Diabetes mellitus

Diabetes mellitus is caused by an absolute or relative insulin deficiency. It has been defined by the World Health Organization (WHO), on the basis of laboratory findings, as a fasting venous plasma glucose concentration of 7.0 mmol/L or more (on more than one occasion or once in the presence of diabetes symptoms) or a random venous plasma glucose concentration of 11.1 mmol/L or more. Sometimes an oral glucose tolerance test (OGTT) may be required to establish the diagnosis in equivocal cases. The interpretation of this test is shown below, but, briefly, diabetes mellitus can be diagnosed if the venous plasma glucose concentration is 7.0 mmol/L or more (fasting) and/or 11.1 mmol/L or more 2 h after the oral ingestion of the equivalent of 75 g of anhydrous glucose. Diabetes mellitus can be classified into the following categories.

Type 1 diabetes mellitus

Previously called insulin-dependent diabetes mellitus, this is the term used to describe the condition in patients for whom insulin therapy is essential because they are prone to develop ketoacidosis. It usually presents during childhood or adolescence. Most of these cases are due to immune-mediated processes and may be associated with other autoimmune disorders such as Addison's disease, vitiligo and Hashimoto's thyroiditis. It has been suggested that many cases follow a viral infection that has damaged the β-cells of the pancreatic islets. Individuals most at risk are those with human leucocyte antigen (HLA) types DR3 and DR4 of the major histocompatibility complex. Autoantibodies to islet cells, insulin, tyrosine phosphatases IA-2 and IA-2β and glutamic decarboxylase (GAD) are found in about 90 per cent of cases. There is a form of type 1 diabetes called idiopathic diabetes mellitus that is not autoimmune mediated but is strongly inherited and more common in black and Asian people. The insulin requirement of affected people can fluctuate widely and the cause is unknown. There is also LADA (latent autoimmune diabetes of adults), sometimes called slow-onset type 1 diabetes.

Type 2 diabetes mellitus

Previously called non-insulin-dependent diabetes mellitus, this is the most common variety worldwide (about 90 per cent of all diabetes mellitus cases). Patients are much less likely to develop ketoacidosis than those with type 1 diabetes, although insulin may sometimes be needed. Onset is most usual during adult life; there is a familial tendency and an association with obesity. There is a spectrum of disorders ranging from mainly insulin resistance with relative insulin deficiency to a predominantly secretory defect with insulin resistance.

Other specific types of diabetes mellitus

A variety of inherited disorders may be responsible for the syndrome, either by reducing insulin secretion or by causing relative insulin deficiency because of resistance to its action or of insulin receptor defects, despite high plasma insulin concentrations.

Genetic defects of β-cell function

- Maturity-onset diabetes of the young (MODY):
  - MODY 1: mutation of the hepatocyte nuclear factor (*HNF4A*) gene,
  - MODY 2: mutation of the glucokinase gene,
  - MODY 3: mutation of the *HNF1A* gene.

Some cases are thought to be point mutations in mitochondrial deoxyribonucleic acid (DNA) associated with diabetes mellitus and deafness and are usually autosomal dominant.

Genetic defects of insulin action

- Type A insulin resistance (insulin receptor defect), for example leprechaunism, lipoatrophy and Rabson–Mendenhall syndrome.

Insulin deficiency due to pancreatic disease

- Chronic pancreatitis.
- Pancreatectomy.
- Haemochromatosis.
- Cystic fibrosis.

Endocrinopathies

- Relative insulin deficiency, due to excessive GH (acromegaly), phaeochromocytoma, glucocorticoid secretion (Cushing's syndrome).

Drugs

- Thiazide diuretics.
- Interferon-α.
- Glucocorticoids.

Infections

- Septicaemia.
- Congenital rubella.
- Cytomegalovirus.

Rare forms of autoimmune-mediated diabetes

- Anti-insulin receptor antibodies.
- Stiff man syndrome, with high levels of GAD autoantibodies.

Genetic syndromes associated with diabetes

- Down's syndrome.
- Turner's syndrome.
- Klinefelter's syndrome.
- Myotonic dystrophy.

Gestational diabetes mellitus

In the UK, about 4–5 per cent of pregnancies are complicated by gestational diabetes mellitus (GDM). It is associated with increased fetal abnormalities, for example high birthweight, cardiac defects and polyhydramnios. In addition, birth complications, maternal hypertension and the need for caesarean section may occur. If maternal diet/lifestyle factors fail to restore glucose levels, insulin is usually required to try to reduce the risk of these complications.

Women at high risk for GDM include those who have had GDM before, have previously given birth to a high-birthweight baby, are obese, have a family history of diabetes mellitus and/or are from high-risk ethnic groups, for example black or South Asian. These women should be screened at the earliest opportunity and, if normal, retested at about 24–28 weeks, as glucose tolerance progressively deteriorates throughout pregnancy. In some units 50 g oral glucose is used and the blood glucose is sampled at 1 h – plasma glucose of more than or equal to 7.8 mmol/L being diagnostic (O'Sullivan's screening test for gestational diabetes). If fasting venous plasma glucose is 7.0 mmol/L or more and/or the random measurement gives a concentration of 11.1 mmol/L or more (some doctors prefer to use a lower cut-off of about 9.0 mmol/L in pregnancy), the woman has GDM. In equivocal cases, an OGTT is indicated. Six weeks post partum, the woman should be reclassified with a repeat OGTT.

Impaired glucose tolerance

The WHO definition of impaired glucose tolerance (IGT) is a fasting venous plasma glucose concentration of less than 7.0 mmol/L and a plasma glucose concentration between 7.8 mmol/L and 11.1 mmol/L 2 h after an OGTT. Some patients with IGT develop diabetes mellitus later and may require an annual OGTT to monitor for this. However, because of the increased risk of vascular complications, secondary causes of IGT should be sought, dietary advice given, if necessary, and the patient followed up. In pregnancy IGT is treated as GDM because of the risks to the fetus.

Impaired fasting glucose

Impaired fasting glucose (IFG), like IGT, refers to a metabolic stage intermediate between normal glucose homeostasis and diabetes mellitus. The definition is that the fasting venous plasma glucose is 6.1 mmol/L or more but less than 7.0 mmol/L, and less than 7.8 mmol/L 2 h after an OGTT.

Subjects at risk of developing diabetes mellitus

A strong family history of diabetes mellitus may suggest that an individual is at risk of developing diabetes mellitus (particularly type 2), as may a family history of GDM, IGT or IFG. Those with predisposing HLA types and autoimmune disease may be susceptible to developing type 1 diabetes. Type 2 diabetes is more common in certain racial groups, such as Afro-Caribbeans, South Asians and Pacific Islanders. One of the reasons why type 2 diabetes is on the increase is the increasing tendency to obesity and central adiposity in urbanized and more sedentary populations consuming high-calorie diets.

The thrifty phenotype (Barker–Hales) hypothesis proposes that nutritional deficiency in fetal and early infancy associated with low birthweight increases the risk of developing type 2 diabetes and insulin resistance.

Insulin resistance syndrome or metabolic syndrome

It has been recognized that certain coronary heart disease risk factors occur together. There is an aggregation of lipid and non-lipid risk factors of metabolic origin. A particular cluster is known as the metabolic syndrome, syndrome X or Reaven's syndrome and is closely linked to insulin resistance. One definition is the presence of three or more of the following features:

- Abdominal obesity (waist circumference):
  - male more than 102 cm (40 in),
  - female more than 88 cm (35 in).
- Fasting plasma triglycerides more than 1.7 mmol/L.
- Fasting plasma high-density lipoprotein (HDL) cholesterol:
  - male less than 1.0 mmol/L,
  - female less than 1.3 mmol/L,
- Blood pressure more than or equal to 130/85 mmHg.
- Fasting blood glucose more than 5.5 mmol/L.

Plasma levels of insulin would be expected to be raised, that is, hyperinsulinaemia. Other associated features may include polycystic ovary syndrome, fatty liver, raised fibrinogen and plasminogen activator inhibitor 1 concentrations, renal sodium retention, hyperuricaemia and dense low-density lipoprotein (LDL) particles (see Chapter 13).

Metabolic features of diabetes mellitus

Patients with type 1 diabetes tend to be diagnosed before the age of 40 years, are usually lean and have experienced weight loss at the time of presentation. They may present with diabetic ketoacidosis. Conversely, patients with type 2 diabetes often present later, usually after the age of 40 years, and are often overweight or obese. The presentation can be insidious and they may have had diabetes years before diagnosis.

Hyperglycaemia

If plasma glucose concentration exceeds about 10 mmol/L, glycosuria would be expected. High urinary glucose concentrations produce an osmotic diuresis and therefore polyuria. Cerebral cellular dehydration due to hyperosmolality, secondary to hyperglycaemia, causes thirst (polydipsia). A prolonged osmotic diuresis may cause excessive urinary electrolyte loss. These 'classic' symptoms are suggestive of diabetes mellitus.

Diabetic patients on insulin may show the following conditions. The 'dawn' phenomenon is the physiological response of the elevation of blood glucose concentration in the early morning prior to breakfast due to nocturnal spikes in GH concentration and a rise in plasma cortisol concentration that increase hepatic gluconeogenesis. Conversely, in some diabetic patients nocturnal hypoglycaemia may evoke a rebound counter-regulatory hyperglycaemia called the Somogyi phenomenon. Patient blood glucose checking at 02.00–04.00 h, or continuous glucose monitoring if available, may distinguish these conditions, as the Somogyi phenomenon reveals hypoglycaemia. It is sometimes possible to ameliorate these conditions by giving intermediate-acting insulin before bedtime.

Abnormalities in lipid metabolism

These may be secondary to insulin deficiency. Lipolysis is enhanced and plasma NEFA concentrations rise. In the liver, NEFAs are converted to acetyl CoA and ketones, or are re-esterified to form endogenous triglycerides and incorporated into VLDLs; the latter accumulate in plasma because lipoprotein lipase, which is necessary for VLDL catabolism, requires insulin for optimal activity. High-density lipoprotein cholesterol concentration tends to be low in type 2 diabetes. If insulin deficiency is very severe, there may also be chylomicronaemia. The rate of cholesterol synthesis is also increased, with an associated increase in plasma LDL concentrations. Consequently, patients with diabetes may show high plasma triglyceride, raised cholesterol and low HDL cholesterol concentrations.

Long-term effects of diabetes mellitus

Vascular disease is a common complication of diabetes mellitus. Macrovascular disease due to abnormalities of large vessels may present as coronary artery, cerebrovascular or peripheral vascular insufficiency. The condition is probably related to alterations in lipid metabolism and associated hypertension. The most common cause of death is cardiovascular disease, including myocardial infarction.

Microvascular disease due to abnormalities of small blood vessels particularly affects the retina (diabetic retinopathy) and the kidney (nephropathy); both may be related to inadequate glucose control. Diabetes is one of the most common causes of patients requiring renal dialysis. Microvascular disease of the kidney is associated with proteinuria.

Kidney disease is associated with several abnormalities, including proteinuria and progressive renal failure. Diffuse nodular glomerulosclerosis (Kimmelstiel–Wilson lesions) may cause the nephrotic syndrome. The presence of small amounts of albumin in the urine (microalbuminuria) is associated with an increased risk of developing progressive renal disease, which may sometimes be prevented by more stringent plasma glucose and blood pressure control. The renal complications may be partly due to the increased glycation of structural proteins in the arterial walls supplying the glomerular basement membrane; similar vascular changes in the retina may account for the high incidence of diabetic retinopathy. Glycation of protein in the lens may cause cataracts.

Infections are also more common in diabetic patients, for example urinary tract or chest infections, cellulitis and candida. Diabetic neuropathy can occur, which can be peripheral symmetric sensory, peripheral painful, acute mononeuropathies or autonomic. It has been suggested that sorbitol is implicated in the aetiology of diabetic neuropathy through the action of aldolase reductase. Erectile dysfunction is also relatively common and in some cases may be partly neurologically mediated.

Diabetic ulcers, for example of the feet, can lead to gangrene and amputation. The ulcers can be ischaemic, neuropathic or infective. The joints can also be affected, for example Charcot's joints. Other features of diabetes mellitus are skin disorders, such as necrobiosis lipoidica, and abscesses.

Principles of management of diabetes mellitus

The management of diabetes mellitus is considered briefly, although consulting a specialist text is

recommended if further information is required. Insulin requirements vary in patients with type 1 diabetes. For example, the dose may need to be increased during any illness or during pregnancy and reduced if there is increased activity or meals are missed.

In patients with type 2 diabetes, plasma glucose concentrations may be controlled by diet, associated with weight reduction, and increased physical activity, but insulin may be required during periods of stress or pregnancy. In this group insulin secretion can be stimulated by the sulphonylurea drugs, such as gliclazide, glipizide, glibenclamide or glimepiride. Biguanides, usually metformin, can also be used and are particularly useful in obese patients. Metformin decreases intestinal glucose absorption and hepatic gluconeogenesis as well as increasing tissue insulin sensitivity. Metformin can inhibit oxidative phosphorylation, which can, under certain circumstances, lead to lactic acid accumulation. Acarbose delays post-prandial absorption of glucose by inhibiting α-glucosidase.

Other oral agents are the thiazolidinediones or 'glitazones', for example rosiglitazone and pioglitazone, which activate γ-peroxisome proliferator-activated receptors and which can reduce insulin resistance by a number of metabolic pathways, some of which involve increasing the transcription of nuclear proteins that control free fatty acid and tissue glucose uptake. Repaglinide is a meglitinide that increases insulin release from pancreatic β-cells and enhances tissue insulin sensitivity. The incretins are gastrointestinal hormones that increase insulin release from the pancreas after eating, for example glucagon-like peptide (GLP-1) and gastric inhibitory peptide (GIP). They are rapidly inactivated by the enzyme dipeptidyl peptidase-4 (DPP-4). Incretin mimetics such as exenatide or liraglutide or DPP-4 inhibitors such as sitagliptin, vildagliptin or saxagliptin are being used in type 2 diabetes mellitus..

It is now recognized that diabetes mellitus is not just a glucose disorder. It is important also to optimize abnormal plasma lipids (see Chapter 13) and correct hypertension, particularly if there is microalbuminuria or proteinuria (see Chapter 19).

Monitoring of diabetes mellitus

Glycosuria

Glycosuria can be defined as a concentration of urinary glucose detectable using relatively insensitive, but specific, screening tests. These tests often depend on the action of an enzyme, such as glucose oxidase, incorporated into a diagnostic strip. Usually, the proximal tubular cells reabsorb most of the glucose in the glomerular filtrate. Glycosuria, as defined above, occurs only when the plasma, and therefore glomerular filtrate, concentrations exceed the tubular reabsorptive capacity. This may be because the plasma and glomerular filtrate concentrations are more than about 10 mmol/L, and therefore the normal tubular reabsorptive capacity is significantly exceeded. Very rarely, if the glomerular filtration rate is much reduced, there may be no glycosuria despite plasma glucose concentrations more than 10 mmol/L. A diagnosis of diabetes mellitus should *never* be made on the basis of glycosuria.

Blood glucose

Blood glucose concentrations may be measured using glucose testing reagent strips. The colour change of the strip can be assessed visually or by using a portable glucose meter and the reaction often involves an enzyme determination of glucose, for example glucose oxidase. Meters should ideally be overseen by laboratory staff expert in point of care testing (see Chapter 30). Although the measurement of blood glucose concentrations involves the discomfort of several skin punctures, many motivated patients are able to adjust their insulin dose more accurately based on these results than on those obtained by testing their urine. This method of testing is also useful in the detection of hypoglycaemia. For patients who do not like blood testing, urinary glucose testing can be used, but of course cannot detect hypoglycaemia and is dependent on the renal glucose threshold.

Glycated haemoglobin

Glycated haemoglobin (HbA_{1c}) is formed by non-enzymatic glycation of haemoglobin and is dependent on the mean plasma glucose concentrations and on the lifespan of the red cell; falsely low values may be found in patients with haemolytic disease. Measurement of blood HbA_{1c} may not reveal potentially dangerous short-term swings and nor does HbA_{1c} detect hypoglycaemic episodes and thus plasma glucose estimations may also be useful.

This was expressed as a percentage of total blood haemoglobin concentration and gives a retrospective assessment of the mean plasma glucose concentration during the preceding 6–8 weeks. The higher the glycated haemoglobin, the poorer the mean diabetic or glycaemic control.

Glycated haemoglobin used to be expressed in percentage units but now is expressed as mmol/mol

and conversion between the units is by the following equation: IFCC-HbA_{1c} (mmol/mol) = [DCCT-HbA_{1c} (%) – 2.15] × 10.929. HbA_{1c} tests are certified by the National Glycohemoglobin Standardization Program (NGSP) to standardize them against the results of the 1993 Diabetes Control and Complications Trial (DCCT) but now are expressed as IFCC (International Federation of Clinical Chemistry) units. Intervention trials for type 1 and type 2 diabetes have shown that trying to optimize glycaemic control, as judged by HbA_{1c}, to about 7 per cent (or above 53 mmol/mol) reduces the risk of microvascular diabetic complications.

Fructosamine

The measurement of plasma fructosamine concentrations may be used to assess glucose control over a shorter time course than that of HbA_{1c} (about 2–4 weeks), but the assay has methodological limitations. Fructosamine reflects glucose bound to plasma proteins, predominantly albumin, which has a plasma half-life of about 20 days but is problematic in patients with hypoalbuminaemia, for example due to severe proteinuria. This assay may sometimes be useful in pregnancy and also if haemoglobin variants, for example HbS or HbC, exist that may interfere with certain HbA_{1c} assays.

Blood ketones

Monitoring of blood ketones may have a place in the home management of type 1 diabetes. A β-hydroxybutyrate below 0.60 mmol/L is normal, whereas values between 0.60 mmol/L and 1.0 mmol/L may necessitate more insulin, and concentrations greater than 1.0 mmol/L a warning to seek medical advice.

Urinary albumin determination and diabetic nephropathy

One of the earliest signs of diabetic renal dysfunction is the development of small amounts of albumin in the urine, called microalbuminuria. Untreated, this can progress to overt albuminuria or proteinuria (more than 300 mg/day), impaired renal function and finally end-stage renal failure.

Microalbuminuria is defined as a urinary albumin excretion of 30–300 mg/day or 20–200 µg/min. An albumin concentration less than 30 mg/day or less than 20 µg/min is defined as normoalbuminuria. A random urine sample or timed overnight collection can be useful to assess urinary albumin excretion, although the standard test is the urinary albumin to creatinine ratio (ACR), which avoids a timed urine collection. This should normally be less than 2.5 g/mol in males and less than 3.5 g/mol in females. An abnormal result should be confirmed in two out of three urine samples in the absence of other causes of proteinuria (see Chapter 19). Apart from being predictive of diabetic renal complications, urinary albumin excretion is also associated with increased vascular permeability and enhanced risk of cardiovascular disease.

Optimization of glycaemic control can slow the progression of microalbuminuria, as can treating hypertension. Some recommend a target blood pressure lower than 140/80 mmHg in type 2 diabetes, or 135/75 mmHg or lower if microalbuminuria is present. The blood pressure targets are usually more aggressive in type 1 diabetes, partly as the lifetime risk of overt nephropathy is greater. Angiotensin-converting enzyme (ACE) inhibitor therapy, such as lisinopril in type 1 diabetic patients with microalbuminuria, can result in a decline in the albumin excretion rate; similar findings have been shown with enalapril in type 2 diabetes. This action of ACE inhibitors is only partially dependent on their blood pressure-lowering ability, and therefore they presumably also have other important renal protective actions. The angiotensin II receptor antagonists (ARAs), for example irbesartan and losartan, have also been shown to have renal protective actions.

Acute metabolic complications of diabetes mellitus

Patients with diabetes mellitus may develop various metabolic complications that require emergency treatment, including coma, and these include the following.

Hypoglycaemia

This is probably the most common cause of coma seen in diabetic patients. Hypoglycaemia is most commonly caused by accidental overadministration of insulin or sulphonylureas or meglitinides. Precipitating causes include too high a dose of insulin or hypoglycaemic drug; conversely, the patient may have missed a meal or taken excessive exercise after the usual dose of insulin or oral hypoglycaemic drugs.

Hypoglycaemia is particularly dangerous, and some patients lack awareness of this; that is to say, they lose warning signs such as sweating, dizziness and headaches. Driving is a major hazard under such circumstances. Patients should monitor their own blood glucose closely, carry glucose preparations to abort severe hypoglycaemia and avoid high-risk activities during which hypoglycaemic attacks could be dangerous.

CASE 1

A 34-year-old woman with known type 1 diabetes mellitus was admitted to hospital following a 'black out' while driving. She had recently increased her insulin dose because she felt unwell with 'flu' but unwisely had missed two meals during the day. The results of some of her biochemistry tests were as follows:

Plasma
Sodium 135 mmol/L (135–145)
Potassium 4.0 mmol/L (3.5–5.0)
Bicarbonate 23 mmol/L (24–32)
Urea 5.4 mmol/L (2.5–7.0)
Creatinine 100 µmol/L (70–110)
Glucose 1.5 mmol/L (5.5–11.1)
pH 7.43 (7.35–7.45)
$Paco_2$ 5.3 kPa (4.6–6.0)
Pao_2 12.1 kPa (9.3–13.3)

DISCUSSION

The blood glucose shows hypoglycaemia, secondary to the patient having increased her insulin dose despite having missed meals. Hypoglycaemia can present with neurological impairment, including impaired memory, loss of consciousness and coma. This can be treated in the emergency situation by giving glucose intravenously to avoid irreversible neurological damage. It is important for patients on insulin to monitor their own blood glucose closely, particularly if they wish to drive.

CASE 2

A 24-year-old woman presented to the casualty department in a coma. The relevant biochemical results were as follows:

Plasma
Sodium 130 mmol/L (135–145)
Potassium 5.9 mmol/L (3.5–5.0)
Bicarbonate 10 mmol/L (24–32)
Chloride 92 mmol/L (95–105)
Glucose 35 mmol/L (5.5–11.1)
pH 7.10 (7.35–7.45)
$Paco_2$ 3.1 kPa (4.6–6.0)
Pao_2 11.1 kPa (9.3–13.3)
Urine was positive for ketones.

DISCUSSION

The patient was shown to have type 1 diabetes mellitus and had presented in diabetic ketoacidosis, with hyperglycaemia, hyponatraemia, hyperkalaemia and a metabolic acidosis.

Diabetic ketoacidosis

Diabetic ketoacidosis may be precipitated by infection, acute myocardial infarction or vomiting. The patient who reasons 'no food, therefore no insulin' could mistakenly withhold insulin. In the absence of insulin, there is increased lipid and protein breakdown, enhanced hepatic gluconeogenesis and impaired glucose entry into cells.

The clinical consequences of diabetic ketoacidosis are due to:

- hyperglycaemia causing plasma hyperosmolality,
- metabolic acidosis,
- glycosuria.

Plasma glucose concentrations are usually in the range 20–40 mmol/L, but may be considerably higher, although euglycaemic diabetic ketoacidosis has been described when plasma glucose concentrations are only slightly elevated.

Hyperglycaemia causes glycosuria and hence an osmotic diuresis. Water and electrolyte loss due to vomiting, which is common in this syndrome, increases fluid depletion. There may be haemoconcentration and reduction of the glomerular filtration rate enough to cause uraemia due to renal circulatory insufficiency. The extracellular hyperosmolality causes a shift of water out of the cellular compartment and severe cellular dehydration occurs. Loss of water from cerebral cells is probably the reason for the confusion and coma. Thus there is both cellular and extracellular volume depletion.

The rate of lipolysis is increased because of decreased insulin activity; more free fatty acids are produced than can be metabolized by peripheral tissues. The free fatty acids are either converted to ketones by the liver or, of less immediate clinical importance, incorporated as endogenous triglycerides into VLDL, sometimes causing severe hypertriglyceridaemia (see Chapter 13).

Hydrogen ions, produced with ketones other than acetone, are buffered by plasma bicarbonate. However, when their rate of production exceeds the rate of bicarbonate generation, the plasma bicarbonate falls. Hydrogen ion secretion causes a fall in urinary pH. The deep, sighing respiration (Kussmaul's respiration)

and the odour of acetone on the breath are classic features of diabetic ketoacidosis.

Plasma potassium concentrations may be raised, secondarily to the metabolic acidosis, before treatment is started. This is due to failure of glucose entry into cells in the absence of insulin and because of the low glomerular filtration rate. Despite hyperkalaemia, there is a total body deficit due to increased urinary potassium loss in the presence of an osmotic diuresis. During treatment, plasma potassium concentrations may fall as potassium re-enters cells, sometimes causing severe hypokalaemia unless potassium is prescribed.

Plasma sodium concentrations may be low (hyponatraemia) or low-normal at presentation, partly because of the osmotic effect of the high extracellular glucose concentration, which draws water from the cells and dilutes the sodium. In the presence of a very high plasma glucose concentration, a normal or raised plasma sodium concentration is suggestive of significant water depletion.

If there is severe hyperlipidaemia, the possibility of pseudohyponatraemia must be considered (see Chapter 2). When insulin is given, gluconeogenesis is inhibited, glucose enters cells and sodium-free water follows along the osmotic gradient. If plasma sodium concentrations rise rapidly, the patient may remain confused or even comatose as long as the plasma osmolality remains significantly raised, despite a satisfactory fall in plasma glucose concentration. This may also occur if isosmolar or stronger saline solutions are given inappropriately.

Hyperphosphataemia followed by hypophosphataemia as plasma phosphate concentrations parallel those of potassium may persist for several days after recovery from diabetic coma. Similarly, hypermagnesaemia can result, partly because of the acidosis.

Plasma and urinary amylase activities may be markedly elevated and, even in the presence of abdominal pain mimicking an 'acute abdomen', do not necessarily indicate acute pancreatitis. In some patients the amylase is of salivary rather than pancreatic origin. Some plasma creatinine assays cross-react with ketones, resulting in a spurious plasma creatinine elevation. Sometimes severe hypertriglyceridaemia and chylomicronaemia result, due to reduced lipoprotein lipase activity in the face of insulin deficiency. A summary of the usual clinical and biochemical findings in a patient presenting with diabetic ketoacidosis is shown in Table 12.4.

Table 12.4 Clinical and biochemical findings in a patient presenting with diabetic ketoacidosis

Findings	Underlying abnormality
Clinical	
Confusion and later coma	Hyperosmolality
Hyperventilation (Kussmaul's respiration)	Metabolic acidosis
Signs of volume depletion	Osmotic diuresis
Biochemical	
Plasma	
Hyperglycaemia	Insulin deficiency
Low plasma bicarbonate	Metabolic acidosis
Initial hyperkalaemia	Intracellular potassium moves out
Mild uraemia	Decreased glomerular filtration rate
Urine	
Glycosuria	Insulin deficiency
Ketonuria	Insulin deficiency

Hyperosmolal non-ketotic coma

In diabetic ketoacidosis there is always plasma hyperosmolality due to the hyperglycaemia, and many of the symptoms, including those of confusion and coma, are related to it. However, the term 'hyperosmolal' coma or 'pre-coma' is usually confined to a condition in which there is marked hyperglycaemia but no detectable ketoacidosis. The reason for these different presentations is not clear. It has been suggested that insulin activity is sufficient to suppress lipolysis but insufficient to suppress hepatic gluconeogenesis or to facilitate glucose transport into cells.

Hyperosmolal non-ketotic (HONK) coma now may be referred to as hyperosmolar hyperglycaemic state (HHS) and may be of sudden onset. It is more common in older patients. Plasma glucose concentrations may exceed 50 mmol/L. The effects of glycosuria are as described above, but hypernatraemia due to predominant water loss is more commonly found than in ketoacidosis and aggravates the plasma hyperosmolality. Cerebral cellular dehydration, which contributes to the coma, may also cause hyperventilation, and a respiratory alkalosis, although sometimes plasma lactic acid may rise, evoking a metabolic acidosis and thus a mixed acid–base disturbance may occur. There may also be an increased risk of thrombosis.

Lactic acidosis

Lactic acidosis can cause a high anion gap metabolic acidosis and coma. It may be due to the use of metformin in certain situations, such as high doses in

the very elderly, those with renal, liver or cardiac failure or those dehydrated or undergoing imaging tests with contrast media (see Chapter 4).

Other causes of coma in patients with diabetes mellitus

In addition to the comas described above, a patient with diabetes mellitus may present with other comas:

- Cerebrovascular accidents are relatively common in diabetic patients because of the increased incidence of vascular disease.
- Diabetic patients can, of course, have any other coma, for example drug overdose.
- Diabetic patients are also more at risk of diabetic nephropathy and renal failure and thus uraemic coma.

The assessment of a diabetic patient presenting in coma or pre-coma is outlined in Table 12.5.

Principles of treatment of diabetic coma

Only the outline of treatment will be discussed. For details of management, the reader should consult a textbook of medical emergencies.

Hypoglycaemia

Hypoglycaemic coma needs prompt glucose replacement to avoid irreversible brain damage, for example 50 mL of 20 per cent glucose intravenously. If intravenous access is not an option, glucagon 1 mg can be given intramuscularly. Once the patient is awake, glucose-containing drinks can be given.

Diabetic ketoacidosis

Repletion of fluid and electrolytes should be vigorous. A 0.9 per cent normal saline solution should be administered, usually 1 L initially and then 1 L over the next hour and then 2 h and repeated at 4 h. Monitoring central venous pressure may be useful to assess fluid replacement. Dextrose–saline may be used when the plasma glucose concentration is less than 15 mmol/L.

If the plasma glucose concentration is more than 20 mmol/L, 10 U soluble insulin should be given. A sliding insulin scale should be instigated. Insulin is given either by continuous intravenous infusion or by intermittent intramuscular injections, as soon as the plasma glucose and potassium concentrations are known. Once the patient is eating, subcutaneous insulin can be given instead.

If the metabolic acidosis is very severe (pH less than 7.0), bicarbonate may be infused, but only until the blood pH rises to between about 7.15 and 7.20. It is unnecessary and often dangerous to correct the plasma bicarbonate concentration completely; it rapidly returns to normal following adequate fluid and insulin therapy. Remember that 8.4 per cent sodium bicarbonate is very hyperosmolar and may cause hypernatraemia and aggravate hyperosmolality. A rapid rise in the blood pH may aggravate the hypokalaemia associated with treatment.

The plasma potassium concentration should be measured before insulin is given. It is almost always raised at presentation due to the metabolic acidosis and reduced glomerular filtration rate, although total body potassium may be decreased. The plasma potassium concentration may fall rapidly once treatment is started, and therefore it should be monitored frequently and potassium given as soon as it starts to fall. Usually 20 mmol/L potassium is given to each litre bag apart from the first litre and provided there is no oliguria or hyperkalaemia. Diabetic ketoacidosis is severe if blood

Table 12.5 Clinical and biochemical features of a diabetic patient presenting in coma

		Laboratory findings				
		Plasma				Urine
Diagnosis	Clinical features	Glucose	Bicarbonate	Lactate	Creatinine	Ketones
Hypoglycaemia	Sweaty, drowsy	Low	N	N	N	Neg
Ketoacidosis	Volume depletion Hyperventilating	High	Low	N	N or up	Pos
Hyperosmolar coma	Volume depletion May be hyperventilating	Very high	N or slightly low	N or up	N or up	Neg
Lactic acidosis	Hyperventilating	Variable	Low	Up	N	Neg
Uraemia	Hyperventilating	Variable	Low	N or up	Up	Neg
Cerebrovascular accident	Neurological	May be raised	May be low	N	N	Neg

N, normal; Neg, negative; Pos, positive.

ketones are greater than 6 mmol/L and the treatment aim is for these to be less than 0.30 mmol/L.

Urinary volume should be monitored; if it fails to rise despite adequate rehydration, further fluid and potassium should be given only if clinically indicated, and then with care. The risk of deep vein thrombosis is increased, in part due to dehydration, and thus heparin 5000 U every 8 h subcutaneously can be given.

Clinical conditions such as infection that may have precipitated the coma should be sought and treated. Frequent monitoring of plasma glucose, potassium and sodium concentrations is essential to assess progress and to detect developing hypoglycaemia, hypokalaemia or hypernatraemia. Acid–base balance should also be assessed.

CASE 3

A 77-year-old man with known type 2 diabetes mellitus presented to the casualty department feeling drowsy. His home blood glucose monitoring had recently averaged about 25 mmol/L and a recent glycated haemoglobin (HbA_{1c}) result obtained by his general practitioner was 12 per cent (108 mmol/mol). The following blood results were returned in hospital:

Plasma

Sodium 160 mmol/L (135–145)
Potassium 5.0 mmol/L (3.5–5.0)
Bicarbonate 21 mmol/L (24–32)
Urea 15 mmol/L (2.5–7.0)
Creatinine 130 µmol/L (70–110)
Glucose 65 mmol/L (5.5–11.1)
Osmolality 380 mmol/kg (285–295)
pH 7.38 (7.35–7.45)
$PaCO_2$ 5.2 kPa (4.6–6.0)
PaO_2 11.8 kPa (9.3–13.3)
Urine was negative for ketones.

DISCUSSION

The patient was found to be in a hyperosmolal non-ketotic (HONK) diabetic coma. Note the severe hyperglycaemia, hypernatraemia and high plasma osmolality and presentation in an elderly patient. HONK coma is associated with type 2 diabetes mellitus. Ketoacidosis is usually absent, as there has been no conversion to ketone metabolism. This is more common in the elderly, and severe dehydration is present and there is an increased risk of thrombotic events and focal neurological signs. Treatment is with careful intravenous rehydration, insulin and heparin.

Hyperosmolal non-ketotic coma

The treatment of HONK coma is similar to that of ketoacidosis. A sudden reduction of extracellular osmolality may be harmful, and it is important to give small doses of insulin to reduce plasma glucose concentrations slowly, for example 1 U/h. These patients are often very sensitive to the action of insulin. Hypo-osmolal solutions are often used to correct volume depletion, but these too should be given slowly. Heparin is usually given, as there is an increased risk of venous thrombosis.

Initial investigation of a diabetic patient presenting in coma

A diabetic patient may be in coma due to hyperglycaemia, hypoglycaemia or any of the causes shown in Tables 12.4 and 12.5. After a thorough clinical assessment, proceed as follows:

- Notify the laboratory that specimens are being taken and ensure that they are delivered promptly. This minimizes delays.
- Take blood immediately for estimation of:
  - glucose,
  - sodium and potassium,
  - urea and creatinine,
  - bicarbonate,
  - arterial blood gases.
- Do a drug screen for aspirin and paracetamol if concomitant drug overdose suspected.
- Determination of plasma lactate will help diagnose a lactic acidosis (see Chapter 4).
- Test a urine sample or blood for ketones.
- A rapid assessment of blood glucose concentration may be obtained using a point-of-care (POCT) device, but results may be dangerously wrong so these should always be checked against the results obtained from the laboratory (see Chapter 30).
- If severe hypoglycaemia is suspected on clinical grounds or because of the results obtained using reagent strips, glucose should be given *immediately* while waiting for the laboratory results. It is less dangerous to give glucose to a patient with hyperglycaemia than to give insulin to a patient with hypoglycaemia.
- The results of point-of-care testing (see Chapter 30) must be interpreted with caution.
- Also look for precipitating causes such as acute myocardial infarction or infection.

Investigation of suspected diabetes mellitus

In most cases a diagnosis can be established from either fasting or random blood glucose determinations. In equivocal cases an OGTT may be required.

Initial investigations

Blood for plasma glucose estimation should be taken if a patient presents with symptoms of diabetes mellitus or glycosuria or if it is desirable to exclude the diagnosis, for example because of a strong family history.

Blood samples may be taken:

- at least 10 h after a fast,
- at random,
- as part of an oral glucose load test.

Diabetes mellitus is confirmed if one of the following is present:

- a fasting venous plasma concentration of 7.0 mmol/L or more on two occasions or once with symptoms,
- a random venous plasma concentration of 11.1 mmol/L or more on two occasions or once with symptoms.

Diabetes mellitus is unlikely if the fasting venous plasma glucose concentration is less than 5.5 mmol/L on two occasions. Samples taken at random times after meals are less reliable for excluding than for confirming the diagnosis.

The indications for performing an OGTT to diagnose diabetes mellitus may include:

- fasting venous plasma glucose concentration between 5.5 mmol/L and less than 7.0 mmol/L – this is debatable as the WHO recommends an OGTT only if fasting plasma glucose is greater than 6.0 mmol/L,
- random venous plasma concentration between 7.0 mmol/L and less than 11.1 mmol/L,
- a high index of clinical suspicion of diabetes mellitus, such as a patient at high risk of gestational diabetes with equivocal blood glucose results.

The OGTT is sometimes also useful in the diagnosis of acromegaly (see Chapter 7).

It has been suggested that an HbA_{1c} of greater than 6.5 per cent is diagnostic of diabetes mellitus, but this is not universally agreed as other factors such as haemoglobin variants and abnormal erythrocyte lifespan may affect HbA_{1c} levels.

Oral glucose tolerance test

Before starting this test, contact your laboratory: local details may vary.

Procedure

The patient should be resting and should not smoke during the test.

The patient fasts overnight (for at least 10 h but not more than 16 h). Water, but no other beverage, is allowed.

A venous sample is withdrawn for plasma glucose estimation. If the glucose concentration is measured in whole blood, the results will be approximately 1.0 mmol/L lower.

A solution containing 75 g of anhydrous glucose in 300 mL of water is hyperosmolar, and not only may cause nausea and occasionally vomiting and diarrhoea, but also, because of delayed absorption, may affect the results of the test. It is therefore more usual to give a solution of a mixture of glucose and its oligosaccharides, because fewer molecules per unit volume have less osmotic effect than the equivalent amount of monosaccharide; the oligosaccharides are all hydrolysed at the brush border, and the glucose immediately enters the cells.

A solution that contains the equivalent of 75 g of anhydrous glucose is: 113 mL of Polycal made up to approximately 300 mL with water.

This solution should be drunk slowly over a few minutes. Further blood is taken 2 h after the ingestion of glucose.

Note that in the investigation of acromegaly, sampling is half-hourly over the 2-h period (see Chapter 7).

Interpretation of the OGTT is shown in Table 12.6. There is controversy as to how best to interpret the OGTT in pregnancy because of the differences in maternal glucose metabolism, as stated earlier.

The following factors may affect the result of the test:

- *Previous diet* No special restrictions are necessary if the patient has been on a normal diet for 3–4 days. However, if the test is performed after a period of carbohydrate restriction, for example as part of a weight-reducing diet, this may cause abnormal glucose tolerance, probably because metabolism is adjusted to the 'fasted state' and so favours gluconeogenesis.
- *Time of day* Most OGTTs are performed in the morning and the reference values quoted are for this time of day. There is evidence that tests performed in the afternoon yield higher plasma glucose concentrations and that the accepted 'reference

Table 12.6 Interpretation of the oral glucose tolerance test (glucose mmol/L); venous plasma preferred

	Venous plasma		Capillary whole blood		Venous whole blood	
	Fasting	2 h	Fasting	2 h	Fasting	2 h
Diabetes mellitus unlikely	<6.1	<7.8	<5.6	<7.8	<5.6	<6.7
Impaired glucose tolerance	<7.0	7.8–11.1	<6.1	7.8–11.1	<6.1	6.7–10.0
Impaired fasting glucose	6.1–6.9	<7.8	5.6–6.0	<7.8	5.6–6.0	<6.7
Diabetes mellitus	≥7.0	≥11.1	≥6.1	≥11.1	≥6.1	≥10.0

values' may not be applicable. This may be due to a circadian variation in islet cell responsiveness.

- *Drug* Steroids, oral contraceptives and thiazide diuretics may impair glucose tolerance.

HYPOGLYCAEMIA (FIG. 12.9)

By definition, hypoglycaemia is present if the plasma glucose concentration is less than 2.5 mmol/L in a specimen collected into a tube containing an inhibitor of glycolysis, for example fluoride oxalate. Blood cells continue to metabolize glucose in vitro, and low concentrations found in a specimen collected without such an inhibitor can be dangerously misleading (pseudohypoglycaemia).

Symptoms of hypoglycaemia may develop at higher concentrations if there has been a rapid fall from a previously raised value, when adrenaline secretion is stimulated and may cause sweating, tachycardia and agitation. As discussed earlier, cerebral metabolism depends on an adequate supply of glucose from ECF, and the symptoms of hypoglycaemia may resemble those of cerebral hypoxia (neuroglycopenia). Faintness, dizziness or lethargy may progress rapidly to coma and, if untreated, permanent cerebral damage or death may occur. Existing cerebral or cerebrovascular disease may aggravate the clinical picture. Whipple's triad is defined as hypoglycaemia, neuroglycopenic symptoms, and relief of these symptoms on raising the blood glucose.

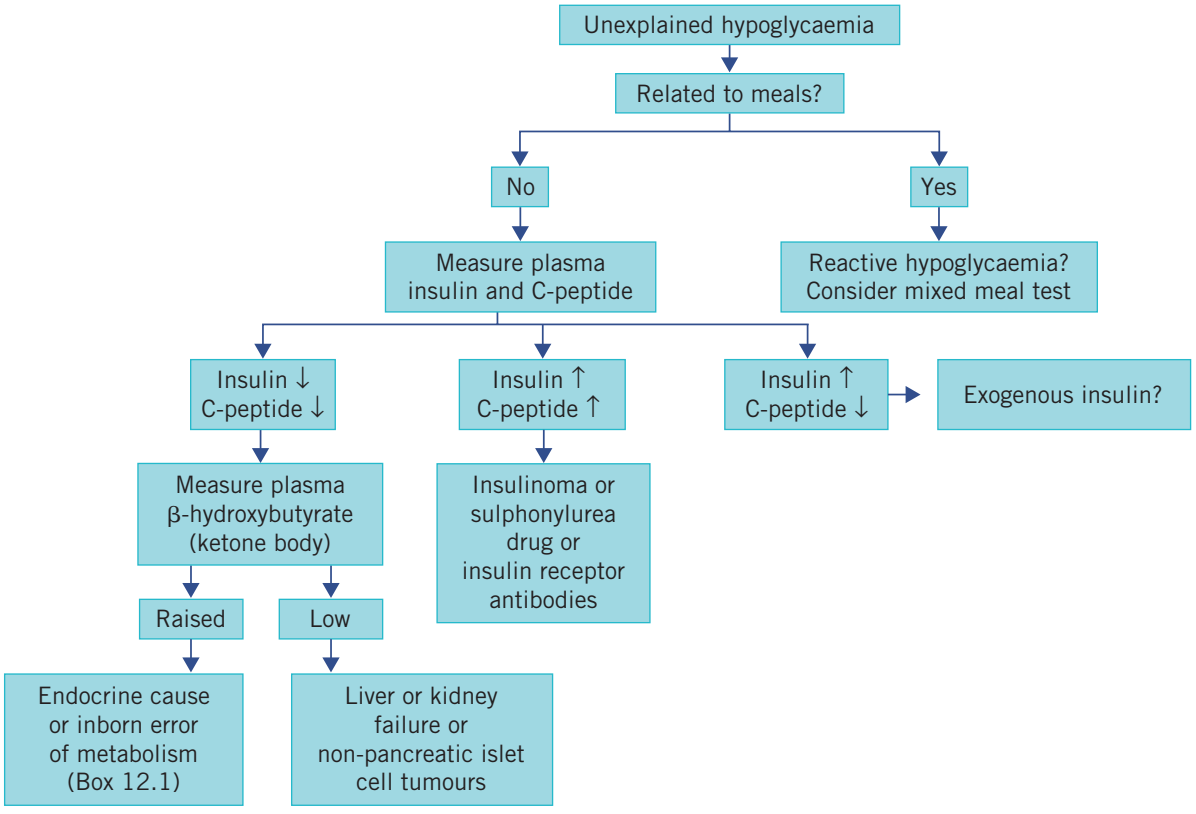

Figure 12.9 Algorithm for the investigation of hypoglycaemia in adults.

Hypoglycaemia is a disease manifestation and not a diagnosis. There is no completely satisfactory classification of its causes. However, one useful approach is to divide hypoglycaemia into (inappropriate) hyperinsulinaemia, (appropriate) hypoinsulinaemia and reactive hypoglycaemia (Box 12.1).

Hypoinsulinaemic hypoglycaemia

Non-pancreatic tumours (non-islet cell tumours)

Although carcinomas (especially of the liver) and sarcomas have been reported to cause hypoglycaemia, this occurs most commonly in association with retroperitoneal tumours of mesenchymal origin, but also with lymphomas, haemangiopericytomas, liver carcinoma and leukaemia. Pleural spindle cell tumours can be associated with a paraneoplastic hypoglycaemia, sometimes called Doege–Potter syndrome. Hypoglycaemia may be the presenting feature. The mechanism is not always clear, but may sometimes be due to the secretion of insulin-like growth factor 2 (IGF-2) or abnormal glycosylated big IGF-2. The IGF-2 suppresses GH and IGF-1. Tumours secreting IGF-2 are characterized by an increased plasma total IGF-2:IGF-1 ratio and low plasma insulin concentration.

Endocrine causes

Hypoglycaemia may occur in hypothyroidism, pituitary or adrenal insufficiency. However, it is rarely the presenting manifestation of these conditions.

Impaired liver function

The functional reserve of the liver is so great that, despite its central role in the maintenance of plasma glucose concentrations, hypoglycaemia is a rare complication of liver disease. It may complicate very severe hepatitis, hypoxic liver disease associated with congestive cardiac failure or liver necrosis if the whole liver is affected. Plasma IGF-1 concentration may be low.

Renal failure

Renal failure can result in hypoglycaemia as the kidney, like the liver, is a gluconeogenic organ.

Hyperinsulinaemic hypoglycaemia

Insulin or other drugs are probably the most common causes. It is most important to take a careful drug history. Unless the facts are deliberately concealed by the patient, the offending drug should be easily identifiable. Hypoglycaemia in a diabetic patient may be caused by accidental insulin overdosage, by changing insulin requirements, or by failure to eat after insulin has been given. Self-administration for suicidal purposes or to gain attention is not unknown, and homicidal use is a remote possibility. Sulphonylureas or meglitinides may also induce hypoglycaemia, especially in the elderly.

Hypoglycaemia due to exogenous insulin suppresses insulin and C-peptide secretion. Measurement of plasma C-peptide concentrations may help to differentiate exogenous insulin administration, when C-peptide secretion is inhibited, from endogenous insulin secretion, when plasma C-peptide is raised, whether it is from an insulinoma or following pancreatic stimulation by sulphonylurea drugs.

An insulinoma is usually a small, histologically benign primary tumour of the islet cells of the pancreas.

Box 12.1 Some causes of hypoglycaemia in adults

Hyperinsulinaemic hypoglycaemia

Inappropriately high insulin concentrations due to:
- Pancreatic tumour – insulinoma
- Hyperplasia of the pancreatic islet cells
- Insulin receptor antibodies
- Autoimmune insulin syndrome
- Exogenous insulin
- Sulphonylureas, meglitinides

Hypoinsulinaemic hypoglycaemia

Endocrine
- Glucocorticoid deficiency/adrenal insufficiency
- Severe hypothyroidism
- Hypopituitarism

Organ failure
- Severe liver disease
- End-stage renal disease
- Severe congestive cardiac failure
- Malaria (particularly if taking quinine)

Some non-pancreatic islet cell tumours
- Insulin-like growth factor (IGF)-2-secreting tumours, e.g. liver, adrenal, breast, mesenchymal, haemangiopericytomas
- Leukaemias, lymphomas, myeloma
- Widespread metastases

Reactive hypoglycaemia

Idiopathic
Post-gastric surgery
Alcohol induced

Miscellaneous causes

Von Gierke's disease (type 1 glycogen storage disease)
Drugs, e.g. salicylates, quinine, haloperidol, pentamidine, sulphonamides

CASE 4

A 45-year-old woman was being investigated in the endocrine unit because of hypoglycaemic episodes, which manifested as sweating and dizzy attacks and which were relieved by sweet drinks. Her renal, liver and thyroid functions were all normal. Some of her fasting biochemical results were as follows:

Plasma
Glucose 2.1 mmol/L (5.5–11.1)
Insulin 168 pmol/L (10–50)
Insulin C-peptide 998 pmol/L (200–650)
A urinary sulphonylurea screen was negative.

DISCUSSION

This patient has raised plasma insulin concentrations in the presence of fasting hypoglycaemia. She was subsequently shown to have an insulinoma. Note the raised plasma insulin and C-peptide concentrations in the presence of hypoglycaemia, suggesting the presence of endogenous insulin secretion (exogenous insulin administration would not be expected to be associated with raised C-peptide concentrations). Her symptoms and their relief by glucose-containing drinks are classic indicators of hypoglycaemic episodes. Insulinomas can be associated with multiple endocrine neoplasia (MEN) syndrome, which should be excluded.

It may present at any age. Multiple tumours may occur and may be part of the syndrome of multiple endocrine neoplasia (MEN). As with other functioning endocrine tumours, hormone secretion is inappropriate and usually excessive. C-peptide and proinsulin are released in parallel with insulin, and plasma concentrations are therefore inappropriately high in the presence of hypoglycaemia. Some insulinomas secrete just proinsulin. Attacks of hypoglycaemia occur typically at night and before breakfast, associated with hunger, and may be precipitated by strenuous exercise. Personality or behavioural changes may be the first feature; some patients present initially to psychiatrists.

Insulin antibodies can form in response to exogenous insulin, probably less so for human insulin than for animal types. Sometimes insulin antibodies form despite the patient never having been exposed to exogenous insulin – autoimmune insulin syndrome (AIS). Insulin receptor antibodies may cause hypoglycaemia, although they sometimes lead to insulin resistance and hyperglycaemia.

Reactive (functional) hypoglycaemia

Some people develop symptomatic hypoglycaemia between 2 and 4 h after a meal or a glucose load. Loss of consciousness is very rare. Similar symptoms may follow a gastrectomy or bariatric gastric banding, when rapid passage of glucose into the intestine, and rapid absorption, may stimulate excessive insulin secretion ('late dumping syndrome'). Reactive hypoglycaemia is uncommon.

Alcohol-induced hypoglycaemia

Hypoglycaemia may develop between 2 and 10 h after the ingestion of large amounts of alcohol. It is found most often in undernourished subjects and chronic alcoholics but may occur in young subjects when they first drink alcohol. Hypoglycaemia is probably caused by the suppression of gluconeogenesis during the metabolism of alcohol. Differentiation of hypoglycaemia from alcoholic stupor may be impossible unless the plasma glucose concentration is estimated. It may be necessary to infuse glucose frequently during treatment, until glycogen stores are repleted and plasma glucose concentrations are stable.

See Chapter 26 for a discussion of hypoglycaemia in neonates and children.

Investigation of adult hypoglycaemia

Some of the causes of hypoglycaemia are shown in Box 12.1 and can be divided into hyperinsulinaemic and hypoinsulinaemic groups. The following scheme may be useful in investigating hypoglycaemia. It is important to exclude pseudohypoglycaemia due to in vitro glucose metabolism, for example an old blood sample or one not collected into fluoride oxalate anticoagulant. Sometimes a cause may be evident from the medical and drug histories and clinical examination.

One of the most important tests in a patient with proven hypoglycaemia is to measure the plasma insulin and C-peptide concentrations when the plasma glucose concentration is low. Plasma for these assays should be separated from cells immediately and the plasma stored at –20°C until hypoglycaemia has been proven. These tests should differentiate exogenous insulin administration and endogenous insulin production, for example an insulinoma, from other causes of hypoglycaemia.

Raised plasma insulin concentrations and suppressed plasma concentrations of C-peptide suggest exogenous insulin administration (hyperinsulinaemic hypoglycaemia). Conversely, a high plasma insulin

and high C-peptide can be seen in sulphonylurea or meglitinide administration, and a urine or plasma drug screen is thus important.

Autoantibodies positive to the insulin receptor or insulin may also evoke hypoglycaemia, such as AIS. If a sulphonylurea drug screen and an insulin autoantibody screen are negative, raised plasma insulin and C-peptide concentrations are suggestive of an insulinoma.

Some tumours release proinsulin, which can also be assayed. Imaging will also be necessary, such as magnetic resonance imaging or computerized tomography scanning, to localize the tumour and to help exclude MEN syndrome (see Chapter 24). If both the plasma insulin and C-peptide concentrations are suppressed, the hypoglycaemia (hypoinsulinaemic hypoglycaemia) can then be divided into non-ketotic and ketotic forms. Hypoglycaemia with low plasma ketone concentrations, that is, β-hydroxybutyrate less than 600 μmol/L, is suggestive of increased insulin or IGF-1 activity such as may occur in non-islet cell tumour hypoglycaemia (NICTH). In NICTH, there is often increased IGF-2 secretion. Some spindle cell tumours, for example of the thorax, may release a variant 'big-IGF-2' resulting in hypoglycaemia (Doege–Potter syndrome).

Hypoinsulinaemic hypoglycaemia with hypoketonaemia can also be seen in hepatic failure or renal disease. Therefore liver and renal function should be checked. Conversely, hypoinsulinaemic hypoglycaemia with high plasma ketones, that is, β-hydroxybutyrate more than 600 μmol/L, can be found in hypopituitarism (see Chapter 7) when the plasma GH concentration is usually low. In addition, consider adrenal insufficiency (see Chapter 8) and hypothyroidism (see Chapter 11), in which plasma GH is usually high. High alcohol intake can also present with hypoinsulinaemic hypoglycaemia and raised ketone concentrations.

However, more commonly, the patient has been referred for investigation of previously documented hypoglycaemia or with a history strongly suggestive of hypoglycaemic attacks. It is also essential to exclude adrenal insufficiency, especially in diabetes mellitus patients with unexplained hypoglycaemia or reduced insulin requirements. If no cause is identified at this point, it may be possible to induce hypoglycaemia by provocation tests, although these are not without the risk of severe hypoglycaemic episodes.

Such tests could be as follows:

- *Overnight fast* A majority of patients with spontaneous hypoglycaemia manifest one plasma glucose concentration less than 2.5 mmol/L during an overnight (18-h) fast when assayed on three separate occasions.
- *Exercise test* Exercise may be used in the induction of insulin-induced hypoglycaemia. Blood is collected at 10-min intervals during 30 min of intense exercise, for example treadmill, and 30 min after stopping. Plasma insulin and C-peptide (and proinsulin, if necessary) are assayed and will be inappropriately high in endogenous hyperinsulinaemia and suppressed appropriately in hypoinsulinaemic hypoglycaemia.
- *Prolonged fast* The prolonged fast, of up to 4 h, may be reserved for cases where there is a high index of suspicion of hypoglycaemia that has not been provoked spontaneously or by the above tests. It should be noted that, during the prolonged fast, the patient must be under close supervision as potentially dangerous.

Blood should be taken every 6 h for plasma glucose and insulin estimations and, if symptoms occur, should be assayed for glucose immediately. The test can be stopped if hypoglycaemia is demonstrated. The patient should be fed after the test. If prolonged fasting does not induce hypoglycaemia, endogenous hyperinsulinism is unlikely to be the cause of the symptoms. A few normal individuals may show plasma glucose levels less than 2.5 mmol/L during the test, but they do not exhibit neuroglycopenic symptoms or Whipple's triad. A plasma insulin to C-peptide ratio of less than 1 has about 89 per cent sensitivity and 100 per cent specificity for insulinoma.

The insulin provocation test is now rarely used (as it can evoke dangerous hypoglycaemia) – in it, insulin administration fails to suppress plasma insulin and C-peptide in cases of insulinoma. Reactive hypoglycaemia should not be diagnosed by a prolonged 75 g OGTT, as normal individuals may show false-positive results. However, the mixed meal, based on the sort of foods that evoke the attacks, can be used to investigate post-prandial neuroglycopenic symptoms. Capillary blood samples are taken prior to and every half-hour for 6 h after mixed-meal ingestion. Reactive hypoglycaemia is a possible diagnosis if the patient develops neuroglycopenic symptoms and the capillary plasma glucose concentration is 3.0 mmol/L or less. Note that venous plasma should ideally not be used, as false-positive results may result because post-prandial glucose concentrations can be 1–2 mmol/L lower than in capillary blood samples.

Treatment of hypoglycaemia

Milder cases can be managed with oral glucose-containing preparations. Severe hypoglycaemia should be treated by urgent intravenous administration of 10–20 mL of at least 10 per cent (and in adults 20 per cent) glucose solution. Some patients may need to be maintained on a glucose infusion until the cause has been established and treated. Intramuscular glucagon 1 mg can also be used if intravenous access is a problem, but this should not be given in cases of insulinoma. An insulinoma should be removed surgically. If this is contraindicated for clinical reasons, diazoxide may maintain normoglycaemia.

Laboratory tests

Estimation of plasma or blood glucose

Glucose is measured in the laboratory by specific enzymatic methods. The supply of glucose to cells depends on extracellular (plasma) concentrations. The measurement of plasma glucose concentrations is preferable to that of whole blood, which is now rarely used. Blood cells, with very low glucose concentrations, 'dilute' glucose, giving results 10–15 per cent lower than in plasma, the actual amount depending on the haematocrit. Capillary blood from a finger prick is used for home glucose monitoring and the results for such samples may fall between those of venous whole blood and venous plasma.

Unless plasma is separated from the blood cells within about an hour of collection, the whole blood sample must be mixed with an inhibitor of glycolysis, such as fluoride. This helps prevent an in vitro fall in the plasma glucose concentration as glycolysis continues, which may result in pseudohypoglycaemia.

Urinary glucose

Enzyme reagent strips specific for glucose, such as those that use a glucose oxidase method, best detect glycosuria. The directions for use are supplied with the strips. Glycosuria may be due to:

- diabetes mellitus,
- glucose-containing infusion,
- renal glycosuria, which may be inherited as an autosomal dominant trait or in Fanconi's syndrome,
- pregnancy.

False-negative results may occur:

- if the urine contains large amounts of ascorbic acid after the ingestion of therapeutic doses,
- after the injection of tetracyclines, which contain ascorbic acid as a preservative.

False-positive results may occur if the urine container is contaminated with detergent.

Reducing substances in the urine can be detected using copper-containing reagents such as those incorporated in Clinitest tablets. These are rarely used now in the management of diabetes mellitus; however, in the neonatal period, the finding of other reducing substances may suggest an inborn error of metabolism, such as galactosaemia (see Chapter 27). It is therefore important to use this test, rather than one that is specific for glucose, in screening for such conditions.

Non-glucose-reducing substances are identified by chromatography and specific tests. The significance of a Clinitest-positive result varies with the substances, which are as follows.

- *Glucose*.
- *Glucuronates* are relatively common urinary reducing substances. Numerous drugs, such as salicylates and their metabolites, are excreted in the urine after conjugation with glucuronate in the liver.
- *Galactose* is found in the urine in galactosaemia.
- *Fructose* may appear in the urine after very large oral doses of sucrose, or after excessive fruit ingestion, but usually fructosuria is due to one of two rare inborn errors of metabolism, both transmitted as autosomal recessive disorders:
  - essential fructosuria is usually a benign condition (hepatic fructokinase deficiency),
  - hereditary fructose intolerance is characterized by hypoglycaemia that may lead to death in infancy.
- *Lactose*. Lactosuria may occur in:
  - late pregnancy and during lactation,
  - lactase deficiency.
- *Pentoses*. Pentosuria is very rare. It may occur in:
  - alimentary pentosuria, after excessive ingestion of fruits such as cherries and grapes – the pentoses are arabinose and xylose,
  - essential pentosuria, a rare recessive disorder due to L-xylulose reductase deficiency, characterized by the excretion of xylose – it is usually benign.
- *Homogentisic acid* appears in the urine in the rare inborn error alkaptonuria. It is usually recognizable because it forms a blackish precipitate in urine on standing. Urea and creatinine may give weak positive results at high concentrations.

Ketonuria

Most simple urine tests for ketones are more sensitive for detecting acetoacetate than acetone; β-hydroxybutyrate does not always react in these tests. Occasional colour reactions resembling, but not identical to, that of acetoacetate may be given by phthalein compounds when used as a laxative.

Ketostix and Acetest are strips and tablets, respectively, impregnated with ammonium sulphate and sodium nitroprusside.

Remember that raised concentrations of urinary ketones can occur not only in diabetic ketoacidosis but also in alcoholic ketoacidosis or starvation, and in some urinary tract infections.

SUMMARY

- Diabetes mellitus is a common medical condition, and an understanding of its biochemistry aids its medical management. Type 1 diabetes mellitus is associated with insulin deficiency and may present with weight loss and urinary ketones in young individuals. There is a relationship with autoimmune disease. Treatment is with insulin. Conversely, type 2 diabetes mellitus is usually associated with insulin resistance, increased body weight and later age presentation. There may be a family history of diabetes mellitus. Treatment involves diet and biguanides, sulphonylureas, glitazones or incretins, although insulin may sometimes be needed.
- Biochemical tests have a major role in the management of diabetes mellitus and in monitoring its complications, such as in the control of blood glucose, HbA_{1c}, plasma lipids and urinary ACR.
- Diabetes mellitus can present with various comas, including hypoglycaemia, diabetic ketoacidosis (type 1), HONK and lactic acidosis.
- Hypoglycaemia can present with neurological impairment and coma. A useful classification is to divide hypoglycaemia into that with high plasma insulin and that with low insulin levels. The causes of hyperinsulinaemic hypoglycaemia include insulinomas and following insulin administration. The causes of hypoinsulinaemic hypoglycaemia include severe hepatic disease, adrenal insufficiency, pituitary failure and non-pancreatic tumours producing insulin-like substances.