insulin Continue on insulin Evaluate aetiology of diabetes* Likely type 1 diabetes Typical type 1 diabetes?

Not overweight No family history of diabetes GAD/IA-2 antibody-positive Low C-peptide Other types? Chronic pancreatitis/abdominal pain – consider alcohol-related or pancreatic malignancy Features of endocrine disease? Abnormal liver function – consider haemochromatosis Three-generation family history – consider monogenic diabetes Renal and urinary tract abnormalities – consider HNF1β Typical type 2 diabetes? Obese or overweight Aged over 40 Family history of diabetes Ethnicity high diabetes risk GAD/IA-2 antibody-negative Elevated C-peptide No other cause Consider introducing oral agents and weaning insulin (careful monitoring required) Likely type 2 diabetes No underlying cause Patient well Commence SC insulin Refer for immediate assessment Evaluate for DKA/HHS and intercurrent illness – see emergency management Probable type 2 diabetes? Possible type 1 diabetes? Self-monitoring of blood glucose and ketones Low threshold to start SC insulin Evaluate aetiology of diabetes* *Evaluation of diabetes aetiology Manage according to diabetes aetiology Diet and lifestyle modification Early initiation of metformin Patient not unwell and Mild or no symptoms of hyperglycaemia and Blood ketones not elevated

Sometimes the definitive classification of the type of diabetes is only made later, once the natural history or responsiveness to different therapies becomes apparent. Physical signs in patients with type 2 diabetes at diagnosis depend on the mode of presentation. In Western populations, more than 80% are overweight and the obesity is often central (truncal or abdominal). Obesity is much less evident in Asians. Hypertension is present in at least 50% of patients with type 2 diabetes. Although dyslipidaemia is also common, skin lesions such as xanthelasma and eruptive xanthomas are rare. Presentation with the complications of diabetes Patients with long-standing diabetes are at risk of developing a variety of complications (see Box 20.35, p. 756) and as many as 25% of people with type 2 diabetes have evidence of diabetic complications at the time of diagnosis. Thus, diabetes may be first suspected when a patient visits an optometrist or podiatrist, or presents with hypertension or a vascular event such as an acute myocardial infarction or stroke. Blood glucose should therefore be checked in all patients presenting with such pathology. The detailed investigation and management of diabetic complications are described on page 755. Diabetes emergencies Diabetic ketoacidosis Diabetic ketoacidosis (DKA) is a medical emergency and remains a serious cause of morbidity, principally in people with type 1 diabetes. Mortality is low in the UK (approximately 2%) but remains high in developing countries and among non-hospitalised patients. Mortality in DKA is most commonly caused in children and adolescents by cerebral oedema, and in adults by hypokalaemia, acute respiratory distress syndrome and comorbid conditions such as acute myocardial infarction, sepsis or pneumonia. DKA is characteristic of type 1 diabetes (see Box 20.12) and is often the presenting problem in newly diagnosed patients. However, an increasing number of patients presenting with DKA have underlying type 2 diabetes. This appears to be particularly prevalent in black and non-Hispanic populations. In established type 1 diabetes, DKA may be precipitated by an intercurrent illness because of failure to increase insulin dose appropriately to compensate for the stress response. Sometimes, there is no evidence of a precipitating infection and DKA develops because of errors in self-management. In young patients with recurrent episodes of DKA, up to 20% may have psychological problems complicated by eating disorders. Pathogenesis A clear understanding of the biochemical basis and pathophysiology of DKA is essential for its efficient treatment (see Fig. 20.7). The cardinal biochemical features are: • hyperketonaemia (≥ 3.0 mmol/L) or ketonuria (more than 2+ on standard urine sticks) • hyperglycaemia (blood glucose ≥ 11 mmol/L (approximately 200 mg/dL)) • metabolic acidosis

(venous bicarbonate < 15 mmol/L and/ or venous pH < 7.3 (H+ > 50 nmol/L)). The hyperglycaemia causes a profound osmotic diuresis leading to dehydration and electrolyte loss, particularly of the development of DKA and death. If the aetiological diagnosis is in doubt, it is important not to delay insulin treatment, which can be withdrawn subsequently if necessary. Hyperglycaemia causes a wide variety of symptoms (Box 20.11). The classical clinical features of type 1 and type 2 diabetes are compared in Box 20.12. Symptoms of polydipsia, polyuria, nocturia and rapid weight loss are prominent in type 1 diabetes but are often absent in patients with type 2 diabetes, many of whom are asymptomatic or have non-specific complaints such as chronic fatigue and malaise. Uncontrolled diabetes is associated with an increased susceptibility to infection and patients may present with skin sepsis (boils) or genital candidiasis, and complain of pruritus vulvae or balanitis. While the distinction between type 1 and type 2 diabetes is usually obvious, overlap occurs, particularly in age at onset, duration of symptoms and family history. There are many patients in whom the type of diabetes is not immediately apparent. For example, patients with type 2 diabetes may present with marked and rapid weight loss and even DKA (10–15% of all cases of DKA), and type 2 diabetes is increasingly diagnosed in children and young adults. Type 1 diabetes can occur at any age, not just in younger people, and may develop more insidiously; the presence of pancreatic autoantibodies confirms the diagnosis of slow-onset type 1 diabetes or LADA. Islet autoantibodies are detectable at high titre in many patients with type 1 diabetes, so a negative result should prompt consideration of other aetiologies. Other causes of diabetes (see Box 20.9), such as MODY, should not be forgotten, particularly in those presenting in childhood or as young adults. A history of pancreatic disease, particularly in patients with a history of alcohol excess, makes insulin deficiency more likely. 20.12 Classical features of type 1 and type 2 diabetes Type 1 Type 2 Typical age at onset < 40 years

> “ 50 years Duration of symptoms Weeks Months to years Body weight Normal or low Obese Ketonuria Yes No Rapid death without treatment with insulin Yes No Autoantibodies Positive in 80–90% Negative Diabetic complications at diagnosis No 25% Family history of diabetes Uncommon Common Other autoimmune disease Common Uncommon 20.11 Symptoms of hyperglycaemia • Thirst, dry mouth • Polyuria • Nocturia • Tiredness, fatigue, lethargy • Change in weight (usually weight loss) • Blurring of vision • Pruritus vulvae, balanitis (genital candidiasis) • Nausea • Headache • Hyperphagia; predilection for sweet foods • Mood change, irritability, difficulty in concentrating, apathy

 water depletion, with loss of skin turgor, furred tongue and cracked lips, tachycardia, hypotension and reduced intra-ocular pressure. Breathing may be deep and sighing (Kussmaul’s sign), the breath is usually fetid, and the sickly-sweet smell of acetone may be apparent. Mental apathy, delirium or a reduced conscious level may be present, although coma is uncommon. Indeed, a patient with dangerous ketoacidosis requiring urgent treatment may walk into the consulting room. For this reason, the term ‘diabetic ketoacidosis’ is to be preferred to ‘diabetic coma’, which implies that there is no urgency until unconsciousness supervenes. In fact, it is imperative that energetic treatment is started at the earliest possible stage. Abdominal pain is sometimes a feature of DKA, particularly in children, and vomiting is common. Serum amylase may be elevated but rarely indicates coexisting pancreatitis. In infected patients, pyrexia may not be

present initially because of vasodilatation secondary to acidosis. Investigations The following investigations are important but should not delay the institution of intravenous fluid and insulin replacement: • Venous blood: for urea and electrolytes, glucose, bicarbonate and acid–base status (venous blood can be used in portable and fixed blood gas analysers, and differences between venous and arterial pH and bicarbonate are minor). • Urine or blood analysis for ketones (p. 726). • Electrocardiogram (ECG). • Infection screen: full blood count, blood and urine culture, C-reactive protein, chest X-ray. Although leucocytosis invariably occurs in DKA, this represents a stress response and does not necessarily indicate infection. Assessment of severity The presence of one or more of the features listed in Box 20.15 is indicative of severe DKA. Management DKA is a medical emergency that should be treated in hospital, preferably in a high-dependency area. If available, the diabetes specialist team should be involved. Regular clinical and biochemical review is essential, particularly during the first 24 hours of treatment. Guidelines for the management of DKA are shown in Box 20.16. Early specialist involvement is recommended for high-risk groups such as older people, young adults (18–25 years), pregnant women, and those with heart or kidney failure or other serious comorbidities. sodium and potassium. Potassium loss is exacerbated by secondary hyperaldosteronism as a result of reduced renal perfusion. Ketosis stems from insulin deficiency, exacerbated by elevated catecholamines and other stress hormones, leading to unrestrained lipolysis and supply of FFAs for hepatic ketogenesis. When this exceeds the capacity to metabolise acidic ketones, these accumulate in blood. The resulting metabolic acidosis forces hydrogen ions into cells, displacing potassium ions. The average loss of fluid and electrolytes in moderately severe DKA in an adult is shown in Box 20.13. About half the deficit of total body water is derived from the intracellular compartment and occurs comparatively early in the development of acidosis with relatively few clinical features; the remainder represents loss of extracellular fluid sustained largely in the later stages, when marked contraction of extracellular fluid volume occurs, with haemoconcentration, a decreased blood volume, and finally a fall in blood pressure with associated renal ischaemia and oliguria. Every patient in DKA is potassium-depleted but the plasma concentration of potassium gives very little indication of the total body deficit. Plasma potassium may even be raised initially due to disproportionate loss of water, catabolism of protein and glycogen, and displacement of potassium from the intracellular compartment by H+ ions. However, soon after treatment is started, there is likely to be a precipitous fall in the plasma potassium due to dilution of extracellular potassium by administration of intravenous fluids, the movement of potassium into cells induced by insulin, and the continuing renal loss of potassium. The magnitude of the hyperglycaemia does not correlate with the severity of the metabolic acidosis; moderate elevation of blood glucose may be associated with life-threatening ketoacidosis. Type 1 diabetes in pregnancy is one situation where DKA can occur with blood glucose levels that are not especially high. Conversely, in other situations, hyperglycaemia predominates and acidosis is minimal, with patients presenting in a hyperosmolar state (p. 738). Clinical assessment The clinical features of ketoacidosis are listed in Box 20.14. In the fulminating case, the striking features are those of salt and 20.14 Clinical features of diabetic ketoacidosis Symptoms • Polyuria, thirst • Weight loss • Weakness • Nausea, vomiting • Leg cramps • Blurred vision • Abdominal pain Signs • Dehydration • Hypotension (postural or supine) • Cold extremities/peripheral cyanosis • Tachycardia • Air hunger (Kussmaul breathing) • Smell of acetone • Hypothermia • Delirium, drowsiness, coma (10%) 20.13 Average loss of fluid and electrolytes in adult diabetic ketoacidosis of moderate severity • Water: 6 L 3 L extracellular • Sodium: 500 mmol – replace with saline • Chloride: 400 mmol 3 L intracellular • Potassium: 350 mmol – replace with dextrose } 20.15 Indicators of severe diabetic ketoacidosis • Blood ketones > 6 mmol/L • Bicarbonate < 5 mmol/L • Venous/arterial pH <

7.0 (H+ > 100 nmol/L) • Hypokalaemia on admission (< 3.5 mmol/L) • Glasgow Coma Scale score < 12 (p. 194) or abnormal AVPU scale score (p. 188) • O2 saturation < 92% on air • Systolic blood pressure < 90 mmHg • Heart rate > 100 or < 60 beats per minute • Anion gap > 16 mmol/L

Insulin A fixed-rate intravenous insulin infusion of 0.1 U/kg body weight/ hr is recommended (Box 20.16). Exceptionally, if intravenous administration is not feasible, soluble insulin can be given by intramuscular injection (loading dose of 10–20 U, followed by 5 U hourly), or a fast-acting insulin analogue can be given hourly by subcutaneous injection (initially 0.3 U/kg body weight, then 0.1 U/kg hourly). The blood glucose concentration should fall by 3–6 mmol/L (approximately 55–110 mg/dL) per hour, or blood ketone concentrations fall by at least 0.5 mmol/L/hr. A more rapid decrease in blood glucose should be avoided, as this might precipitate hypoglycaemia and the serious complication of cerebral oedema, particularly in children. Failure of blood glucose to fall within 1 hour of commencing insulin infusion should lead to a re-assessment of insulin dose. Ketosis, dehydration, acidaemia, infection and stress combine to produce severe insulin resistance in some cases, but most will respond to a low-dose insulin regimen. When the blood glucose has fallen, 10% dextrose infusion is introduced and insulin infusion continued to encourage glucose uptake into cells and restoration of normal metabolism. In recent years, it has also become increasingly common to continue with the use of long-acting insulin analogues administered subcutaneously during the initial management of DKA; this provides background insulin for when the intravenous insulin is discontinued, to reduce the risk of in-hospital DKA. Restoration of the usual insulin regimen, by subcutaneous injection, should not be instituted until the patient is both biochemically stable and able to eat and drink normally. Fluid replacement In adults, rapid fluid replacement in the first few hours is usually recommended (Box 20.16). Caution is advised in children and young adults because of the risk of cerebral oedema. Most guidelines favour correction of the extracellular fluid deficit with isotonic saline (0.9% sodium chloride). If the plasma sodium is greater than 155 mmol/L, 0.45% saline may be used initially. Introduction of 10% glucose is recommended when the blood glucose falls below 14 mmol/L (252 mg/dL). The 0.9% saline infusion should be continued to correct circulating volume so both glucose and saline infusions are used concurrently. Time: 0–60 mins • Establish IV access, assess patient and perform initial investigations • Commence 0.9% sodium chloride: If systolic BP > 90 mmHg, give 1 L over 60 mins If systolic BP < 90 mmHg, give 500 mL over 10–15 mins, then re-assess; if BP remains < 90 mmHg, repeat and seek senior review • Commence insulin treatment: 50 U human soluble insulin in 50 mL 0.9% sodium chloride infused intravenously at 0.1 U/kg body weight/hr Continue with SC basal insulin analogue if usually taken by patient • Perform further investigations: see text • Establish monitoring schedule: Hourly capillary blood glucose and ketone testing Venous bicarbonate and potassium after 1 and 2 hrs, then every 2 hrs for first 6 hrs Plasma electrolytes every 4 hrs Clinical monitoring of O2 saturation, pulse, BP, respiratory rate and urine output every hour • Treat any precipitating cause Time: 60 mins to 6 hrs • IV infusion of 0.9% sodium chloride with potassium chloride added as indicated below: 1 L over 2 hrs 1 L over 2 hrs 1 L over 4 hrs 1 L over 4 hrs 1 L over 6 hrs • Add 10% glucose 125 mL/hr IV when glucose < 14 mmol/L (252 mg/dL) • Be more cautious with fluid replacement in older or young people, pregnant patients and those with renal or heart failure; if plasma sodium is > 155 mmol/L, 0.45% sodium chloride may be used • Adjust potassium chloride infusion: Plasma potassium (mmol/L) Potassium replacement (mmol/L of infusion)

> 5.5 Nil 3.5–5.5

< 3.5 Senior review – additional potassium required Time: 6–12 hrs • Clinical status, glucose, ketonaemia and acidosis should be improving; request senior review if not • Continue IV fluid replacement • Continue insulin administration • Assess for complications of treatment (fluid overload, cerebral oedema) • Avoid hypoglycaemia Time: 12–24 hrs • By 24 hrs, ketonaemia and acidosis should have resolved (blood ketones < 0.3 mmol/L, venous bicarbonate > 18 mmol/L) • If patient is not eating and drinking: Continue IV insulin infusion at lower rate of 2–3 U/hr Continue IV fluid replacement and biochemical monitoring • If ketoacidosis has resolved and patient is able to eat and drink: Re-initiate SC insulin with advice from diabetes team; do not discontinue IV insulin until 30 mins after SC short-acting insulin injection Additional procedures • Consider urinary catheterisation if anuric after 3 hrs or incontinent • Insert nasogastric tube if obtunded or there is persistent vomiting • Insert central venous line if cardiovascular system is compromised, to allow fluid replacement to be adjusted accurately; also consider in older patients, pregnant women, renal or cardiac failure, other serious comorbidities and severe DKA • Measure arterial blood gases; repeat chest X-ray if O2 saturation < 92% • Institute ECG monitoring in severe cases • Give thromboprophylaxis with low-molecular-weight heparin Adapted from Joint British Diabetes Societies Inpatient Care Group. The Management of Diabetic Ketoacidosis in Adults, 2nd edn; September 2013; abcd.care. (BP = blood pressure; ECG = electrocardiogram; IV = intravenous; SC = subcutaneous) 20.16 Emergency management of diabetic ketoacidosis

738 • DIABETES MELLITUS Potassium Careful monitoring of potassium is essential to the management of DKA because both hypo- and hyperkalaemia can occur and are potentially life-threatening. Potassium replacement is not usually recommended with the initial litre of fluid because pre-renal failure may be present secondary to dehydration. Treatment with 0.9% sodium chloride with potassium chloride 40 mmol/L is recommended if the serum potassium is below 5.5 mmol/L and the patient is passing urine (Box 20.16). If the potassium falls below 3.5 mmol/L, the potassium replacement regimen needs to be reviewed. Aim to maintain potassium between 4.0 and 5.5 mmol/L. Cardiac rhythm should be monitored in severe DKA because of the risk of electrolyte-induced cardiac arrhythmia. Bicarbonate Adequate fluid and insulin replacement should resolve the acidosis. The use of intravenous bicarbonate therapy is not recommended. Acidosis may reflect an adaptive response, improving oxygen delivery to the tissues, and so excessive bicarbonate may induce a paradoxical increase in cerebrospinal fluid acidosis and has been implicated in the pathogenesis of cerebral oedema in children and young adults. Phosphate There is no evidence of benefit with phosphate replacement unless low levels are detected in the presence of respiratory or muscle weakness. Ongoing management Where possible, refer the patient to the diabetes specialist team within 24 hours of admission. It is important to review the precipitating factors that led to DKA, glycaemic control and insulin injection technique, as well as to discuss prevention of recurrence and to provide blood ketone meters where available. There is a significant mortality associated with recurrent DKA and so early educational assessment and treatment review are critical. Hyperglycaemic hyperosmolar state Hyperglycaemic hyperosmolar state (HHS) is a medical emergency that is different from DKA and so treatment requires a different approach. There is no precise definition of HHS but it is characterised by hypovolaemia, severe hyperglycaemia (> 30 mmol/L (600 mg/dL)) and hyperosmolality (serum osmolality > 320

mOsmol/kg), without significant ketonaemia (< 3 mmol/L) or acidosis (pH > 7.3 (H+ < 50 nmol/L), bicarbonate

> 15 mmol/L). As with DKA, there is glycosuria, leading to an osmotic diuresis with loss of water, sodium, potassium and other electrolytes. However, in HHS, hyperglycaemia usually develops over a longer period (a few days to weeks), causing more profound hyperglycaemia and dehydration (fluid loss may be 10–12 L in a person weighing 100 kg). The reason that patients with HHS do not develop significant ketoacidosis is unclear, although it has been speculated that insulin levels may be too low to stimulate glucose uptake in insulin-sensitive tissues, but are still sufficient to prevent lipolysis and subsequent ketogenesis. A mixed picture of HHS and DKA can occur. Although typically occurring in older patients, HHS is increasingly seen in younger adults. Common precipitating factors include infection, myocardial infarction, cerebrovascular events or drug therapy (e.g. glucocorticoids). Poor prognostic signs include hypothermia, hypotension (systolic blood pressure < 90 mmHg), tachy- or bradycardia, severe hypernatraemia (sodium > 160 mmol/L), serum osmolality > 360 mOsmol/kg, and the presence of other serious comorbidities. Mortality rates are higher than in DKA – up to 20% in the USA – reflecting the age and frailty of the population and the more frequent presence of comorbidities. The principles of therapy are shown in Box 20.17. The aims are to normalise osmolality, replace fluid and electrolyte losses, and normalise blood glucose, at the same time as preventing complications such as arterial or venous thrombosis, cerebral oedema and central pontine demyelinosis (Ch. 14). Comorbidities also need to be taken into account; for example, rapid fluid replacement may precipitate cardiac failure in patients with coronary artery disease. Historically, management of HHS has followed DKA guidelines, but increasing recognition of the differences between HHS and DKA has led to new approaches in HHS. In particular, rapid shifts in osmolality should be avoided through more measured fluid replacement regimens that are guided by serial calculations of serum osmolality. Key recommendations are that 0.9% sodium chloride solution alone is used for initial treatment, and that insulin is introduced only when the rate of fall in blood glucose has plateaued. If osmolality cannot be measured frequently, osmolarity can be calculated as follows and used as a surrogate (based on plasma values in mmol/L): Plasma osmolarity Na glucose urea =

- 2[ ] [ ] [ ] The normal value is 280–296 mOsmol/L and consciousness is impaired when it is high (> 340 mOsmol/L), as commonly occurs in HHS. A limitation of this approach is that hyperglycaemia, by increasing serum osmolality, causes the movement of water out of cells, therefore reducing measured Na+ levels by dilution. In hyperglycaemic patients, the corrected [Na+] should be taken into account. This is calculated by adding 1.6 mmol/L to the measured [Na+] for every 5.55 mmol/L (100 mg/dL) increment of serum glucose above normal. Hypoglycaemia Hypoglycaemia is uncommon in people without diabetes but relatively frequent in people with diabetes, mainly due

to insulin therapy, and less frequently to use of oral insulin secretagogues such as sulphonylurea drugs, and rarely with other antidiabetic drugs. In people with diabetes, hypoglycaemia is defined as a blood glucose of less than 3.9 mmol/L (70 mg/dL). Severe hypoglycaemia – the need for external assistance to provide glucose, glucagon or other corrective action actively – is greatly feared by people with diabetes and has a major impact on their willingness and ability to achieve target glucose levels. When hypoglycaemia develops in non-diabetic people, it is called ‘spontaneous’ hypoglycaemia; its definition, causes and investigation are described on page 676. The critical importance of glucose as a fuel source for the brain means that, in health, a number of mechanisms are in place to ensure that glucose homeostasis is maintained. If blood glucose falls, three primary physiological defence mechanisms operate: • endogenous insulin release from pancreatic β cells is suppressed • release of glucagon from pancreatic α cells is increased • the autonomic nervous system is activated, with release of catecholamines both systemically and within the tissues.

Circumstances of hypoglycaemia Risk factors and causes of hypoglycaemia in patients taking insulin or sulphonylurea drugs are listed in Box 20.19. Severe hypoglycaemia can have serious morbidity (e.g. convulsions, coma, focal neurological lesions) and has a mortality of up to In addition, stress hormones, such as cortisol and growth hormone, are increased in the blood. These actions reduce whole-body glucose uptake and increase hepatic glucose production, maintaining a glucose supply to the brain. People with type 1 diabetes cannot regulate insulin once it is injected subcutaneously, and so it continues to act, despite the development of hypoglycaemia. In addition, within 5 years of diagnosis, most patients will have lost their ability to release glucagon specifically during hypoglycaemia. The reasons for this are unknown, but may result from loss of α-cell regulation by insulin or other products of the β cell. These two primary defects mean that hypoglycaemia occurs much more frequently in people with type 1 and longer-duration type 2 diabetes. Clinical assessment Symptoms of hypoglycaemia (Box 20.18) comprise two main groups: those related to acute activation of the autonomic nervous system and those secondary to glucose deprivation of the brain (neuroglycopenia). Symptoms of hypoglycaemia are idiosyncratic, differing with age and duration of diabetes, and also depending on the circumstances in which hypoglycaemia occurs. Hypoglycaemia also affects mood, inducing a state of increased tension and low energy. Learning to recognise the early onset of hypoglycaemia is an important aspect of the education of people with diabetes treated with insulin. 20.18 Most common symptoms of hypoglycaemia Autonomic • Sweating • Trembling • Pounding heart • Hunger • Anxiety Neuroglycopenic • Delirium • Drowsiness • Speech difficulty • Inability to concentrate • Incoordination • Irritability, anger Non-specific • Nausea • Tiredness • Headache N.B. Symptoms differ with age; children exhibit behavioural changes (such as naughtiness or irritability), while older people experience more prominent neurological symptoms (such as visual disturbance and ataxia). Time 0–60 mins • Commence IV 0.9% sodium chloride 1 L over 1 hr • Commence insulin infusion (0.05 U/kg/hr) only if there is significant ketonaemia (3-hydroxybutyrate > 1.0 mmol/L) • Perform initial investigations • Perform clinical assessment to assess degree of dehydration, mental status and any source of potential sepsis • Assess foot risk score • Establish monitoring regimen – generally hourly glucose and calculated osmolality (2Na+ + glucose + urea) for first 6 hrs then 2-hourly if responding • Insert urinary catheter to monitor hourly urine output and calculate fluid balance • Commence LMWH in a prophylactic dose • Consider antibiotic therapy if sepsis

suspected Time 60 mins to 6 hrs • Continue with 0.9% sodium chloride infusion 0.5–1.0 L/hr, depending on clinical assessment and response (target positive balance of 2–3 L by 6 hrs) • Calculate osmolality hourly and aim for gradual decline (3–8 mOsmol/kg/hr); if osmolality is increasing and fluid balance adequate, consider 0.45% sodium chloride • If blood glucose is falling at less than 5 mmol/L/hr, check fluid balance and, if adequate, commence low-dose IV insulin (0.05 U/ kg/hr); if insulin is already running, increase rate to 0.1 U/kg/hr • Maintain potassium in the reference range (3.6–5.0 mmol/L), as with DKA (see Box 20.16) • Avoid hypoglycaemia – aim to keep blood glucose at 10–15 mmol/L (180–270 mg/dL) in the first 24 hrs. If blood glucose falls below 14 mmol/L (252 mg/dL), commence 5% or 10% glucose infusion in addition to 0.9% saline • Monitor fluid balance Time 6–12 hrs • Ensure clinical and biochemical parameters are improving • Assess for complications of treatment • Continue IV fluid replacement to target 3–6 L positive balance by 12 hrs • Continue treatment of underlying precipitant • Avoid hypoglycaemia Time 12–24 hrs • Ensure clinical and biochemical parameters are improving; measurement can be reduced to 4-hourly; biochemistry does not usually normalise by 24 hrs • Assess for complications of treatment • Continue IV fluid replacement to target remaining estimated fluid loss by 24 hrs • Continue IV insulin with or without 5% or 10% glucose to maintain blood glucose at 10–15 mmol/L (180–270 mg/dL) • Continue treatment of underlying precipitant • Avoid hypoglycaemia Time 24 hrs to day 3 • Ensure clinical and biochemical parameters are improving or normalised; continue IV fluids until eating and drinking; variable-rate insulin and fluids may be required if not • Convert to appropriate SC insulin regimen when stable • Assess for signs of fluid overload • Encourage early mobilisation • Carry out daily foot checks • Continue LMWH until discharge • Ensure review by diabetes team Adapted from Joint British Diabetes Societies Inpatient Care Group. The Management of the Hyperosmolar Hyperglycaemic State (HHS) in Adults with Diabetes; 2012; abcd.care. (DKA = diabetic ketoacidosis; IV = intravenous; LMWH = low-molecular-weight heparin; SC = subcutaneous) 20.17 Emergency management of hyperglycaemic hyperosmolar state

 4% in insulin-treated patients. Rarely, sudden death during sleep occurs in otherwise healthy young patients with type 1 diabetes (‘dead-in-bed syndrome’) and may result from hypoglycaemiainduced cardiac arrhythmia. Severe hypoglycaemia is very disruptive and impinges on many aspects of the patient’s life, including employment, driving (see Box 20.24), travel, sport and personal relationships. Nocturnal hypoglycaemia in patients with type 1 diabetes is common but often undetected, as hypoglycaemia does not usually waken a person from sleep. Patients may describe poor quality of sleep, morning headaches and vivid dreams or nightmares, or a partner may observe profuse sweating, restlessness, twitching or even seizures. The only reliable way to identify this problem is to measure blood glucose during the night. High glucose levels in the morning are not, as commonly perceived, an indicator of nocturnal hypoglycaemia. Exercise-induced hypoglycaemia occurs in people with wellcontrolled, insulin-treated diabetes because of hyperinsulinaemia. Suppression of endogenous insulin secretion to allow increased hepatic glucose production to meet the increased metabolic demand is key to the normal physiological response to exercise. In insulin-treated diabetes, insulin levels may actually increase with exercise because of improved blood flow at the site of injection, and this increases the risk of hypoglycaemia. This means that both insulin and muscle contraction will increase glucose uptake, causing a fall in blood glucose. This occurs most commonly with prolonged and/or aerobic exercise. In addition, the ‘double hit’ of hypoglycaemia with exercise reflects the additional increased risk of nocturnal hypoglycaemia that can occur after exercise, possibly as a result of glycogen depletion. In contrast, high-intensity exercise because of the marked stimulation to adrenaline (epinephrine)

production may actually cause blood glucose to rise significantly. Education is key to preventing exercise-induced hypoglycaemia. Hypoglycaemia may also occur within the hospital setting. This may result from errors in insulin dose or type of insulin prescribed, infusion of IV insulin without glucose, changes in meal timings or content and failure to provide usual snacks, reduced carbohydrate intake because of vomiting or reduced appetite, or factors related to the hospital admission, e.g. concurrent illness or discontinuation of long-term glucocorticoid therapy. Awareness of hypoglycaemia For most individuals, the glucose level (threshold) at which they first become aware of hypoglycaemia is not constant but varies according to the circumstances in which hypoglycaemia arises (e.g. during the night or during exercise). In addition, with longer duration of disease, and particularly in response to frequent hypoglycaemia, the threshold for generation of symptom responses to hypoglycaemia shifts to a lower glucose concentration. This cerebral adaptation has a similar effect on the counter-regulatory hormonal response to hypoglycaemia. Taken together, this means that individuals with type 1 diabetes may have reduced (impaired) awareness of hypoglycaemia. Symptoms can be experienced less intensely, or even be absent, despite blood glucose concentrations below 3.0 mmol/L (55 mg/dL). Such individuals are at an especially high risk of severe hypoglycaemia. The prevalence of impaired awareness of hypoglycaemia increases with time; overall, it affects around 20–25% of people with type 1 diabetes and under 10% with insulin-treated type 2 diabetes. Management Acute treatment of hypoglycaemia Treatment of hypoglycaemia depends on its severity and on whether the patient is conscious and able to swallow (Box 20.20). Oral carbohydrate usually suffices if hypoglycaemia is recognised early. If parenteral therapy is required, then as soon as the patient is able to swallow, glucose should be given orally. Full recovery may not occur immediately and reversal of cognitive impairment may not be complete until 60 minutes after normoglycaemia is restored. When hypoglycaemia has occurred in a patient treated with a long- or intermediate-acting insulin or a long-acting sulphonylurea, such as glibenclamide, the possibility of recurrence should be anticipated; to prevent this, infusion of 10% dextrose, titrated to the patient’s blood glucose, or provision of additional carbohydrate may be necessary. If the patient fails to regain consciousness after blood glucose is restored to normal, then cerebral oedema and other causes of impaired consciousness – such as alcohol intoxication, a post-ictal state or cerebral haemorrhage – should be considered. Cerebral oedema has a high mortality and morbidity. Following recovery, it is important to try to identify a cause and make appropriate adjustments to the patient’s therapy. Unless the reason for a hypoglycaemic episode is clear, the patient should reduce the next dose of insulin by 10–20% and seek medical advice about further adjustments in dose. The management of self-poisoning with oral antidiabetic agents is described on page 141. Prevention of hypoglycaemia Patient education is fundamental to the prevention of hypoglycaemia. Risk factors for, and treatment of, hypoglycaemia should be discussed. The importance of regular blood glucose monitoring and the need to have glucose (and glucagon) readily available should be stressed. A review of insulin and carbohydrate 20.19 Hypoglycaemia in diabetes: common causes and risk factors Medical issues • Rapid improvement in and/or strict glycaemic control • Previous severe hypoglycaemia • Impaired awareness of hypoglycaemia • Long-duration type 1 diabetes • Duration of insulin therapy in type 2 diabetes • Lipohypertrophy at injection sites causing variable insulin absorption • Severe hepatic dysfunction • Impaired renal function • Inadequate treatment of previous hypoglycaemia • Terminal illness • Bariatric surgery involving bowel resection • Unrecognised other endocrine disorder, e.g. Addison’s disease Reduced carbohydrate intake • Gastroparesis due to autonomic neuropathy causing variable carbohydrate absorption • Malabsorption, e.g. coeliac disease • Eating disorder Lifestyle issues • Exercise • Irregular lifestyle

• Increasing age • Alcohol • Early pregnancy • Breastfeeding • No or inadequate glucose monitoring • Factitious (deliberately induced)

20.20 Emergency treatment of hypoglycaemia Biochemical or symptomatic hypoglycaemia (self-treated) In the UK, it is recommended that all glucose levels < 4.0 mmol/L (72 mg/dL) are treated ('4 is the floor'). People with diabetes who recognise developing hypoglycaemia are encouraged to treat immediately. Options available include: • Oral fast-acting carbohydrate (10–15 g) is taken as glucose drink or tablets or confectionery, e.g. 5–7 Dextrosol tablets (or 4–5 Glucotabs), 90–120 mL original Lucozade, 150–200 mL pure fruit juice, 3–4 heaped teaspoons of sugar dissolved in water) • Repeat capillary glucose measurement 1–15 mins later. If still < 4.0 mmol/L, repeat above treatment • If blood glucose remains < 4.0 mmol/L after three cycles (30–45 mins), contact a doctor. Consider glucagon 1 mg IM or 150–200 mL 10% glucose over 15 mins IV • Once blood glucose is > 4.0 mmol/L, take additional long-acting carbohydrate of choice • Do not omit insulin injection if due but review regimen Severe (external help required) This means individuals are either unconscious or unable to treat hypoglycaemia themselves. Treatment is usually by a relative or by paramedical or medical staff. Immediate treatment as below is needed. • If patient is semiconscious or unconscious, parenteral treatment is required: IV 75–100 mL 20% dextrose over 15 mins (= 15 g; give 0.2 g/kg in children)* Or IV 150–200 mL 10% dextrose over 15 mins Or IM glucagon (1 mg; 0.5 mg in children) – may be less effective in patients on sulphonylurea/under the influence of alcohol • If patient is conscious and able to swallow: Give oral refined glucose as drink or sweets (= 25 g) or 1.5–2 tubes of Glucogel/Dextrogel Or Apply glucose gel or jam or honey to buccal mucosa • Repeat blood glucose measurement after 10–15 mins and manage as per biochemical hypoglycaemia Adapted from Joint British Diabetes Societies. The hospital management of hypoglycaemia in adults with diabetes mellitus (2013). Available at: abcd.care. *Use of 50% dextrose is no longer recommended. management during exercise is particularly useful. Advice for patients when travelling is summarised in Box 20.21. Relatives and friends also need to be familiar with the symptoms and signs of hypoglycaemia and should be instructed in how to help (including how to inject glucagon). It is important to recognise that all current insulin replacement regimens are suboptimal and do not accurately replicate normal physiological insulin profiles. Understanding the pharmacokinetics and pharmacodynamics of the insulin regimen in use by the patient will help prevent further hypoglycaemia (p. 748). For example, an individual experiencing regular nocturnal hypoglycaemia between midnight and 0200 hrs may be found to be taking twice-daily soluble and intermediate-acting insulins before breakfast and before the main evening meal between 1700 and 1900 hrs. In this case, the peak action of the isophane insulin will coincide with the period of maximum sensitivity to insulin – namely, 2300–0200 hrs – and increase the risk of nocturnal hypoglycaemia. To address this, the evening dose of depot intermediate-acting insulin should 20.21 Avoidance and treatment of hypoglycaemia during travel • Carry a supply of fast-acting carbohydrate (non-perishable, in suitable containers): Screwtop plastic bottles for glucose drinks Packets of powdered glucose (for use in hot, humid climates) Confectionery (foil-wrapped in hot climates) • Ask companions to carry additional oral carbohydrate, and glucagon • Perform frequent blood glucose testing (carry spare meter and/or visually read strips) • Use fast-acting insulin analogues for long-distance air travel be deferred until bedtime (after 2300 hrs), shifting its peak action period to 0500–0700 hrs. It is also a sensible precaution for patients to measure their blood glucose before they retire to bed and to have a carbohydrate snack if the

reading is less than 6.0 mmol/L (approximately 110 mg/dL). Management of diabetes The aims are to improve symptoms of hyperglycaemia and minimise the risks of long-term microvascular and macrovascular complications. Treatment methods for diabetes include dietary/ lifestyle modification, oral antidiabetic drugs and injected therapies. Initial investigation and management is outlined in Figure 20.10. In patients with suspected type 1 diabetes, urgent treatment with insulin is required and prompt referral to a specialist is usually needed. In patients with suspected type 2 diabetes, the first approach to management involves advice about dietary and lifestyle modification. Oral antidiabetic drugs are usually added in those who do not achieve glycaemic targets, or who have symptomatic hyperglycaemia at diagnosis and a high HbA1c. However, the guidelines in some countries are to introduce medication immediately on diagnosis of diabetes without waiting to assess the impact of diet and lifestyle changes. Patients with type 2 diabetes who present with marked symptomatic hyperglycaemia or DKA will require initial management with insulin treatment. For most people, types 1 and 2 diabetes are chronic conditions that will impact on their day-to-day activities and require sustained changes to lifestyle. Education is key to achieving and maintaining a healthy lifestyle and to managing diabetes. Early educational intervention at diagnosis and repeated education are essential if these goals are to be successfully achieved. Management of people with diabetes should be individualised where possible, taking into account personal and cultural beliefs, individual circumstances, comorbidities and other factors. Diabetes is a complex disorder that progresses in severity with time, so people with diabetes should be seen at regular intervals for the remainder of their lives, either at a specialist diabetic clinic or in primary care where facilities are available and staff are trained in diabetes care. A checklist for follow-up visits is given in Box 20.22. The frequency of visits is variable, ranging from weekly during pregnancy to annually in the case of patients with well-controlled type 2 diabetes. In parallel with treatment of hyperglycaemia, other risk factors for complications of diabetes need to be addressed, including treatment of hypertension (p. 510) and dyslipidaemia (p. 373), and advice on smoking cessation (p. 94).

 have been developed that allow for a more detailed examination of daily glucose profiles. These can be used continuously as part of day-to-day diabetes management or intermittently as an educational tool. Urine testing for glucose is not recommended because variability in renal threshold means that some patients with inadequate glycaemic control will not find glucose in their urine. Therapeutic goals The target HbA1c depends on the individual patient. Early on in diabetes (i.e. patients managed by diet or one or two oral agents), a target of 48 mmol/mol or less may be appropriate. However, a higher target of 58 mmol/mol may be more appropriate in older patients with pre-existing cardiovascular disease, or those treated with insulin and therefore at risk of hypoglycaemia. In general, the benefits of lower target HbA1c (primarily, a lower risk of microvascular disease) need to be weighed against any increased risks (primarily, hypoglycaemia in insulin-treated patients). Type 2 diabetes is usually a progressive condition Self-assessment of glycaemic control In people with type 2 diabetes, there is not usually a need for regular self-assessment of blood glucose, unless they are treated with insulin, or at risk of hypoglycaemia while taking sulphonylureas. Blood glucose testing can be used for selfeducation (i.e. demonstrating how different food and exercise regimes affect blood glucose) and may be useful in acute illness. Blood glucose targets vary according to individual circumstances but, in general, fasting glucose levels of 5–7 mmol/L (90– 126 mg/dL), pre-meal values of 4–7 mmol/L (72–126 mg/dL) and 2-hour post-meal values of 4–8 mmol/L (72–144 mg/dL) represent optimal control. Insulin-treated patients should be taught how to monitor their own blood glucose using

capillary blood glucose meters. Immediate knowledge of blood glucose levels can be used by patients to guide their insulin dosing and to manage exercise and illness. This can be supplemented with blood testing for ketones when blood glucose is high and/or during intercurrent illness. More recently, continuous glucose monitoring systems (CGMS) Fig. 20.10 The recommended approach for the management of type 2 diabetes. First-line drug treatment should be metformin. Second- and third-line treatment should be chosen based on the efficacy, hypoglycaemia risk, weight effects and other side-effects, and costs of the therapy in discussion with the patient. (DPP-4-i = dipeptidyl peptidase 4 inhibitor; fxs = fractures; GI = gastrointestinal; GLP-1-RA = glucagon-like peptide 1 receptor agonist; GU = genitourinary; HF, heart failure; SGLT2-i = sodium and glucose transporter 2 inhibitor; SU, sulphonylurea; TZD = thiazolidinedione) Adapted from the American Diabetes Association/European Association for the Study of Diabetes joint position statement, 2015. Diabetes Care 2015; 38:140–149. Healthy eating, weight control, increased physical activity and diabetes education If HbA1c target not achieved after ~3 months of monotherapy, proceed to two-drug combination (order not meant to denote any specific preference – choice dependent on a variety of patient- and disease-specific factors) If HbA1c target not achieved after ~3 months of dual therapy, proceed to three-drug combination (order not meant to denote any specific preference – choice dependent on a variety of patient- and disease-specific factors) If HbA1c target not achieved after ~3 months of triple therapy and patient (1) on oral combination, move to injectables; (2) on GLP-1-RA, add basal insulin; or (3) on optimally titrated basal insulin, add GLP-1-RA or mealtime insulin. In refractory patients consider adding TDZ or SGLT2-1 Monotherapy Triple therapy Combination injectable therapy Efficacy Hypoglycaemia risk Weight Side-effects Costs Dual therapy Efficacy Hypoglycaemia risk Weight Side-effects Costs Thiazolidinedione Sulphonylurea DPP-4 inhibitor SGLT2 inhibitor GLP-1 receptor agonist Insulin (basal) Metformin + Metformin + Metformin + Metformin + Metformin + Metformin + high moderate risk gain hypoglycaemia low high low risk gain oedema,HF, fxs low intermediate low risk neutral rare high intermediate low risk loss GU, dehydration high high low risk loss GI high highest high risk gain hypoglycaemia variable Thiazolidinedione + Sulphonylurea + TZD DPP-4-i or SGLT2-i or GLP-1-RA or Insulin or SU TZD DPP-4-i DPP-4-i DPP-4-i or SGLT2-i SU SGLT2-i SGLT2-i or GLP-1-RA or GLP-1-RA GLP-1-RA or or or or Insulin Insulin TZD SU TZD TZD SU or or or or or or or Insulin Insulin or DPP-4 inhibitor + SGLT2 inhibitor + GLP-1 receptor agonist + Insulin (basal) + Metformin + Metformin + Metformin + Metformin + Basal insulin + Mealtime insulin or Metformin + Metformin + Metformin + Metformin high low risk neutral/loss GI/lactic acidosis low

alcohol consumption, should not be under-estimated in improving glycaemic control for people with both type 1 and type 2 diabetes. Many people find this difficult to sustain and constant reinforcement of the benefits of lifestyle change will usually be required. Patients should be encouraged to stop smoking. Healthy eating All people with diabetes need to pay special attention to their diet (Box 20.23; see also p. 694). They should have access to a dietitian at diagnosis, at review and at times of treatment change. Nutritional advice should be tailored to individuals and take account of their age, lifestyle, culture and personal circumstances. Structured education programmes are available for both common types of diabetes and, if possible, a clear referral mechanism for diabetes education should be in place. Between 80% and 90% of people with type 2 diabetes are overweight and so the majority require dietary advice for achieving weight loss, to include caloric restriction. There is, however, limited evidence for the ideal macronutrient

composition of the diet in type 2 diabetes. In general, high fat intake (especially saturated fats) is associated with a raised HbA1c, but it is unclear how the type and amount of fat influence post-prandial glucose control. Reduction of caloric intake and weight loss should be the major goals. Some evidence for the Mediterranean diet, low-carbohydrate diets and meal replacements is emerging. Whichever approach is taken, weight loss in overweight and obese individuals with diabetes markedly improves glycaemic control and slows diabetes progression. Carbohydrate While it is recognised that the total amount of carbohydrate is the major determinant of post-prandial glucose (p. 694), there is little evidence to support specific strategies for carbohydrate intake in type 2 diabetes or to identify the ideal amount of carbohydrate in their diet. Current UK government Food Standards Agency recommendations are that the total carbohydrate intake should be no more than 50% of energy, and of this non-milk extrinsic sugars (e.g. table sugar, honey, (Fig. 20.11) unless there are major diet and lifestyle changes, so that there is usually a need to increase diabetes medication over time to achieve the individualised target HbA1c. In people with type 2 diabetes, treatment of coexisting hypertension and dyslipidaemia is usually required. This can be decided by assessing absolute risk of a cardiovascular disease event (p. 510) and adjusting targets to individual circumstances. The target for blood pressure is usually below 140/80 mmHg, although some guidelines suggest 130/80 mmHg. For lipid-lowering, there is a reduction in cardiovascular risk even with normal cholesterol levels, but statin therapy is usually recommended when the 10-year cardiovascular event risk is at least 20%. As a rule, anyone with type 2 diabetes who is over the age of 40 years should receive a statin, irrespective of baseline cholesterol levels. Some guidelines do not propose a target level once the patient is started on a statin but others suggest a total cholesterol of less than 4.0 mmol/L (approximately 150 mg/dL) and an LDL cholesterol of less than 2.0 mmol/L (approximately 75 mg/dL). Similar targets are appropriate in type 1 diabetes, although there is a shortage of data from clinical trials. Patient education, diet and lifestyle The importance of lifestyle changes, such as undertaking regular physical activity, observing a healthy diet and reducing Fig. 20.11 Time course of changes in HbA1c during the United Kingdom Prospective Diabetes Study (UKPDS). In the UKPDS there was loss of glycaemic control with time in patients receiving monotherapy, independently of their randomisation to conventional or intensive glycaemic control, consistent with progressive decline in β-cell function (see Fig. 20.8). Adapted from UK Prospective Diabetes Study Group. UKPDS 33. Lancet 1998; 352:837–853.

Conventional Upper limit of normal Years from randomisation Intensive

HbA1c(%)

20.22 How to review a patient in the diabetes clinic Lifestyle issues • General health • Work or school • Smoking • Alcohol intake • Stress or depression • Sexual health • Exercise Body weight and BMI Blood pressure • Individualised target of 130–140/70–80 mmHg, depending on risk factors and presence of nephropathy Urinalysis • Analyse fasting specimen for glucose, ketones, albumin (both macro- and micro-albuminuria) Biochemistry • Renal, liver and thyroid function • Lipid profile and estimated 10-year cardiovascular risk to guide need for lipid-lowering therapy (p. 487) Glycaemic control • Glycated haemoglobin (HbA1c); individualised target between 48 and 58 mmol/mol • Inspection of home blood glucose monitoring record (if carried out by patient) Hypoglycaemic episodes • Number and cause of severe (requiring assistance for treatment) events and frequency of mild (self-treated) episodes and biochemical hypoglycaemia • Awareness of

hypoglycaemia • Driving advice Assessment of injection sites if insulin-treated Eye examination • Visual acuities (near and distance) • Ophthalmoscopy (with pupils dilated) or digital photography Examination of lower limbs and feet • Assessment of foot risk (p. 721)

744 • DIABETES MELLITUS Weight management In patients with diabetes, weight management is important, as a high percentage of people with type 2 diabetes are overweight or obese, and many antidiabetic drugs, including insulin, encourage weight gain. Obesity, particularly central obesity with increased waist circumference, also predicts insulin resistance and cardiovascular risk. Management of obesity is described on page 700. Weight loss can be achieved through a reduction in energy intake and an increase in energy expenditure through physical activity. Lifestyle interventions or pharmacotherapy for obesity, when associated with weight reduction, have beneficial effects on HbA1c, but long-term benefits in terms of glycaemic control and microvascular disease have not been adequately assessed. More recently, bariatric surgery (p. 703) has been shown to induce marked weight loss in obese individuals with type 2 diabetes and this is often associated with significant improvements in HbA1c and withdrawal of or reduction in diabetes medications. Exercise All patients with diabetes should be advised to achieve a significant level of physical activity and to maintain this in the long term. This can include activities such as walking, gardening, swimming or cycling. Supervised and structured exercise programmes may be of particular benefit in type 2 diabetes. Various guidelines exist for physical activity in the general population. The American Diabetes Association recommends that all adults with diabetes are encouraged to reduce sedentary time, and suggest that adults over 18 years of age should do either 150 minutes per week of moderate-intensity exercise or 75 minutes per week of vigorous-intensity exercise, or a combination thereof. Musclestrengthening (resistance) exercise is recommended on 2 or more days of the week. Adults over 65 years or those with disabilities should follow the recommended guidelines if possible or be as physically active as they are able. Recent evidence also indicates that extended sedentary time (> 90 mins) should be avoided. People with type 1 diabetes appear to exercise less frequently than the general population, perhaps because of perceived concerns about hypoglycaemia and difficulties in insulin management around exercise. However, the health benefits of exercise are equally important in type 1 diabetes, so this should be addressed in the clinic and specialist advice sought on insulin and carbohydrate management before, during and after exercise. Alcohol Alcohol is recognised as having both beneficial and harmful effects on cardiovascular disease and this also appears to apply in patients with diabetes. Alcohol can therefore be taken in moderation in diabetes, with the aim of keeping within national guidelines relating to recommendations for people without diabetes (e.g. in the UK, the weekly recommended maximum is 14 units for women and men). However, alcohol can reduce hypoglycaemia awareness and, by suppressing gluconeogenesis, increase hypoglycaemia risk. The latter occurs when individuals are in the fasted state and so people with diabetes who drink should be advised to eat at the same time. In addition, all patients with diabetes should be made aware of the high calorie glucose and fructose sugars) should not be more than 11%. Low glycaemic index (GI) diets have, in some short-term trials, been shown to improve HbA1c, but the literature concerning GI and glycaemic control is mixed. The GI of a carbohydrate-containing food is a measure of the change in blood glucose following its ingestion relative to the rise in blood glucose observed following a liquid OGTT. Different foods can be ranked by their effect on post-prandial glycaemia. Low-GI foods, such as starchy foods (e.g. basmati rice, spaghetti, porridge, noodles, granary bread, and beans and lentils), may reduce post-prandial glucose excursions. However, different methods of food processing and preparation can influence the GI of foods, and this may

limit their benefit. Low-carbohydrate diets may lead to significant reductions in body weight and improved glycaemic control in the short term, although high dropout rates and poor adherence have limited widespread application of this approach. Increased consumption of whole grains has not been shown to improve glycaemic control. Fat There is limited evidence on the ideal fat content in the diet of people with diabetes. Current UK government Food Standards Agency recommendations are that intake of total fat should be not more than 35% of energy intake, of which not more than 11% should consist of polyunsaturated fats. The type of fatty acids consumed may be more important when looking at glycaemic targets and risk of cardiovascular disease. Mediterranean diets rich in monounsaturated fats appear more beneficial (Box 20.23). The influence of dietary fats on plasma lipid profile and cardiovascular disease is discussed on page 697. Salt People with diabetes should follow the advice given to the general population: namely, adults should limit their sodium intake to no more than 6 g daily. 20.23 Dietary management of diabetes Aims of dietary management • Achieve good glycaemic control • Reduce hyperglycaemia and avoid hypoglycaemia • Assist with weight management: Weight maintenance for type 1 diabetes and non-obese type 2 diabetes Weight loss for overweight and obese type 2 diabetes • Reduce the risk of micro- and macrovascular complications • Ensure adequate nutritional intake • Avoid ‘atherogenic’ diets or those that aggravate complications, e.g. high protein intake in nephropathy Dietary constituents and recommended % of energy intake • Carbohydrate: 50%: Sucrose: up to 10% • Fat (total): < 35%: n-6 Polyunsaturated: < 10% n-3 Polyunsaturated: eat 1 portion (140 g) oily fish once or twice weekly Monounsaturated: 10–20% Saturated: < 10% • Protein: 10–15% (do not exceed 1 g/kg body weight/day) • Fruit/vegetables: 5 portions daily

sulphonylureas and insulin (particularly older people or those with renal failure); such individuals need careful blood glucose monitoring and, if necessary their treatment regimens may need to be adjusted (Box 20.25). Diabetes therapies that do not cause hypoglycaemia may prove safest during Ramadan if glycaemic control permits. DPP-4 inhibitors or GLP-1 receptor agonists may be especially useful because their effect on insulin secretion is glucose-dependent. Drugs to reduce hyperglycaemia Patients whose glycaemic control deteriorates after a period of satisfactory control need their therapy to be adjusted. However, this is not a homogeneous group; it includes some patients with late-onset type 1 diabetes who develop an absolute deficiency of insulin, some with type 2 diabetes whose β-cell failure is advanced, and others who are not adhering to the recommended lifestyle changes or medication. Weight loss suggests worsening β-cell function. During continuing follow-up, the majority of patients will require combinations of antidiabetic drugs, often with additional insulin replacement, to obtain satisfactory glycaemic control. For many years, only a few choices of drug were available for type 2 diabetes – the biguanide metformin, the sulphonylureas and insulin. Insulin is the only treatment for type 1 diabetes, although sometimes metformin is used with insulin in type 1 diabetes. Acarbose is also available but is little used in most countries. Since the late 1990s, however, several new classes of agent have been approved for use in type 2 diabetes, with more in development. These include thiazolidinediones, dipeptidyl peptidase 4 (DPP-4) inhibitors, glucagon-like peptide 1 (GLP-1) receptor agonists, and sodium and glucose transporter 2 (SGLT2) inhibitors. The effects of these drugs are compared in Box 20.26. This makes for an exciting time in diabetes pharmacotherapy but exactly how, when and in what order these agents should be used remains uncertain. The older drugs are cheaper and have established benefits for reducing microvascular disease; they are therefore usually recommended

as first-line therapy. Use of the newer drugs is not supported by evidence for reduction in microvascular disease (because the trials have not yet been done) and they are much more expensive, so are often reserved for later therapy after failure of metformin and sulphonylureas. The American Diabetes Association/European Association for the Study of Diabetes (ADA/EASD) consensus content of some alcohols and the implications for body weight management, which are often overlooked. Driving European legislation on driving has had a major impact on people with diabetes. Legislation will vary from country to country and so individuals should contact their nurse or doctor to find out if their treatment means they need to inform the licensing authority (Box 20.24). To drive a car or ride a motorcycle in the UK, people with diabetes who take insulin replacement therapy must notify the Driver and Vehicle Licensing Agency (DVLA). They must have adequate awareness of hypoglycaemia, have had no more than one episode of severe hypoglycaemia in the preceding 12 months, meet the standards for visual acuity and visual fields, and not be regarded as a likely risk to the public while driving. In addition, blood glucose testing is required to be performed no more than 2 hours before the start of a journey and every 2 hours while driving. Blood glucose levels should be over 5 mmol/L (90 mg/dL) before driving; if they are below 4.0 mmol/L (72 mg/dL) or there are symptoms of hypoglycaemia, the person should not drive. Legislative requirements for people on insulin therapy who drive larger vehicles such as buses or lorries require, in addition, an annual examination by a diabetes specialist, along with review of 3 months of glucose meter readings. Legislation differs between countries and patients and health-care specialists need to be aware of current requirements. 20.24 Diabetes and driving • Licensing regulations vary considerably between countries. In the UK, diabetes requiring insulin therapy or any complication that could affect driving should be declared to the Driver and Vehicle Licensing Agency; ordinary driving licences are ‘period-restricted’ for insulin-treated drivers; and vocational licences (large goods vehicles and public service vehicles) may be granted but require very strict criteria to be met • The main risk to driving performance is hypoglycaemia. Visual impairment and other complications may occasionally cause problems • Insulin-treated diabetic drivers should: Check blood glucose before driving and 2-hourly during long journeys Keep an accessible supply of fast-acting carbohydrate in the vehicle Take regular snacks or meals during long journeys Stop driving if hypoglycaemia develops Refrain from driving until at least 45 mins after treatment of hypoglycaemia (delayed recovery of cognitive function) Carry identification in case of injury 20.25 Recommendations for management of diabetes during Ramadan • Monitor blood glucose: depending on treatment regimen, glucose levels should be checked daily or several times a day. Patients treated with insulin and insulin secretagogues should measure glucose before, during and after fasting (2–4 times daily) • Consult diabetes team for medication adjustment at least 1 month prior to Ramadan. Treatment should be evaluated and modified according to risk of hypoglycaemia. Avoid or reduce sulphonylureas and/or insulin daily dosage • Avoid skipping pre-dawn meals • Avoid strenuous physical activity during fasting period • Adjust medication dose and eat a snack in the presence of hypoglycaemia. Break the fast if there is severe or recurrent hypoglycaemia Ramadan The Qur’an requires Muslims to fast during the month of Ramadan from sunrise to sunset. While people with diabetes are a recognised exception to this and are not required to fast, many will choose to do so. In this context, patient education, regular glucose monitoring and adjustment of treatment regimens are essential and should occur weeks prior to Ramadan. The highest risk of hypoglycaemia is in patients treated with

 At the molecular level, metformin acts as a weak inhibitor of mitochondrial respiration, which increases intracellular adenosine monophosphate (AMP) and

reduces adenosine triphosphate (ATP). This has direct effects on the flux through gluconeogenesis, and activates the intracellular energy sensor, AMP-activated protein kinase (AMPK), leading to multiple beneficial metabolic effects. However, metformin is still effective in mice lacking AMPK, and a number of AMPK-independent mechanisms have been proposed. Clinical use Metformin is a potent blood glucose-lowering treatment that is weight-neutral or causes weight loss, does not cause hypoglycaemia and has established benefits in microvascular disease. It is employed as first-line therapy in all patients who tolerate it, and its use is maintained when additional agents are added as glycaemia deteriorates (see Fig. 20.10). Metformin is usually introduced at low dose (500 mg twice daily) to minimise the risk of gastrointestinal side-effects. The usual maintenance dose is 1 g twice daily. There is a modified-release formulation of metformin, which may be better tolerated by patients with gastrointestinal side-effects. Metformin can increase susceptibility to lactic acidosis, although this is much less common than was previously thought. As metformin is cleared by the kidneys, it can accumulate in renal impairment, so the dose should be halved when estimated glomerular filtration rate (eGFR) is 30–45 mL/min/1.73 m2, and it should not be used below an eGFR of 30 mL/min/1.73 m2. It should be omitted temporarily during any acute illness where acute kidney injury is possible, as this greatly increases the risk of lactic acidosis; insulin treatment may be required while metformin is withheld. Its use is also contraindicated in patients with significantly impaired hepatic function and in those who drink alcohol in excess, in whom the risk of lactic acidosis is significantly increased. Sulphonylureas Sulphonylureas are ‘insulin secretagogues’, i.e. they promote pancreatic β-cell insulin secretion. Similar to metformin, the long-term benefits of sulphonylureas in lowering microvascular guidelines are shown in Figure 20.10. These position metformin in the first line, and then aim to encourage choice of second-line treatment to be personalised for each patient. This personalisation is largely based on the adverse risk profile of the drug – in particular, risk of hypoglycaemia (avoid where hypoglycaemia would be a problem, e.g. in drivers of heavy goods vehicles) and weight gain. There is little evidence to guide the clinician and patient in choosing the second- or third-line treatment, and until biomarkers are identified that predict who will respond best and/or experience the fewest side-effects with one drug rather than another, this individualisation of treatment needs to be largely empirical. A trial-and-error approach may be best: stop a drug that does not work or that causes side-effects and trial the next drug. At the time of writing, the ADA/EASD guidelines were already out of date; in 2015/16, the SGLT2 inhibitor empagliflozin and the GLP-1 receptor agonist liraglutide were shown to reduce adverse cardiovascular outcomes and mortality. It is likely that the guidelines will change to take these exciting results into account and we will probably see these newer, more expensive drugs used earlier in the diabetes trajectory. Biguanides Metformin is the only biguanide available. Its long-term benefits were shown in the UK Prospective Diabetes Study (UKPDS, p. 756) and it is now widely used as first-line therapy for type 2 diabetes, irrespective of body weight. It is also given as an adjunct to insulin therapy in obese patients with type 1 diabetes. Approximately 25% of patients develop mild gastrointestinal side-effects with metformin, but only 5% are unable to tolerate it even at low dose. The main side-effects are diarrhoea, abdominal cramps, bloating and nausea. Mechanism of action The mechanism of action of metformin has not been precisely defined. While classically considered an ‘insulin sensitiser’ because it lowers insulin levels, its main effects are on fasting glucose and are insulin-independent. Metformin reduces hepatic glucose production, may also increase insulin-mediated glucose uptake, and has effects on gut glucose uptake and utilisation. 20.26 Effects of drugs used in the treatment of type 2 diabetes Insulin Sulphonylureas and meglitinides Metformin Alphaglucosidase inhibitors Thiazolidinediones (glitazones) DPP-4 inhibitors (gliptins) GLP-1 receptor agonists SGLT2 inhibitors Fasting blood

glucose ↓ ↓ ↓ ↓ ↓ ↓ ↓ ↓ Post-prandial blood glucose ↓ ↓ ↓ ↓ ↓ ↓ ↓ ↓ Plasma insulin ↑ ↑ ↓ ↓ ↓ ↑ ↑ ↓ Body weight ↑ ↑ → → ↑ → ↓ ↓ Cardiovascular benefit? No No Possible No Probable (pioglitazone) No Yes Yes Risk of hypoglycaemia ++ + – – – – – – Tolerability Good Good Moderate Moderate Moderate Good Moderate Limited experience (↓ = small reduction; DPP-4 = dipeptidyl peptidase 4; GLP-1 = glucagon-like peptide 1; SGLT2 = sodium and glucose transporter 2)

bladder cancer. These observations have led to a dramatic reduction in the use of pioglitazone. Pioglitazone can be very effective at lowering blood glucose in some patients and appears more effective in insulin-resistant patients. In addition, it has a beneficial effect in reducing fatty liver and NASH (p. 882). Pioglitazone is usually added to metformin with or without sulphonylurea therapy (see Fig. 20.10). It may be given with insulin therapy, when it can be very effective, but the combination of insulin and TZDs markedly increases fluid retention and risk of cardiac failure, so should be used with caution. Incretin-based therapies: DPP-4 inhibitors and GLP-1 receptor agonists The incretin effect is the augmentation of insulin secretion seen when a glucose stimulus is given orally rather than intravenously, and reflects the release of incretin peptides from the gut (see Fig. 20.3). The incretin hormones are primarily glucagon-like peptide 1 (GLP-1) and gastric inhibitory polypeptide (GIP), which act to potentiate insulin secretion (see Fig. 20.2). These are rapidly broken down by dipeptidyl peptidase 4 (DPP-4). The incretin effect is diminished in type 2 diabetes, and this has stimulated the development of two incretin-based therapeutic approaches. The ‘gliptins’, or DPP-4 inhibitors, prevent breakdown and therefore enhance concentrations of endogenous GLP-1 and GIP. The first DPP-4 inhibitor to market was sitagliptin; others now available include vildagliptin, saxagliptin, linagliptin and alogliptin. These drugs are very well tolerated and are weight-neutral (see Box 20.26). Recent cardiovascular outcome studies have shown mixed results with the DPP-4 inhibitors. The Trial to Evaluate Cardiovascular Outcomes after Treatment with Sitagliptin (TECOS) study reported no adverse cardiovascular outcomes for sitagliptin, but the Saxagliptin Assessment of Vascular Outcomes Recorded in Patients with Diabetes Mellitus – Thrombolysis in Myocardial Infarction (SAVOR-TIMI) study found an increased risk of heart failure in patients treated with saxagliptin. The GLP-1 receptor agonists have a similar structure to GLP-1 but have been modified to resist breakdown by DPP-4. These agents are not orally active and have to be given by subcutaneous injection. However, they have a key advantage over the DPP-4 inhibitors: because the GLP-1 activity achieved is supra-physiological, it delays gastric emptying and, at the level of the hypothalamus, decreases appetite. Thus, injectable GLP-1 receptor agonists lower blood glucose and result in weight loss – an appealing therapy, as the majority of patients with type 2 diabetes are obese. Currently available GLP-1 receptor agonists include exenatide (twice daily), exenatide modified-release (once weekly), liraglutide (once daily), lixisenatide (once daily) and albiglutide (once weekly). Recently, GLP-1 receptor agonists and long-acting insulin analogue have been combined, enabling co-administration of insulin and GLP-1 receptor agonists with one injection. The GLP-1 receptor agonists vary in their side-effect profile, depending on whether they are administered daily or weekly, but the main side-effect that often limits use is nausea. The Liraglutide Effect and Action in Diabetes: Evaluation of Cardiovascular Outcome Results (LEADER) study has recently demonstrated that liraglutide, when added to usual therapy, results in improved cardiovascular outcomes over placebo in patients at high risk for cardiovascular disease; this contrasts with the Evaluation of Lixisenatide in Acute Coronary Syndrome (ELIXA) study, which showed that lixisenatide was neutral with respect to cardiovascular disease.

complications of diabetes were established in the UKPDS (p. 756). Mechanism of action Sulphonylureas act by closing the pancreatic β-cell ATP-sensitive potassium (KATP) channel, decreasing K+ efflux, which ultimately triggers insulin secretion (see Fig. 20.2C). Meglitinides (e.g. repaglinide and nateglinide) also work in this way and, although short-acting, are essentially sulphonylurea-like drugs. Clinical use Sulphonylureas are an effective therapy for lowering blood glucose and are often used as an add-on to metformin, if glycaemia is inadequately controlled on metformin alone (see Fig. 20.10). The main adverse effects of sulphonylureas are weight gain and hypoglycaemia. The weight gain is not ideal in patients with diabetes who are already overweight or obese, although sulphonylureas are effective treatments in this group. Hypoglycaemia occurs because the closure of KATP channels brings about unregulated insulin secretion, even with normal or low blood glucose levels. There are a number of sulphonylureas. In the UK, gliclazide is the most commonly used; in contrast, in the USA, glibenclamide (also known as glyburide) is widely used. Glibenclamide, however, is long-acting and prone to inducing hypoglycaemia, so should be avoided in older patients. Other sulphonylureas include glimepiride and glipizide. The dose–response of all sulphonylureas is steepest at low doses; little additional benefit is obtained when the dose is increased above half-maximal doses. Alpha-glucosidase inhibitors The α-glucosidase inhibitors delay carbohydrate absorption in the gut by inhibiting disaccharidases. Acarbose and miglitol are available and are taken with each meal. Both lower post-prandial blood glucose and modestly improve overall glycaemic control. They can be combined with a sulphonylurea. The main side-effects are flatulence, abdominal bloating and diarrhoea. They are used widely in the Far East but infrequently in the UK. Thiazolidinediones Mechanism of action These drugs (also called TZDs, ‘glitazones’ or PPARγ agonists) bind and activate peroxisome proliferator-activated receptor-γ, a nuclear receptor present mainly in adipose tissue, which regulates the expression of several genes involved in metabolism. TZDs enhance the actions of endogenous insulin, both directly (in the adipose cells) and indirectly (by altering release of ‘adipokines’, such as adiponectin, which alter insulin sensitivity in the liver). Plasma insulin concentrations are not increased and hypoglycaemia does not occur. TZDs increase preadipocyte differentiation, resulting in an increase in fat mass and body weight. Clinical use TZDs have been prescribed widely since the late 1990s but a number of adverse effects have become apparent and their use has declined. One popular TZD, rosiglitazone, was reported to increase the risk of myocardial infarction and was withdrawn in 2010. The other TZD in common use, pioglitazone, does not appear to increase the risk of myocardial infarction but may exacerbate cardiac failure by causing fluid retention, and recent data show that it increases the risk of bone fracture and possibly

748 • DIABETES MELLITUS Insulin therapy Manufacture and formulation Insulin was discovered in 1921 and transformed the management of type 1 diabetes, which was a fatal disorder until then. Up to the 1980s, insulin was obtained by extraction and purification from pancreases of cows and pigs (bovine and porcine insulins), and some patients still prefer to use animal insulins. Recombinant DNA technology enabled large-scale production of human insulin. Unmodified (‘soluble’ or ‘regular’) insulin aggregates into hexamers in subcutaneous tissues; these must dissociate before systemic absorption can occur and this process helps extend the duration of action to nearly 8 hours. The amino acid sequence of insulin can be altered to produce analogues of insulin, which differ in their rate of absorption from the site of injection. For example, in insulin lispro, the penultimate lysine and proline residues on the C-terminal end of the β chain are reversed (Fig. 20.13). This prevents the insulin molecules from aggregating as hexamers in subcutaneous tissues after injection and so speeds absorption, leading to a more rapid onset and

shorter duration of action than soluble insulin (Box 20.27). The onset of action of insulin analogues may be further hastened by the addition of excipients to the formulation (e.g. nicotinamide and arginine to insulin aspart). Conversely, in insulin glargine, a substitution of glycine for asparagine in the α chain and the addition of two additional arginine residues to the C-terminal end of the β chain serves to prolong the duration of action of the insulin to over 24 hours. The amino acid modifications shift the isoelectric point from a pH of 5.4 to 6.7, making the molecule less soluble at a physiological pH (see Fig. 20.13). Duration of action can also be extended by adding chemicals to soluble insulin solution or by adding other molecules to the insulin structure. Chemical additives include protamine and zinc at neutral pH (isophane or NPH insulin) or excess zinc ions (lente insulins). In insulin detemir and degludec, the duration of action is extended by adding fatty acids to a slightly truncated C-terminal end of the β chain (Fig. 20.13). Following subcutaneous injection, these bind to albumin in the All the incretin-acting drugs have been reported to be associated with an increased risk of pancreatitis, although this risk is small: between 1 and 10 cases per 1000 patients treated. Unlike sulphonylureas, both incretin-based therapies promote insulin secretion only when there is a glucose 'trigger' for it. Thus, when the blood glucose is normal, the insulin secretion is not augmented and so these agents do not cause hypoglycaemia when used as monotherapy or with other drugs that do not cause hypoglycaemia. SGLT2 inhibitors The sodium and glucose transporter 2 (SGLT2) inhibitor, dapagliflozin, was licensed for use in 2012. Subsequently, canagliflozin and empagliflozin have also been licensed. Glucose is filtered freely in the renal glomeruli and reabsorbed in the proximal tubules. SGLT2 is involved in reabsorption of glucose (Fig. 20.12). Inhibition results in approximately 25% of the filtered glucose not being reabsorbed, with consequent glycosuria. Although this helps to lower blood glucose and results in calorie loss and subsequent weight loss, the glycosuria does also lead to genital fungal infections. There has been increasing use of these agents over the last few years; however, the recent announcement of the Empagliflozin, Cardiovascular Outcomes, and Mortality in Type 2 Diabetes (EMPA-REG Outcomes) trial has the potential to change dramatically the way these drugs are now used. Empagliflozin therapy resulted in a 35% reduction in cardiovascular mortality and a similar reduction in admissions to hospital with heart failure. This result was much greater than anticipated and the mechanism behind it is still being investigated, but this landmark study was the first to show such striking benefits in mortality reduction from a glucose-lowering agent; as such, these drugs should now, at the very least, be used in all patients who fulfil the inclusion criteria of the trial – prior myocardial infarction, coronary artery disease, stroke, unstable angina or occlusive peripheral arterial disease. Euglycaemic diabetic ketoacidosis (i.e. DKA not associated with marked hyperglycaemia) has been recognised as a rare complication of this class of drugs. Fig. 20.12 Glucose filtration and reabsorption by the nephron. Some 90% of filtered glucose is reabsorbed by sodium and glucose transporter 2 (SGLT2) and 10% by SGLT1. SGLT2 inhibitors reduce net reabsorbed glucose by 25%. For a mean plasma glucose of 8 mmol/L (144 mg/dL), this results in a glucose loss of approximately 80 g per day in the urine, which in turn reduces plasma glucose. This equates to 320 kcal per day and subsequent weight loss. S1 segment Proximal tubule Distal S2/S3 segment -90% reabsorption ˜ 90% reabsorption ˜ 10% reabsorption Glucose Collecting duct No glucose SGLT2 -10% reabsorption SGLT1

discomfort of injecting bigger volumes and also to reduce variability in insulin delivery from the subcutaneous depot. Therefore, U 200, U 300 and U 500 formulations of insulin are available, which

are, respectively, two, three and five times more concentrated than standard insulin. Expert advice should be sought before using concentrated insulin because errors in prescribing can cause severe hypoglycaemia. Subcutaneous multiple dose insulin therapy In most patients, insulin is injected subcutaneously several times a day into the anterior abdominal wall, upper arms, outer thighs and buttocks (Box 20.28). Accidental intramuscular injection often occurs in children and thin adults. The rate of absorption of insulin may be influenced by many factors other than the insulin formulation, including the site, depth and volume of injection, skin temperature (warming), local massage and exercise. Absorption is delayed from areas of lipohypertrophy at injection sites (p. 721), which results from the local trophic action of insulin, so repeated injection at the same site should be avoided. Other routes of administration (intravenous and intraperitoneal) are reserved for specific circumstances. Once absorbed into the blood, insulin has a half-life of just a few minutes. It is removed mainly by the liver and also the kidneys, so plasma insulin concentrations are elevated in patients with liver disease or renal failure. Rarely, the rate of clearance can be affected by binding to insulin antibodies. blood, from which the insulin slowly disassociates. The duration of action of insulin degludec may also be extended as the fatty acid moiety promotes the formation of multi-hexamers of insulin in the subcutaneous tissues (Box 20.27). Isophane and lente insulins are cloudy preparations and have to be resuspended prior to injection to ensure adequate mixing of the components. The more modern, structurally modified, long-acting insulins (e.g. glargine, detemir and degludec) are clear and do not require resuspension. Pre-mixed formulations containing short-acting and isophane insulins in various proportions are available. In most countries, the insulin concentration in available formulations has been standardised at 100 U/mL. Increasing levels of obesity, which are associated with increased daily insulin requirements, have stimulated pharmaceutical companies to develop more concentrated insulin formulations to reduce the Fig. 20.13 Amino acid structure of insulin and insulin analogues. The areas in the shaded colours show the modifications made to the normal structure of insulin. These are important in altering the pharmocokinetic properties of the analogues. Gly Ile Val Glu Gln CysCys S S S S S S Cys Thr Ser Ser Leu Leu Tyr Gln Glu Asn Asn Tyr Cys Ile Phe Val Val Val Arg Gln His Leu Cys Cys Gly Gly Glu

Gly Gly Lys Ser His Leu Leu Leu Glu Glu Ala Thr Arg Phe Phe Tyr Thr Pro Pro Lys Asp Lys Thr Arg Arg Gly Arg Phe Phe Tyr Thr Pro Lys Fast-acting analogues Lispro Aspart Glulisine Glargine Detemir/Degludec Long-acting analogues 20.27 Duration of action (in hours) of insulin preparations Insulin Onset Peak Duration Rapid-acting (insulin analogues: lispro, aspart, glulisine) < 0.5 0.5–2.5 3–4.5 Short-acting (soluble (regular)) 0.5–1 1–4 4–8 Intermediate-acting (isophane (NPH), lente) 1–3 3–8 7–14 Long-acting (bovine ultralente) 2–4 6–12 12–30 Long-acting (insulin analogues: glargine, detemir, degludec) 1–2 None 18–26 20.28 How to inject insulin subcutaneously • Needle sited at right angle to the skin • Subcutaneous (not intramuscular) injection • Delivery devices: glass syringe (requires resterilisation), plastic syringe (disposable), pen device (reusable, some disposable), infusion pump

 vial several times before administration. Fixed-mixture insulins also have altered pharmacodynamic profiles, such that the peak insulin action and time to peak effect are significantly reduced compared with separately injecting the same insulins. This increases the risk of hypoglycaemia. Multiple injection regimens (intensive insulin therapy) are popular, with short-acting insulin being taken before each meal, and intermediate- or long-acting insulin being injected once or twice daily (basal-bolus regimen, Box 20.30). This type of regimen is more

physiological and allows greater freedom with regard to meal timing, as well more variable day-to-day physical activity. Insulin can be administered using a disposable plastic syringe with a fine needle (which can be re-used several times), but this has largely been replaced by pen injectors containing insulin in cartridges sufficient for multiple dosing. These are also available as pre-loaded disposable pens. For the most part, insulin analogues have replaced soluble and isophane insulins, especially for people with type 1 diabetes, because they allow greater flexibility and convenience and reduce risk of hypoglycaemia (see Box 20.26). Unlike soluble insulin, which should be injected 30–60 minutes before eating, rapid-acting insulin analogues can be administered immediately before, during or even after meals, although are better injected 15 minutes before eating. Long-acting insulin analogues are also better able than isophane insulin to maintain 'basal' insulin levels for up to 24 hours. Despite these pharmacokinetic benefits, the impact of insulin analogues on overall glycaemic control is minor, but studies consistently show a significant reduction in frequency of hypoglycaemia, particularly overnight. The complications of insulin therapy are listed in Box 20.29; the most important of these is hypoglycaemia (p. 738). A common problem is fasting hyperglycaemia ('the dawn phenomenon'), which arises through a combination of the normal circadian rhythm and release of hormones such as growth hormone and cortisol during the later part of the night, as well as diminishing levels of overnight isophane insulin. The dawn phenomenon is not a consequence of prior nocturnal hypoglycaemia. Insulin dosing regimens The choice of regimen depends on the desired degree of glycaemic control, the severity of underlying insulin deficiency, the patient's lifestyle, and his or her ability to adjust the insulin dose. The time–action profile of different insulin regimens, compared to the secretory pattern of insulin in the non-diabetic state, is shown in Figure 20.14. People with type 1 diabetes are best managed by multiple daily insulin injections or an insulin pump. In type 2 diabetes, insulin is usually initiated as a once-daily long-acting insulin, either alone or in combination with oral antidiabetic agents. However, in time, more frequent insulin injections are usually required. Twice-daily administration of a short-acting and intermediateacting insulin (usually soluble and isophane insulins), given in combination before breakfast and the evening meal, is the simplest regimen and is still commonly used in many countries. Initially, two-thirds of the total daily requirement of insulin is given in the morning in a ratio of short-acting to intermediate-acting of 1 : 2, and the remaining third is given in the evening. Pre-mixed formulations are available that contain different proportions of soluble and isophane insulins (e.g. 30 : 70 and 50 : 50). These are useful as they avoid the need for directly mixing insulins, but are inflexible as the individual components cannot be adjusted independently. They need to be resuspended by shaking the 20.29 Side-effects of insulin therapy • Hypoglycaemia • Weight gain • Peripheral oedema (insulin treatment causes salt and water retention in the short term) • Insulin antibodies • Local allergy (rare) • Lipohypertrophy or lipoatrophy at injection sites Fig. 20.14 Profiles of plasma insulin associated with different insulin regimens. The schematic profiles are compared with the insulin responses (mean ± 1 standard deviation) observed in non-diabetic adults shown in the top panel (shaded area). These are theoretical patterns of plasma insulin and may differ considerably in magnitude and duration of action between individuals. Plasma insulin Soluble before meals, long-acting insulin late evening

Clock time (hrs) Soluble before meals, isophane late evening Soluble and isophane, twice daily Non-diabetic state Injection of insulin Soluble or fast-acting analogue Isophane Long -acting analogue Meal Key

clinical trials in children and adults in the hospital or free-living setting aim to determine how effective this approach will be in optimising management of type 1 diabetes. Widespread use may, however, be limited by cost. Alternative routes of insulin delivery have also been investigated. Clinical trials with intrapulmonary (inhalation),

transdermal and oral insulins are ongoing but as yet none has proven commercially viable. Inhaled insulin has been approved for use in the USA as a mealtime insulin, but experience with this is very limited. Subcutaneous continuous insulin therapy Subcutaneous continuous insulin therapy, commonly know as the insulin pump, is a system of insulin delivery

that uses a battery-operated medical device to deliver insulin continuously to the individual with type 1 diabetes. Device configurations vary between manufacturers but will include the pump with controls, processing module and batteries, a disposable insulin reservoir, and a disposable insulin set including cannula for

subcutaneous insertion and a tubing system to deliver insulin from the reservoir to the cannula. Some recent versions are disposable or semi-disposable and eliminate tubing from the infusion set (patch pumps). Insulin pumps allow the individual more flexibility with bolus insulin injections in both timing and shape (e.g. using an extended

bolus when covering high-fat/protein meals such as steak, or when diabetes is complicated by gastroparesis), and also in changing basal insulin infusion rates. This is especially useful overnight when basal rates can be reduced to prevent low glucose, but increased pre-dawn to prevent high glucose. In addition, the

temporary basal rates can be used to lessen the risk of hypoglycaemia with exercise. Determining an individual’s basal rate on the pump requires help from a specialist, but in essence is determined by fasting for periods of at least 4 hours while periodically evaluating the blood glucose levels and adjusting the pump infusion rate to maintain glucose in

the normal range. Basal rates will change and can be influenced by factors such as increasing duration of disease, puberty, weight gain or loss, drugs that affect insulin sensitivity (e.g. glucocorticoids), and a change in fitness levels with exercise on overall glycaemic control. An example of an insulin pump is shown in Figure 20.15.

Closed loop insulin therapy A further iteration in insulin pump therapy in recent years is the development of a ‘closed loop’ system, also known as the artificial pancreas (Fig. 20.16). These systems aim to integrate insulin pumps with continuous glucose monitoring systems (CGMS). In a closed loop system, the CGMS device communicates

with the insulin pump via a computerised program. This means that real-time glucose data obtained through the CGMS can be used to calculate an insulin dosage to be dispensed through the insulin pump (Fig. 20.17). Features might include a ‘low-glucose suspend’ function, where detection of hypoglycaemia or a glucose level falling

below a pre-set threshold (e.g. 4.0 mmol/L (72 mg/dL)) signals the pump to stop dispensing insulin until the wearer can treat the hypoglycaemia with food or glucose tabs. Current 20.30 Example of a meal bolus calculation RL has type 1 diabetes treated with an insulin pump. His pre-breakfast glucose (G) is 12 mmol/L (216 mg/dL). He is

having a breakfast meal of cereal with milk containing 30 g of carbohydrate (CHO) in total. His insulin:carbohydrate ratio (ICR) is 10 (1 U of insulin for every 10 g of CHO) and his insulin sensitivity factor (ISF) is 2 (1 U of insulin to bring down blood glucose by 2 mmol/L (36 mg/dL)). He wants to achieve a glucose target (GT) of 8 mmol/L (144

mg/dL) after eating. Calculation of estimated bolus dose: Bolus dose CHO ICR G G ISF U of T

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insulin Fig. 20.15 Insulin pump. An insulin pump is an alternative means of delivering insulin in type 1 diabetes. Different types are available and include the pump device itself (with controls, processing module and batteries), a disposable reservoir for insulin (inside the pump) and a disposable infusion set (with tubing and a cannula for subcutaneous insertion). Alternative configurations include disposable or semi-disposable pumps, and pumps without infusion tubing. Insulin pumps deliver rapid-acting insulin continuously, and can be adjusted by the user, based on regular glucose monitoring and carbohydrate counting. Electronic device containing a plastic cartridge of insulin, battery and internal computer to program insulin delivery Insulin infusion set containing flexible tubing and cannula for insertion Fig. 20.16 Artificial pancreas. The artificial pancreas (AP) can vary in its set up and the different components employed in its delivery but core to an AP system are: (1) a continuous glucose monitor (CGM) measuring interstitial glucose levels every 5–15 minutes; (2) a smartphone (or personal glucose monitor) with an app that uses the glucose information from the CGM along with modifications inserted by the user to calculate how much insulin should be delivered. This is communicated wirelessly to (3) the insulin pump that delivers insulin subcutaneously as directed.

752 • DIABETES MELLITUS donor pancreas into a person with type 1 diabetes. The isolated pancreatic islets are usually infused into the patient’s liver via the portal vein. This approach has now been successfully adopted in a number of centres around the world (Fig. 20.18). At present, islet transplantation is usually suitable only for patients with unstable glycaemic control

characterised by recurrent severe hypoglycaemia that cannot be corrected by standard conventional and intensive insulin therapies. Progress is being made towards meeting the needs of supply, purification and storage of islets, but problems remain relating to transplant rejection, and destruction by the patient's autoantibodies against β cells. Nevertheless, the development of methods of inducing tolerance to transplanted islets and the potential use of stem cells (p. 58) mean that this may still prove the most promising approach in the long term. Adoption of newer immunosuppressive protocols has resulted in far better outcomes and now nearly 50% of transplanted patients will be insulin-independent at 3 years post transplantation. Management of diabetes in special situations Diabetes in pregnancy The management of women with pre-existing diabetes who are pregnant or who have developed diabetes in pregnancy (gestational diabetes) is discussed in detail on page 1278 and summarised in Box 20.31. This is a highly specialised area and requires careful and attentive management, as elevated maternal Transplantation Whole-pancreas transplantation is carried out in a small number of patients with diabetes each year, but it presents problems relating to exocrine pancreatic secretions and long-term immunosuppression is necessary. There are currently four main types of whole-pancreas transplantation: • pancreas transplant alone • simultaneous pancreas–kidney (SPK) transplant, when pancreas and kidney are transplanted simultaneously from the same deceased donor • pancreas-after-kidney (PAK) transplant, when a cadaveric, or deceased, donor pancreas transplant is performed after a previous, and different, living or deceased donor kidney transplant • simultaneous deceased donor pancreas and live donor kidney (SPLK) transplant. The principal complications occurring immediately after surgery include thrombosis, pancreatitis, infection, bleeding and rejection. Prognosis is improving: 1 year after transplantation more than 95% of all patients are still alive and 80–85% of all pancreases are still functional. After transplantation, patients will need life-long immunosuppression, which carries with it an increased risk of infection and cancer. An alternative form of transplantation is allogenic islet transplantation, which involves the transplantation of islets from a Fig. 20.17 Continuous glucose monitoring (CGM) profiles: sensor data. A CGM profile from an individual without diabetes. B CGM profile from an individual with type 1 diabetes. The green box shows the reference range. CGM devices may be worn for 7–14 days and the glucose profile of each day illustrated by a different colour. Based on this, the person with diabetes and their health-care team can review overall profiles and adjust treatment as necessary to improve control and avoid hypoglycaemia.

5.6 7.8 3.9 3.3 3.9 3.3 11.1 16.7 Glucose (mmol/L) Glucose (mmol/L) 12:00 a.m.

5.6 7.8 11.1 16.7 2.00 a.m. 4:00 a.m. 6:00 a.m. 8:00 a.m. 10:00 a.m. 12:00 p.m. Time through the day 2:00 p.m. 4:00 p.m. 6:00 p.m. 8:00 p.m. 10:00 p.m. 12:00 a.m. 12:00 a.m. 2.00 a.m. 4:00 a.m. 6:00 a.m. 8:00 a.m. 10:00 a.m. 12:00 p.m. Time through the day 2:00 p.m. 4:00 p.m. 6:00 p.m. 8:00 p.m. 10:00 p.m. 12:00 a.m. B A

blood glucose in pregnancy is associated with significant maternal and fetal morbidity. Children, adolescents and young adults with diabetes Most type 1 diabetes is diagnosed in children below 18 years of age, with peak incidence rates between 5 and 7 years of age and at puberty. The management of diabetes in children and adolescents presents particular challenges, which should be addressed in specialised clinics with multidisciplinary input (Box 20.32). Some of the unique

aspects of childhood type 1 Fig. 20.18 Transplanting islet cells. (1) Pancreas obtained from suitable human donor. (2) Pancreatic islets containing insulin-producing β cells are isolated first in a Ricordi chamber. (3) Islets, once separated and purified, are infused into the hepatic portal vein. (4) Once embedded in the liver, pancreatic islets secrete insulin in response to changes in portal vein glucose.

Box 20.31 Diabetes in pregnancy • Control of established diabetes before and during pregnancy: must be meticulous, to reduce the risk of complications such as pre-eclampsia, congenital malformations and stillbirth. • Gestational diabetes: most commonly an inability to increase insulin secretion adequately to compensate for pregnancy-induced insulin resistance. • Screening for gestational diabetes: all women at high risk should have an oral glucose tolerance test at 24–28 weeks. Measurement of HbA1c and/or blood glucose at booking visit is usually recommended. • Management of gestational diabetes: reduce intake of refined carbohydrate, and add metformin, glibenclamide and/or insulin if necessary to optimise glycaemic control. • Self-monitoring of glucose: targets are a pre-prandial level of < 5.3 mmol/L (95 mg/dL) and a 1-hour or 2-hour post-prandial level of < 7.8 mmol/L (140 mg/dL) and < 6.4 mmol/L (114 mg/dL), respectively. 20.32 Diabetes in adolescence • Type of diabetes: type 1 diabetes is predominant in children and adolescents, but type 2 diabetes is now presenting in unprecedented numbers of obese, inactive teenagers. Monogenic diabetes (MODY) should also be considered (see Box 20.10, p. 733). • Physiological changes: hormonal, physical and lifestyle changes in puberty affect dietary intake, exercise patterns and sensitivity to insulin, necessitating alterations in insulin regimen. • Emotional changes: adolescence is a phase of transition into independence (principally from parental care). Periods of rebellion against parental control, experimentation (e.g. with alcohol) and a more chaotic lifestyle are common, and often impact adversely on control of diabetes. • Glycaemic control: a temporary deterioration in control is common, although not universal. It is sometimes more important to maintain contact and engagement with a young person than to insist on tight glycaemic control. • Diabetic ketoacidosis: a few adolescents and young adults present with frequent episodes of DKA, often because of non-adherence to insulin therapy. This is more common in females. Motivating factors may include weight loss, rebellion, and manipulation of family or schooling circumstances. • Adolescent diabetes clinics: these challenges are best tackled with support from a specialised multidisciplinary team, including paediatricians, physicians, nurses and psychologists. Support is required for the patient and parents. diabetes management include changing insulin sensitivity related to sexual maturity and physical growth, unique vulnerability to hypoglycaemia (especially in children below 6 years of age) and possibly hyperglycaemia, as well as DKA. In addition, family dynamics, child care and schooling, developmental stages and

 20.33 Recommended therapeutic targets in childhood and adolescence Plasma glucose levels • Before meals 4.0–7.0 mmol/L (72–126 mg/dL) • After meals 5.0–9.0 mmol/L (90–160 mg/dL) HbA1c • < 53 mmol/mol (7.0%) with a target of 48 mmol/L Recommended screening • HbA1c up to four times per year • Thyroid disease at diagnosis and annually thereafter • Diabetic retinopathy annually from 12 years • Albuminuria (albumin:creatinine ratio (ACR) 3–30 mg/mmol; ‘microalbuminuria’) to detect diabetic kidney disease, annually from 12 years • Hypertension annually from 12 years Adapted from National Institute for Health and Care Excellence NG18 – Diabetes (type 1 and type 2) in children and young people: diagnosis and management; 2015. 20.34 How to carry out pre-operative assessment of patients with diabetes • Assess glycaemic control: Consider delaying surgery and refer to the diabetes team if HbA1c

75 mmol/mol; this should be weighed against the need for surgery • Assess cardiovascular status Optimise blood pressure Perform an ECG for evidence of (possibly silent) ischaemic heart disease and to assess QTc (p. 448) • Assess foot risk (p. 761) Patients with high-risk feet should have suitable pressure relief provided during post-operative nursing • For minor/moderate operations where only one meal will be omitted, plan for the patient to be first on the list and 180 mg/dL) seems appropriate. Achieving such a target may require the use of intravenous insulin and dextrose in some individuals. Surgery and diabetes Patients with diabetes are reported to have up to 50% higher perioperative mortality than patients without diabetes. Surgery causes catabolic stress and secretion of counter-regulatory hormones (including catecholamines and cortisol) in both normal and diabetic individuals. This results in increased glycogenolysis, gluconeogenesis, lipolysis, proteolysis and insulin resistance. Starvation exacerbates this process by increasing lipolysis. In the non-diabetic person, these metabolic effects lead to a secondary increase in the secretion of insulin, which exerts a controlling influence. In diabetic patients, either there is absolute deficiency of insulin (type 1 diabetes) or insulin secretion is delayed and impaired (type 2 diabetes), so that in untreated or poorly controlled diabetes, the uptake of metabolic substrate into tissues is significantly reduced, catabolism is increased and, ultimately, metabolic decompensation in the form of DKA may develop in both types of diabetes. In addition, hyperglycaemia impairs wound healing and innate immunity, leading to increased risk of infection. Patients with diabetes are also more likely to have underlying pre-operative morbidity, especially cardiovascular disease. Finally, management errors in diabetes may cause dangerous hyperglycaemia or hypoglycaemia. Careful preoperative assessment and perioperative management are therefore essential, ideally with support from the diabetes specialist team. Pre-operative assessment Unless a surgical intervention is an emergency, patients with diabetes should be assessed well in advance of surgery so that poor glycaemic control and other risk factors can be addressed (Box 20.34). There is good evidence that a higher HbA1c is associated with adverse perioperative outcome. In general, an upper limit for an acceptable HbA1c should be between 64 and 75 mmol/mol (8% and 9%). However, since optimisation of care may take weeks or months to achieve, the benefits need to be weighed against the need for early surgical intervention. Perioperative management Figure 20.19 outlines a general approach to perioperative management of diabetes, although this may need to be adapted according to the patient, the surgical procedure and local guidelines. Patients with diabetes who are considered low-risk can attend as day cases or be admitted on the day of surgery. ability to self-care all have to be considered in the management plan, as well as, in older children and adolescents, issues of body image, eating disorders and recreational drug and alcohol use. It is also notable that there is very limited clinical research in children with diabetes and so most recommendations are based on expert opinion. The prevalence of type 2 diabetes in those below 20 years has been increasing and is estimated to

> increase fourfold in the next 40 years. Management of these children and young adults is difficult. Coeliac disease and thyroid disease are much more common in children with type 1 diabetes than in the general population and so it is currently recommended that these conditions are screened for. Current recommendations for screening in type 1 diabetes are shown in Box 20.33. Hyperglycaemia in acute medical illness Hyperglycaemia is often found in patients who are admitted to hospital as an emergency. In most people this occurs in the context of a known diagnosis of diabetes; in some individuals, however, it is a consequence of stress hyperglycaemia (p. 728), while in others it is due to undiagnosed diabetes. Hyperglycaemia on admission to hospital is associated with increased length of stay and increased mortality in a wide variety of acute medical emergencies, including acute coronary syndrome and acute stroke. Intuitively, intensive glycaemic control with intravenous insulin should improve outcomes during acute illness. However, recent studies have shown that strategies aiming for near-normal blood glucose levels in acutely ill patients are associated with either increased mortality or no overall benefit. The reasons for the adverse outcomes are not established, but intensive glycaemic control is inevitably associated with an increased risk of hypoglycaemia because of the inherent limitations of modern insulins, the restricted frequency of glucose monitoring in a ward environment and the relative imprecision of near-patient blood glucose meters. The activation of the sympathetic nervous system and release of counter-regulatory hormones during acute hypoglycaemia could have deleterious consequences for the acutely ill patient. There is no consensus on the optimum glucose targets in acutely ill patients but extremes of blood glucose should be avoided, and so a target of between 6 and 12 mmol/L (105

Fig. 20.19 Management of diabetic patients undergoing surgery and general anaesthesia. (eGFR = estimated glomerular filtration rate; GLP-1 = glucagon-like peptide 1; IV = intravenous; U&Es = urea and electrolytes) Minor operation/ only one meal omitted HbA1c ≤ 64 mmol/mol? Yes No Aim for ‘first on list’ Omit any oral antidiabetic drugs and GLP-1 analogues on morning of operation Omit quick- or medium-acting insulins prior to missed meal. Continue long-acting insulin (e.g. glargine or detemir) but consider reducing dose if surgical list is in afternoon No need for IV insulin unless unable to eat post-operatively, blood glucose > 14 mmol/L (250 mg/dL), or ketones present in urine or blood Resume usual medication with first meal; if it is lunch for patient using mixed insulin, give half of usual morning dose Major operation/ prolonged fast Omit any oral antidiabetic drugs and GLP-1 analogues on morning of operation Omit quick- or medium-acting insulins prior to missed meal. Continue long-acting insulin (e.g. glargine or detemir) Start IV insulin infusion and IV fluids early on morning of operation and maintain on IV insulin until eating and drinking Once patient is eating, prescribe usual oral or injectable treatment with a meal and discontinue insulin infusion 1 hr later Withhold metformin if eGFR < 30 mL/min/1.73 m2 Check U&Es at least daily while on IV insulin and fluids; ensure adequate potassium replacement and avoid hyponatraemia from dextrose infusion Occasionally, patients may be admitted the night before to ensure optimal

management. Post-operative management Patients who need to continue fasting after surgery should be maintained on intravenous insulin and fluids until they are able to eat and drink (Fig. 20.19). During this time, care must be taken with fluid balance and electrolyte levels. Insulin infusion necessitates dextrose infusion to maintain a supply of glucose but this combination drives down plasma potassium (p. 360) and can result in hyponatraemia. Intravenous fluids during prolonged insulin infusion should therefore include saline and potassium supplementation. UK guidelines recommend the use of dextrose/ saline (0.45% saline with 5% dextrose and 0.15% potassium chloride). Once a patient's usual treatment has been reinstated, care must be taken to continue to control the blood glucose, ideally between 6 and 10 mmol/L (105–180 mg/dL), in order to optimise wound healing and recovery. Patients normally controlled on tablets may require temporary subcutaneous insulin treatment until the increased 'stress' of surgery, wound healing or infection has resolved. Complications of diabetes Despite all the treatments now available, the outcome for patients with diabetes remains disappointing. Long-term complications of diabetes still cause significant morbidity and mortality (Boxes 20.35 and 20.36). Excess mortality in diabetes is caused mainly by large blood vessel disease, particularly myocardial infarction and stroke. Macrovascular disease also causes substantial morbidity from myocardial infarction, stroke, angina, cardiac failure and intermittent claudication. The pathological changes of atherosclerosis in diabetic patients are similar to those in the non-diabetic population but occur earlier in life and are more extensive and severe. Diabetes amplifies the effects of the other major cardiovascular risk factors: smoking, hypertension and dyslipidaemia (Fig. 20.20). Moreover, patients with type 2 diabetes are more likely to have additional cardiovascular risk factors, which co-segregate with insulin resistance in the metabolic syndrome (p. 730). Mortality statistics from the USA indicate that cardiovascular death rates are 1.7 times higher in adults with diabetes aged 20 years or older compared to adults in the same age group who do not have diabetes, while similar figures for myocardial infarction show a 1.8 times greater rate. Hospitalisation rates for stroke were 1.5 times higher in adults with diabetes than in those without diabetes. In addition, 60% of non-traumatic amputations among people aged 20 years or older were reported to be in people with diabetes. Type 1 diabetes is also associated with increased cardiovascular risk. Recent data from Scotland show that the age-adjusted incidence rate ratio for first cardiovascular event was 3 times higher in women and 2.3 times higher in men with type 1 diabetes compared to those without diabetes.

 body. The development of the characteristic clinical syndromes of diabetic retinopathy, nephropathy, neuropathy and accelerated atherosclerosis is thought to result from the local response to generalised vascular injury. For example, in the wall of large vessels, increased permeability of arterial endothelium, particularly when combined with hyperinsulinaemia and hypertension, may increase the deposition of atherogenic lipoproteins. The mechanisms linking hyperglycaemia to these pathological changes are, however, poorly characterised. Preventing diabetes complications Glycaemic control The evidence that improved glycaemic control decreases the risk of developing microvascular complications of diabetes was established by the DCCT in type 1 diabetes and the UKPDS in type 2 diabetes. The DCCT was a large study that lasted 9 years; it randomised patients with type 1 diabetes to intensive treatment (mean HbA1c 53 mmol/mol) and conventional treatment (mean HbA1c 75 mmol/mol). There was a 60% overall reduction in the risk of developing diabetic complications in patients with type 1 diabetes on intensive therapy with strict glycaemic control, compared with those on conventional therapy. No single factor other than glycaemic control had a significant effect on outcome. However, the group that was intensively treated to lower blood glucose had three times the rate of severe hypoglycaemia. The UKPDS

randomised patients to intensive treatment (mean HbA1c 53 mmol/mol) versus conventional treatment (mean HbA1c 64 mmol/mol). This study showed that, in type 2 diabetes, the frequency of diabetic complications is lower and progression is slower with good glycaemic control and effective treatment of hypertension, irrespective of the type of therapy used. Extrapolation from the UKPDS suggests that, for every 11 mmol/mol Disease of small blood vessels is a specific complication of diabetes and is termed diabetic microangiopathy. It contributes to mortality through renal failure caused by diabetic nephropathy, and is responsible for substantial morbidity and disability: for example, blindness from diabetic retinopathy, difficulty in walking, chronic ulceration of the feet from peripheral neuropathy, and bowel and bladder dysfunction from autonomic neuropathy. The risk of microvascular disease is positively correlated with the duration and degree of sustained hyperglycaemia, however it is caused and at whatever age it develops. Pathophysiology The histopathological hallmark of diabetic microangiopathy is thickening of the capillary basement membrane, with associated increased vascular permeability, which occurs throughout the Fig. 20.20 Association between HbA1c and risk of microvascular and macrovascular diabetes complications. These data were obtained amongst participants in the UK Prospective Diabetes Study and were adjusted for effects of age, sex and ethnicity; the incidences show what could be expected amongst white men aged 50–54 years at diagnosis of type 2 diabetes, followed up for 10 years. Microvascular disease included retinopathy requiring photocoagulation, vitreous haemorrhage and renal failure. Macrovascular disease included fatal and non-fatal myocardial infarction and sudden death. A 1% change in HbA1c is equivalent to a reduction of 11 mmol/mol. < 6 6–7 7–8 8–9 9–10

> 10 HbA1c (%)

Incidence per 1000 patient-years Microvascular disease Macrovascular disease (myocardial infarction) Risk versus non-diabetic controls (mortality ratio) • Overall 2.6 • Coronary heart disease

Cerebrovascular disease

Peripheral vascular disease 2.8 • All other causes, including renal failure 2.7 Causes of death in diabetes (approximate proportion) • Cardiovascular disease 70% • Renal failure 10% • Cancer 10% • Infections 6% • Diabetic ketoacidosis 1% • Other 3% Risk factors for increased morbidity and mortality in diabetes • Duration of diabetes • Early age at onset of disease • High glycated haemoglobin (HbA1c) • Raised blood pressure • Proteinuria; microalbuminuria • Dyslipidaemla • Obesity } 20.36 Mortality in diabetes 20.35 Complications of diabetes Microvascular/neuropathic Retinopathy, cataract • Impaired vision Nephropathy • Renal failure Peripheral neuropathy • Sensory loss • Pain • Motor weakness Autonomic neuropathy • Gastrointestinal problems (gastroparesis; altered bowel habit) • Postural hypotension Foot disease • Ulceration • Arthropathy Macrovascular Coronary circulation • Myocardial ischaemia/infarction Cerebral circulation • Transient ischaemic attack • Stroke Peripheral circulation • Claudication • Ischaemia

and accounts for between 20% and 50% of patients starting renal replacement therapy. About 30% of patients with type 1 diabetes have developed diabetic nephropathy 20 years after diagnosis, but the risk after this time falls to less than 1% per year, and from the outset the risk is not equal in all patients (Box 20.38). The risk of nephropathy in Caucasian populations with type 2 diabetes is similar to those with type 1 diabetes but the rate of progression may be exacerbated by concomitant obesity and other risk factors. The risk of nephropathy is much greater in some ethnic groups, with epigenetic and genetic factors thought to influence this increased risk. Some patients do not develop nephropathy, however, despite having long-standing, poorly controlled diabetes, suggesting that they do not have a genetic predisposition. While variants in a few genes have been implicated in diabetic nephropathy, the major differences in individual risk remain unexplained. With improved standards of care focusing on glycaemic control and blood pressure lowering, the proportion of patients with overt nephropathy is reducing; however, due to the global rise in the incidence of type 2 diabetes, the prevalent number of people with diabetes and end-stage renal failure continues to rise. The pathophysiology is not fully understood and there are several postulated mechanisms by which hyperglycaemia causes the pathological changes seen in diabetic nephropathy. The central features are activation of the renin–angiotensin system, leading to both intrarenal and systemic effects, as well as direct toxic effects of prolonged hyperglycaemia, leading to renal inflammation and fibrosis. The pattern of progression of renal abnormalities in diabetes is shown schematically in Figure 20.21. Pathologically, the first changes coincide with the onset of microalbuminuria and include thickening of the glomerular basement membrane and accumulation of matrix material in the mesangium. Subsequently, nodular deposits (Fig. 20.22) are characteristic, and glomerulosclerosis worsens as heavy proteinuria develops, until glomeruli are progressively lost and renal function deteriorates. Diagnosis and screening Microalbuminuria (Box 20.39) is the presence in the urine of small amounts of albumin, at a concentration below that detectable using a standard urine dipstick. Overt nephropathy is defined as the presence of macroalbuminuria (urinary albumin

> 300 mg/24 hrs, detectable on urine dipstick). Microalbuminuria is a good predictor of progression to nephropathy in type 1 diabetes. It is a less reliable predictor of nephropathy in older patients with type 2 diabetes, in whom it may be accounted for by other diseases (p. 394), although it is a potentially useful marker of an increased risk of macrovascular disease. Management The presence of established microalbuminuria or overt nephropathy should prompt vigorous efforts to reduce the 20.37 Diabetes management in old age • Glycaemic control: the optimal target for glycaemic control in older people has yet to be determined. Strict glycaemic control should be avoided in frail patients with comorbidities and in older patients with long duration of diabetes. • Cognitive function and affect: may benefit from improved glycaemic control but it is important to avoid hypoglycaemia. • Hypoglycaemia: older people have reduced symptomatic awareness of hypoglycaemia and limited knowledge of symptoms, and are at greater risk of, and from, hypoglycaemia. • Mortality: the mortality rate of older people with diabetes is more than double that of age-matched non-diabetic people, largely because of increased deaths from cardiovascular disease. reduction in HbA1c, there is a 21% reduction in death

related to diabetes, a 14% reduction in myocardial infarction and 30–40% reduction in risk of microvascular complications (Fig. 20.20). These landmark trials demonstrated that diabetic complications are preventable and that the aim of treatment should be ‘nearnormal’ glycaemia. More recent studies, however, such as the Action to Control Cardiovascular Risk in Diabetes (ACCORD), showed increased mortality in a subgroup of patients who were aggressively treated to lower HbA1c to a target of less than 48 mmol/mol. The patients in this study had poor glycaemic control at baseline, a long duration of diabetes and a high prevalence of cardiovascular disease. It appears that, while a low target HbA1c is appropriate in younger patients with earlier diabetes who do not have underlying cardiovascular disease, aggressive glucose-lowering is not beneficial in older patients with long duration of diabetes and multiple comorbidities (Box 20.37). Control of other risk factors Randomised controlled trials have shown that aggressive management of blood pressure minimises the microvascular and macrovascular complications of diabetes. Angiotensin-converting enzyme (ACE) inhibitors are valuable in improving outcome in heart disease and in treating diabetic nephropathy (see below). The management of dyslipidaemia with a statin limits macrovascular disease in people with diabetes (p. 375). This often results in the necessary use of multiple medications, which exacerbates the problem of adherence to therapy by patients; it is not unusual for a patient to be taking two or more diabetes therapies, two or more blood pressure drugs and a statin. Diabetic retinopathy Diabetic retinopathy (DR) is one of the most common causes of blindness in adults between 30 and 65 years of age in developed countries. The prevalence of DR increases with duration of diabetes, and almost all individuals with type 1 diabetes and the majority of those with type 2 diabetes will have some degree of DR after 20 years. The pathogenesis, clinical features and management of diabetic retinopathy, as well as screening and prevention, are described on page 1174. Other causes of visual loss in type 2 diabetes are also covered in Chapter 27. Diabetic nephropathy Diabetic nephropathy is an important cause of morbidity and mortality in both type 1 and type 2 diabetes. It is now the most common cause of end-stage renal failure in developed countries 20.38 Risk factors for diabetic nephropathy • Poor glycaemic control • Long duration of diabetes • Presence of other microvascular complications • Ethnicity (e.g. Asians, Pima Indians) • Pre-existing hypertension • Family history of diabetic nephropathy • Family history of hypertension

 Blockade of the renin–angiotensin system using either ACE inhibitors or angiotensin 2 receptor blockers (ARBs) has been shown to have an additional benefit over similar levels of blood pressure control achieved with other antihypertensive agents and is recommended as first-line therapy. The addition of a diuretic and/or salt restriction increase both the anti-proteinuric and antihypertensive effect of angiotensin blockade and therefore constitute an ideal second-line treatment. The benefit from blockade of the renin–angiotensin system arises from a reduction in the angiotensin II-mediated vasoconstriction of efferent arterioles in glomeruli (see Fig. 15.1D, p. 385). The resulting dilatation of these vessels decreases glomerular filtration pressure

and, therefore, the hyperfiltration and protein leak. Both ACE inhibitors and ARBs increase risk of hyperkalaemia (p. 362) and, in the presence of renal artery stenosis (p. 406), may induce marked deterioration in renal function. Therefore, electrolytes and renal function should be checked after initiation or each dose increase. If blockade of the renin–angiotensin system is not possible, blood pressure should managed with standard treatment, such as calcium channel blockers and diuretics. There may be a role for spironolactone (an aldosterone antagonist) but this is limited by hyperkalaemia. Halving the amount of albuminuria with an ACE inhibitor or ARB results in a nearly 50% reduction in long-term risk of progression to end-stage renal disease. Some patients do progress, however, with worsening renal function. Renal replacement therapy (p. 420) is often required at a higher eGFR than in other causes of renal failure, due to fluid overload or symptomatic uraemia. Renal transplantation dramatically improves the life of many, and any recurrence of diabetic nephropathy in the allograft is usually too slow to be a serious problem; associated macrovascular and microvascular disease elsewhere may still progress, however. Pancreatic transplantation (generally carried out at the same time as renal transplantation) can produce insulin independence and delay or reverse microvascular disease, but the supply of organs is limited and this option is available to few. For further information on management, see Chapter 15. Diabetic neuropathy Diabetic neuropathy causes substantial morbidity and increases mortality. It is diagnosed on the basis of symptoms and signs, after the exclusion of other causes of neuropathy (p. 1138). Depending on the criteria used for diagnosis, it affects between 50% and 90% of patients with diabetes, and of these, 15–30% will have painful diabetic neuropathy (PDN). Like retinopathy, neuropathy occurs secondary to metabolic disturbance, and prevalence is related to the duration of diabetes and the degree of metabolic control. Pathological features can occur in any peripheral nerves. They include axonal degeneration of both myelinated and unmyelinated fibres, with thickening of the Schwann cell basal lamina, patchy segmental demyelination and abnormal intraneural capillaries (with basement membrane thickening and microthrombi). Various classifications of diabetic neuropathy have been proposed. One is shown in Box 20.40 but motor, sensory and autonomic nerves may be involved in varying combinations, so that clinically mixed syndromes usually occur. Clinical features Symmetrical sensory polyneuropathy This is frequently asymptomatic. The most common clinical signs are diminished perception of vibration sensation distally, ‘glove 20.39 Screening for microalbuminuria • Screening identifies incipient nephropathy in type 1 and type 2 diabetes; is an independent predictor of macrovascular disease in type 2 diabetes • Risk factors include high blood pressure, poor glycaemic control and smoking • Early morning urine is measured for the albumin:creatinine ratio (ACR). Microalbuminuria is present if: Male ACR 2.5–30 mg/mmol creatinine Female ACR 3.5–30 mg/mmol creatinine • An elevated ACR should be followed by a repeat test: There is established microalbuminuria if 2 out of 3 tests are positive An ACR > 30 mg/mmol creatinine is consistent with overt nephropathy Fig. 20.22 Nodular diabetic glomerulosclerosis. There is thickening of basement membranes, mesangial expansion and a Kimmelstiel–Wilson nodule (arrow), which is pathognomonic of diabetic kidney disease. Fig. 20.21 Natural history of diabetic nephropathy. In the first few years of type 1 diabetes mellitus, there is hyperfiltration, which declines fairly steadily to return to a normal value at approximately 10 years (blue line). In susceptible patients (about 30%), after about 10 years, there is sustained proteinuria, and by approximately 14 years it has reached the nephrotic range (red line). Renal function continues to decline, with the end stage being reached at approximately 16 years. Microalbuminuria Sustained proteinuria Nephrotic range proteinuria

GFR (mL / min) Proteinuria (g / 24 hrs) Years Hyperfiltration Hypertension Renal failure risk of progression of nephropathy and of cardiovascular disease by: • aggressive reduction of blood pressure • aggressive reduction of cardiovascular risk factors • optimisation of glycaemic control

pressure on the plantar aspects of the metatarsal heads, with the development of callus skin at these and other pressure points. Electrophysiological tests (p. 1074) demonstrate slowing of both motor and sensory conduction, and tests of vibration sensitivity and thermal thresholds are abnormal. A diffuse small-fibre neuropathy causes altered perception of pain and temperature, and is associated with symptomatic autonomic neuropathy; characteristic features include foot ulcers and Charcot neuroarthropathy. Asymmetrical motor diabetic neuropathy Sometimes called diabetic amyotrophy, this presents as severe and progressive weakness and wasting of the proximal muscles of the lower (and occasionally the upper) limbs. It is commonly accompanied by severe pain, felt mainly on the anterior aspect of the leg, and hyperaesthesia and paraesthesiae. Sometimes there may also be marked loss of weight (‘neuropathic cachexia’). The patient may look extremely ill and be unable to get out of bed. Tendon reflexes may be absent on the affected side(s). Sometimes there are extensor plantar responses and the cerebrospinal fluid protein is often raised. This condition is thought to involve acute infarction of the lower motor neurons of the lumbosacral plexus. Other lesions involving this plexus, such as neoplasms and lumbar disc disease, must be excluded. Although recovery usually occurs within 12 months, some deficits are permanent. Management is mainly supportive. and stocking’ impairment of all other modalities of sensation (Fig. 20.23), and loss of tendon reflexes in the lower limbs. In symptomatic patients, sensory abnormalities are predominant. Symptoms include paraesthesiae in the feet (and, rarely, in the hands), pain in the lower limbs (dull, aching and/or lancinating, worse at night, and felt mainly on the anterior aspect of the legs), burning sensations in the soles of the feet, cutaneous hyperaesthesia and, when severe, an abnormal gait (commonly wide-based), often associated with a sense of numbness in the feet. Weakness and atrophy, in particular of the interosseous muscles, develops, leading to structural changes in the foot with loss of lateral and transverse arches, clawing of the toes and exposure of the metatarsal heads. This results in increased 20.40 Classification of diabetic neuropathy Somatic • Polyneuropathy: Symmetrical, mainly sensory and distal Asymmetrical, mainly motor and proximal (including amyotrophy) • Mononeuropathy (including mononeuritis multiplex) Visceral (autonomic) • Cardiovascular • Gastrointestinal • Genitourinary • Sudomotor • Vasomotor • Pupillary Fig. 20.23 Diabetic foot disease. Patients with diabetes can have neuropathy, peripheral vascular disease or both. Clawing of the toes is thought to be caused by intrinsic muscle atrophy and subsequent imbalance of muscle function, and causes greater pressure on the metatarsal heads and pressure on flexed toes, leading to increased callus and risk of ulceration. A Charcot foot occurs only in the presence of neuropathy, and results in bony destruction and ultimately deformity (this X-ray shows a resulting ‘rocker bottom foot’). The angiogram reveals disease of the superficial femoral arteries (occlusion of the left and stenosis of the right). Insets (Proximal arterial occlusion) From http://emedicine.medscape.com/article/460178-overview#a0104; (Toe clawing) Bowker JH, Pfeifer MA. Levin and O’Neal’s The diabetic foot, 7th edn. Philadelphia: Mosby, Elsevier Inc.; 2008; (Neuropathic foot ulcer) Levy MJ, Valabhji J. Vascular II: The diabetic foot. Surgery 2008; 26:25–28; (Digital gangrene) Swartz MH. Textbook of physical diagnosis, 5th edn. Philadelphia: WB Saunders, Elsevier Inc.; 2006. Glove and stocking neuropathy Clawing of toes Digital gangrene Neuropathic ulcer Dry, cracked skin Callus Loss of leg hair

Peripheral vascular disease Peripheral neuropathy Charcot foot Proximal arterial occlusion Absent pulses Cold feet

760 • DIABETES MELLITUS Gastroparesis Gastroparesis is diagnosed when there is an objectively measured delay in gastric emptying in the absence of mechanical obstruction. It is most commonly a manifestation of autonomic neuropathy in diabetes, but can occur with eating disorders such as anorexia nervosa or bulimia that are also associated with diabetes. Prevalence rates are estimated to be approximately 5% in type 1 diabetes and 1% in type 2 diabetes. The main symptoms are chronic nausea, vomiting (especially of undigested food), abdominal pain and a feeling of fullness/early satiety. Diagnosis is most commonly made by 99m-technetium scintigraphy following a solid-phase meal with standard imaging over 4 hours. In this test it is important to recognise that high glucose levels can delay gastric emptying and so every attempt should be made to conduct the test when glucose levels are below 15 mmol/L (270 mg/dL). Other tests include upper gastrointestinal endoscopy, wireless motility capsules and breath testing (pp. 774, 776 and 777). Management is difficult, with glucose levels directly impacting on gastric motility and, conversely, gastroparesis affecting absorption of ingested carbohydrate. Insulin pump therapy may be especially useful in this context; patients on conventional injection therapy may benefit from injecting rapid-acting insulin after a meal rather than before. Recommended dietary changes include following low-fibre and low-residue diets, as well as eating smaller amounts more frequently. Enteral nutrition is rarely required unless gastroparesis is very severe. Recommended pharmacological and interventional therapy is shown in Box 20.43. Erectile dysfunction Erectile failure (impotence) affects 30% of diabetic males and is often multifactorial. Although neuropathy and vascular causes are common, psychological factors, including depression, anxiety and reduced libido, may be partly responsible. Alcohol and antihypertensive drugs, such as thiazide diuretics and β-adrenoceptor antagonists (β-blockers), may cause sexual dysfunction and in some patients there may be an endocrine 20.41 Clinical features of autonomic neuropathy Cardiovascular • Postural hypotension • Resting tachycardia • Fixed heart rate Gastrointestinal • Dysphagia, due to oesophageal atony • Abdominal fullness, nausea and vomiting, unstable glycaemia, due to delayed gastric emptying (‘gastroparesis’) • Nocturnal diarrhoea ± faecal incontinence • Constipation, due to colonic atony Genitourinary • Difficulty in micturition, urinary incontinence, recurrent infection, due to atonic bladder • Erectile dysfunction and retrograde ejaculation Sudomotor • Nocturnal sweats without hypoglycaemia • Gustatory sweating • Anhidrosis; fissures in the feet Vasomotor • Feet feel cold, due to loss of skin vasomotor responses • Dependent oedema, due to loss of vasomotor tone and increased vascular permeability • Bulla formation Pupillary • Decreased pupil size • Resistance to mydriatics • Delayed or absent reflexes to light Mononeuropathy Either motor or sensory function can be affected within a single peripheral or cranial nerve. Unlike the gradual progression of distal symmetrical and autonomic neuropathies, mononeuropathies are severe and of rapid onset, but they eventually recover. The nerves most commonly affected are the 3rd and 6th cranial nerves (resulting in diplopia), and the femoral and sciatic nerves. Rarely, involvement of other single nerves results in paresis and paraesthesiae in the thorax and trunk (truncal radiculopathies). Nerve compression palsies are more common in diabetes, frequently affecting the median nerve and giving the clinical picture of carpal tunnel syndrome, and less commonly the ulnar nerve. Lateral popliteal nerve compression occasionally causes foot drop. Compression palsies may be more common because of glycosylation and thickening of connective tissue and/or because of increased susceptibility of nerves affected by diabetic microangiopathy. Autonomic neuropathy This is not necessarily associated with peripheral somatic neuropathy. Parasympathetic

or sympathetic nerves may be predominantly affected in one or more visceral systems. The resulting symptoms and signs are listed in Box 20.41 and tests of autonomic function in Box 20.42. The development of autonomic neuropathy is related to poor metabolic control less clearly than to somatic neuropathy, and improved control rarely results in improved symptoms. Within 10 years of developing overt symptoms of autonomic neuropathy, 30–50% of patients are dead, many from sudden cardiorespiratory arrest. Patients with postural hypotension (a drop in systolic pressure of 30 mmHg or more on standing from the supine position) have the highest subsequent mortality. 20.42 How to test cardiovascular autonomic function Simple reflex tests Normal Borderline Abnormal Heart rate responses To Valsalva manœuvre (15 secs)1: ratio of longest to shortest R–R interval ≥ 1.21 ≤ 1.20 To deep breathing (6 breaths over 1 min): maximum– minimum heart rate ≥ 15 11–14 ≤ 10 To standing after lying: ratio of R–R interval of 30th to 15th beats ≥ 1.04 1.01–1.03 ≤ 1.00 Blood pressure response2 To standing: systolic blood pressure fall (mmHg) ≤ 10 11–29 ≥ 30 Specialised tests • Heart rate and blood pressure responses to sustained handgrip • Heart rate variability using power spectral analysis of ECG monitoring • Heart rate and blood pressure variability using time–domain analysis of ambulatory monitoring • MIBG (meta-iodobenzylguanidine) scan of the heart 1Omit in patients with previous laser therapy for proliferative retinopathy. 2Avoid arm with arteriovenous fistula in dialysed patients.

(p. 502 and Fig. 20.23); with infection is a secondary phenomenon following disruption of the protective epidermis. Most ulcers develop at the site of a plaque of callus skin, beneath which tissue necrosis occurs and eventually breaks through to the surface. In many cases, multiple components are involved but sometimes neuropathy or ischaemia predominates (Box 20.44). Ischaemia alone accounts for a minority of foot ulcers in diabetic patients, with most being either neuropathic or neuro-ischaemic. Charcot neuroarthropathy is a progressive condition affecting the bones and joints of the foot; it is characterised by early inflammation and then joint dislocation, subluxation and pathological fractures of the foot of neuropathic patients, often resulting in debilitating deformity (Fig. 20.23 and p. 720). Charcot neuroarthropathy can arise in any condition that causes neuropathy (including syphilis, spinal cord injury, syringomyelia etc.) but diabetes is the most common cause. The pathophysiological mechanisms remain poorly understood but may involve unperceived trauma, leading to progressive destruction (the ‘neurotraumatic’ theory) and/or increased blood flow that results in a mismatch of bone destruction and synthesis (the ‘neurovascular’ theory). More recent evidence points to disordered inflammation mediated via the nuclear factor kappa B (NFκB)/receptor activator of NFκB ligand (RANKL) pathway, opening the way for trials of the RANKL inhibitor denosumab (p. 1048). Management Management can be divided into primary prevention and treatment of an active problem. All patients should be educated in preventative measures (Box 20.45). The feet of people with diabetes should be screened annually, following the steps listed on page 721. Two simple tests are required to grade risk: a 10 g monofilament should be used to assess sensation at five points on each foot, and foot pulses should be palpated (dorsalis pedis and/or posterior tibial). Combined with the clinical scenario, these tests guide appropriate referral and monitoring (Fig. 20.24). Removal of callus skin with a scalpel is best done by a podiatrist who has specialist training and experience in diabetic foot problems. Foot ulcer Once a foot ulcer develops, patients should ideally be referred to a multidisciplinary foot team, involving a diabetes specialist, a podiatrist, a vascular surgeon and an orthotist. Treatment involves: débridement of dead tissue; prompt, often prolonged, treatment with

antibiotics if required, as infection can accelerate tissue necrosis and lead to gangrene; and pressure relief using customised insoles, specialised orthotic footwear and sometimes total contact plaster cast or an irremovable aircast boot. If an ulcer cause, such as testosterone deficiency or hyperprolactinaemia. For further information, see page 440. Management Management of neuropathies is outlined in Box 20.43. The diabetic foot The foot is a frequent site of complications in patients with diabetes and for this reason foot care is particularly important. Tissue necrosis in the feet is a common reason for hospital admission in diabetic patients. Treatment of the foot complications of diabetes accounts for more inpatient days than any other diabetes-related complication. Aetiology Foot ulceration occurs as a result of trauma (often trivial) in the presence of neuropathy and/or peripheral vascular disease 20.44 Clinical features of the diabetic foot Neuropathy Ischaemia Symptoms None Paraesthesiae Pain Numbness None Claudication Rest pain Structural damage Ulcer Sepsis Abscess Osteomyelitis Digital gangrene Charcot joint Ulcer Sepsis Gangrene Gastroparesis • Dopamine antagonists (metoclopramide, domperidone) • Erythromycin • Botulinum toxin • α-adrenoceptor agonist (midodrine) • Gastric pacemaker; percutaneous enteral (jejunal) feeding (see Fig. 19.10, p. 708) • Clonidine • Octreotide Diarrhoea (p. 783) • Loperamide • Broad-spectrum antibiotics Constipation • Stimulant laxatives (senna) Atonic bladder • Intermittent self-catheterisation (p. 1093) Excessive sweating • Anticholinergic drugs (propantheline, poldine, oxybutinin) • Clonidine • Topical antimuscarinic agent (glycopyrrolate cream) Erectile dysfunction (p. 440) • Phosphodiesterase type 5 inhibitors (sildenafil, vardenafil, tadalafil) – oral • Dopamine agonist (apomorphine) – sublingual • Prostaglandin E1 (alprostadil) – injected into corpus cavernosum or intra-urethral administration of pellets • Vacuum tumescence devices • Implanted penile prosthesis • Psychological counselling; psychosexual therapy (NSAIDs = non-steroidal anti-inflammatory drugs) 20.43 Management options for peripheral sensorimotor and autonomic neuropathies Pain and paraesthesiae from peripheral somatic neuropathies • Intensive insulin therapy (strict glycaemic control) • Anticonvulsants (gabapentin, pregabalin, carbamazepine, phenytoin) • Tricyclic antidepressants (amitriptyline, imipramine) • Other antidepressants (duloxetine) • Substance P depleter (capsaicin – topical) • Opiates (tramadol, oxycodone) • Membrane stabilisers (mexiletine, IV lidocaine) • Antioxidant (α-lipoic acid) Postural hypotension • Support stockings • Fludrocortisone • NSAIDs

 of weight-bearing on the affected foot. The rationale is that if no pressure is applied through the foot, the destructive process involving the bones will not result in significant deformity when the acute inflammatory process subsides. Immobilisation is often achieved by a total contact plaster cast or ‘aircast’ boot. The acute phase frequently lasts 3–6 months and sometimes longer. In the post-acute phase, there is consolidation and remodelling of fracture fragments, eventually resulting in a stable foot. Further information Books and journal articles Diabetes Control and Complications Trial Research Group. The effect of intensive treatment of diabetes on the development and progression of long-term complications in insulin-dependent diabetes mellitus. N Engl J Med 1993; 329:977–986. Nathan DM, Cleary PA, Backlud JY, et al. Diabetes Control and Complications Trial/Epidemiology of Diabetes Interventions and Complications (DCCT/EDIC) Study Research Group. Intensive diabetes treatment and cardiovascular disease in patients with type 1 diabetes. N Engl J Med 2005; 353:2643–2653. UK Prospective Diabetes Study (UKPDS) Group. Intensive bloodglucose control with sulphonylureas or insulin compared with conventional treatment and risk of complications in patients with type 2 diabetes (UKPDS 33). Lancet 1998; 352:837–853, 854–865. Websites cdc.gov/diabetes/ Diabetes Public Health Resource. Useful American site with resources for patients and health-care professionals. diabetes.org American Diabetes Association. Includes information on research and advocacy issues.

diabetes.org.uk Diabetes UK. Includes information for patients and leaflets. idf.org International Diabetes Federation. Useful information on international aspects of care and education. joslin.org Joslin Diabetes Center. Well-written resource for patients and health-care professionals, and information on diabetes research. mydiabetesmyway.scot.nhs.uk An interactive diabetes website for patients with diabetes and their carers. ndei.org National Diabetes Education Initiative. Web-based education for health-care professionals, including case studies and slides. is neuro-ischaemic, a vascular assessment is often carried out, by ultrasound or angiography, as revascularisation by angioplasty or surgery may be required to allow the ulcer to heal. In cases of severe secondary infection or gangrene, an amputation may be required. This can be limited to the affected toe or involve more extensive limb amputation. Charcot neuroarthropathy Acute Charcot neuroarthropathy almost always presents with signs of inflammation – a hot, red, swollen foot. The initial X-ray may show bony destruction but is often normal. As about 40% of patients with a Charcot joint also have a foot ulcer, it can be difficult to differentiate from osteomyelitis. Magnetic resonance imaging (MRI) of the foot is often helpful. The mainstay of treatment for an active Charcot foot is immobilisation and, ideally, avoidance Fig. 20.24 Risk assessment and management of foot problems in diabetes. Adapted from Scottish Intercollegiate Guidelines Network (SIGN) guideline number 116. Moderate Low High Active Urgent referral to specialist team Current foot ulcer, infection, critical ischaemia, gangrene or unexplained hot, red swollen foot Previous foot ulcer or amputation Sensation impaired and foot pulses absent Skin callus or foot deformity? Yes No Inability to selfcare for feet Sensation impaired or foot pulses absent Sensation unimpaired and foot pulses present Annual assessment by specialist podiatrist Annual assessment by podiatrist Annual screening by health-care professional Management Screening • Check footwear for foreign bodies • Wear suitable, well-fitting shoes • Cover minor cuts with sterile dressings • Do not burst blisters • Avoid over-the-counter corn/ callus remedies Moderate- and high-risk patients As above plus: • Do not attempt corn removal • Avoid high and low temperatures Podiatric care • A podiatrist is an integral part of the diabetes team to ensure regular and effective podiatry and to educate patients in care of the feet Orthotic footwear • Specially manufactured and fitted orthotic footwear is required to prevent recurrence of ulceration and to protect the feet of patients with Charcot neuroarthropathy 20.45 Care of the feet in patients with diabetes Preventative advice All diabetic patients • Inspect feet every day • Wash feet every day • Moisturise skin if dry • Cut or file toenails regularly • Change socks or stockings every day • Avoid walking barefoot

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