

Diabetes mellitus and other disorders of metabolism

19

Q19.1

The glucose uptake in this organ is obligatory and is not dependent on insulin. It is a major consumer of glucose and its requirement is 1 mg/kg bodyweight per minute or 100 g daily in a 70 kg man.

- A. Liver
 - B. Muscle
 - C. Fat
 - D. Kidney
 - E. Brain
-

Q19.2

The process by which liver combines 3-carbon molecules derived from breakdown of fat (glycerol), muscle glycogen (lactate) and protein (e.g. alanine) into the 6-carbon glucose molecule

- A. Glycogenolysis
 - B. Lipolysis
 - C. Glycolysis
 - D. Gluconeogenesis
 - E. Triglyceride synthesis
-

Q19.3

A middle-aged alcoholic man presents with a bullous eruption. He has a family history of porphyria. Urine examination reveals increased levels of urinary uroporphyrin. This is due to an abnormality of which one of the following?

- A. Protoporphyrinogen oxidase
 - B. Hepatic uroporphyrinogen decarboxylase
 - C. Porphobilinogen deaminase
 - D. δ -ALA synthetase
 - E. Haemoglobin oxidase
-

Q19.4

A 32-year-old woman has a history of depression. After an alcoholic binge she develops abdominal pain, nausea and vomiting. On examination she has hypertension, tachycardia and polyneuropathy. Urinary examination reveals excess porphobilinogen. This is due to an abnormality in which one of the following enzymes?

- A. Protoporphyrinogen oxidase
 - B. Hepatic uroporphyrinogen oxidase
 - C. Porphobilinogen deaminase
 - D. Delta ALA synthetase
 - E. Haemoglobin oxidase
-

Q19.5

A 28-year-old insulin-dependent diabetic is found unconscious, at home, by his wife. She calls for an ambulance but in the interim she uses his bedside blood test and finds that his blood sugars are extremely low. Select the best option for what she can administer next

- A. Intravenous 5% glucose
- B. Intramuscular glucagon
- C. Intravenous 50% glucose
- D. Oral glucose
- E. Oral Lucozade

Q19.6

A 35-year-old Jewish patient complains of pain in the left hypochondrium. On examination he has pigmentation in sun-exposed areas of his skin and hepatosplenomegaly including a massive spleen. Lab investigations include anaemia and hypersplenism. There is also a history of repeated fractures of the bone. Which one of the following deficiencies is responsible for this clinical picture?

- A. Cystathione synthetase
- B. Phosphorylase
- C. Phenylalanine hydroxylase
- D. Homogentisic acid oxidase
- E. Glucocerebrosidase

Q19.7

A 65-year-old diabetic patient presents in a coma. Na 155 mmol/L, K 5 mmol/L, Cl 110 mmol/L, HCO₃ 30 mmol/L, urea 15 mmol/L, glucose 50 mmol/L and arterial pH 7.35. His calculated plasma osmolality is

- A. 300 mOsm/kg
- B. 328 mOsm/kg
- C. 385 mOsm/kg
- D. 350 mOsm/kg
- E. 285 mOsm/Kg

Q19.8

A 22-year-old presents with a coma. His labs are as follows: Na 140 mmol/L, K 5 mmol/L, Cl 100 mmol/L, HCO₃ 5 mmol/L, urea 8 mmol/L, arterial pH 7.0 and blood glucose 30 mmol/L. The anion gap is

- A. 17
- B. 40
- C. 20
- D. 30
- E. Less than 17

Q19.9

A 57-year-old diabetic patient on metformin presents in a coma. Blood glucose is 9 mmol/L, Na 140 mmol/L, K 5 mmol/L, Cl 100 mmol/L, HCO₃ 5 mmol/L. There is no ketosis. Which one of the following is the best option for treatment?

- A. Intravenous insulin and 5% dextrose
- B. Rehydration and infusion of 1.26% bicarbonate
- C. Ion exchange resin
- D. Salbutamol
- E. Hypertonic saline

Q19.10

A 38-year-old patient has incomplete erection secondary to longstanding diabetes. There is no history of angina and no previous myocardial infarction. The best option for treatment is which one of the following?

- A. Insertion of alprostadil into the urethra
- B. Intracavernosal injection of alprostadil
- C. Papaverine
- D. Moxisylyte (thymoxamine)
- E. Sildenafil citrate

Q19.11

After the diagnosis of diabetes, the earliest functional abnormality in diabetic nephropathy is

- Decreased glomerular filtration rate
- Rising plasma creatinine
- Decrease in the size of the kidney with a decreased glomerular filtration rate
- Persistent proteinuria
- Renal hypertrophy associated with a raised glomerular filtration rate

Q19.12

- Enables basal non-insulin-stimulated glucose uptake into many cells
- Transports glucose into the beta-cell: a prerequisite for glucose sensing
- Enables non-insulin-mediated glucose uptake into brain neurones
- Enables much of the peripheral action of insulin. It is the channel through which glucose is taken up into muscle and adipose tissue cells following stimulation of the insulin receptor

Select the best match for each of the above among a family of specialized glucose-transporter (GLUT) proteins

- GLUT-2
- GLUT-1
- GLUT-3
- GLUT-4

Q19.13

- A 19-year-old boy was diagnosed with maturity-onset diabetes a year ago. The hyperglycaemia is progressive, microvascular complications are frequent and there are no non-diabetes related features. It has been localized to the long arm of chromosome 20

- A 23-year-old patient has had maturity-onset diabetes from birth. She had a low birthweight. There has been little deterioration of hyperglycaemia with age. Microvascular complications are rare. It has been localized to the small arm of chromosome 7

- A 22-year-old patient was diagnosed with maturity-onset diabetes 3 years ago. Hyperglycaemia is progressive and microvascular complications are frequent. It is localized to the long arm of chromosome 12

- A 22-year-old patient has maturity-onset diabetes but progression is unclear. There are few data about microvascular complications. There is pancreatic agenesis in homozygotes. It is localized to the long arm of chromosome 13

- A 24-year-old patient has maturity-onset diabetes but progression is unclear. There are few data about microvascular complications. Other features include renal cysts, proteinuria and renal failure. It is localized to the long arm of chromosome 17

Select the best match for each of the above

- Hepatic nuclear factor-4a
- Glucokinase
- Hepatic nuclear factor-1b
- Hepatic nuclear factor-1a
- Insulin-promoter factor-1

Q19.14

- Tolbutamide
- Acarbose
- Glibenclamide
- Rosiglitazone
- Gliclazide
- Metformin

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Select the mechanism of action of each of the above

- α -Glucosidase inhibitor
- Reduces insulin resistance by interaction with peroxisome proliferator-activated receptor gamma
- Reduces gluconeogenesis, thus suppressing hepatic glucose output, and it increases insulin sensitivity
- Promotes insulin secretion in response to glucose and other secretagogues

Q19.15

- An 83-year-old diabetic
- A 65-year-old diabetic whose body mass index is 45
- A 35-year-old patient with diabetic ketoacidosis
- A 45-year-old diabetic whose body mass index is 22 and who has renal impairment
- A 60-year-old diabetic who has been adhering to diet and oral therapy and now has HbA_{1c} 11%

Select the best option for each of the above

- Insulin
- Metformin
- Tolbutamide
- Gliclazide
- Glibenclamide

Q19.16

- An 18 year-old diabetic whose blood glucose before breakfast is persistently too high
- A 23-year-old diabetic whose blood glucose before lunch is persistently too high
- A 21-year-old diabetic whose blood glucose before lunch is persistently too low

- A 24-year-old diabetic whose blood glucose before the evening meal is persistently too high
- A 29-year-old diabetic whose blood glucose before going to bed is persistently too low

Select the best option for each of the above

- Increase morning long-acting insulin or lunch short-acting insulin
- Reduce evening short-acting insulin
- Increase morning short-acting insulin
- Reduce morning short-acting insulin or increase mid-morning snack
- Increase evening long-acting insulin
- Reduce evening long-acting insulin

Q19.17

- Coronary artery disease
- Peripheral vascular disease
- Stroke
- Diabetic retinopathy
- Diabetic nephropathy
- Diabetic neuropathy

Select the best match for each of the above complications of diabetes mellitus

- Microvascular disease
- Macrovascular disease

Q19.18

- A 57-year-old diabetic on fundoscopy has dot haemorrhages, blot haemorrhages and hard exudates
- A 38-year-old diabetic has cotton-wool spots, venous beading, venous loops and intraretinal microvascular abnormalities
- A 48-year-old diabetic has new blood vessels, subhyaloid haemorrhages and vitreous haemorrhage
- A 49-year-old diabetic has retinal fibrosis and traction retinal detachment

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5. A 38-year-old diabetic has hard exudates encroaching on the macula

Select the best match for each of the above

- A. Non-urgent referral to the ophthalmologist
- B. Urgent referral to the ophthalmologist
- C. Annual screening only

- B. Reduces hepatic VLDL secretion
- C. Binds bile acids in the gut preventing enterohepatic circulation
- D. Inhibits the rate-limiting step in the synthesis of cholesterol
- E. Inhibits lipid synthesis in the liver by reducing free fatty acid concentrations owing to an inhibitory effect on lipolysis in fat tissue

Q19.19

- 1. A 49-year-old diabetic has dot haemorrhages
- 2. A 67-year-old diabetic has blot haemorrhages
- 3. A 57-year-old diabetic has hard exudates
- 4. A 43-year-old diabetic has cotton-wool spots

Select the best match for each of the above

- A. Exudation of fluid rich in lipids and proteins
- B. Leakage of blood into the deeper layers of retina
- C. Capillary microaneurysms
- D. Oedema resulting from retinal infarcts
- E. New vessel formation

Q19.20

- 1. Colestyramine
- 2. Gemfibrozil
- 3. Simvastatin
- 4. Nicotinic acid
- 5. Omega-3 marine triglycerides

Select the mechanism of action of each of the above

- A. Limits substrate availability for hepatic triglyceride synthesis, modulates LDL/ligand interaction, promotes action of lipoprotein lipase and stimulates reverse transport of cholesterol

Q19.21

- 1. Colestyramine
- 2. Gemfibrozil
- 3. Simvastatin
- 4. Nicotinic acid
- 5. Omega-3 marine triglycerides

Select the expected lipid lowering effect of each of the above

- A. 30–40% reduction in LDL cholesterol, little effect on triglycerides or HDL
- B. Reduction of LDL by 10–15% and triglycerides by 25–35%, HDL concentrations increase by 0–15%
- C. Reduce LDL and triglycerides by 5–10%, modest HDL increase
- D. Reduces triglycerides in severe hypertriglyceridaemia, no favourable change in other lipids and may aggravate hypercholesterolaemia in a few patients
- E. 8–15% reduction in LDL, little or no effect on HDL cholesterol and 5–15% rise in triglyceride concentration

Q19.22

- 1. A middle-aged adult who develops muscle cramps and myoglobinuria after exercise
- 2. A 23-year-old patient with Marfan-like features, mental handicap and homocystine is excreted in urine

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3. A 22-year-old patient with whitish hair, pink-white skin, grey-blue eyes, nystagmus, photophobia and strabismus
4. A 19-year-old patient with brain damage, mental retardation and epilepsy. Phenolpyruvate and its derivatives are excreted in urine
5. A 24-year-old patient with deposition of blackish-brown pigment in cartilages

Select the enzyme defect for each of the above

- A. Cystathionine synthetase
- B. Phosphorylase
- C. Phenylalanine hydroxylase
- D. Homogentisic acid oxidase
- E. Tyrosinase

Q19.23

1. A 62-year-old woman with multiple myeloma presents with shortness of breath. Echocardiography shows thickening of the ventricular walls and low voltage complexes are seen on the ECG
2. A 42-year-old man has a family history of amyloidosis and he presents with peripheral sensorimotor neuropathy
3. A 63-year-old woman with longstanding rheumatoid arthritis presents with proteinuria. Renal biopsy reveals amyloidosis
4. A 43-year-old patient with Down's syndrome has longstanding premature dementia
5. A patient with chronic renal failure on long-term haemodialysis develops carpal tunnel syndrome due to deposition of amyloid

Select the best match for each of the above

- A. AA amyloidosis
- B. β_2 -Microglobulin
- C. Deposits of A4 protein
- D. Immunoglobulin light chain-associated (AL) amyloid
- E. Transthyretin-associated (ATTR) protein

Q19.24

The following patients are diabetic according to the World Health Organization diagnostic criteria of 1999

- A. An 18-year-old girl who has thirst, polyuria and polydipsia. Glycosuria is present and a single plasma glucose is 7 mmol/L (126 mg/dL)
- B. A 19-year-old army recruit who has no symptoms undergoes routine screening tests. Fasting venous plasma glucose on two different occasions is 8 mmol/L (140 mg/dL) and 7.9 mmol/L (135 mg/dL)
- C. An asymptomatic pilot of a commercial airline as a part of an annual examination has two random venous samples where plasma glucose is 11.2 mmol/L and 11.1 mmol/L (200 mg/dL and 210 mg/dL)
- D. A 28-year-old man whose fasting venous plasma glucose is 6 mmol/L and level 2 h after 75 g glucose is load is 10 mmol/L
- E. A 23-year-old woman who is 6 months pregnant. Fasting venous plasma glucose is 7.1 mmol/L and levels 2 h after 75 g glucose load is 12 mmol/L

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Q19.25

A 35-year-old diabetic (compared to the general population) is

- A. Twice as likely to have a stroke
- B. Three to five times as likely to have myocardial infarction
- C. Fifty times as likely to have amputation of the foot for gangrene
- D. Likely to lose her premenopausal protection from coronary artery disease
- E. At risk of excess mortality from diabetic nephropathy rather than cardiovascular disease

Q19.26

A 26-year-old diabetic on twice-daily mixed insulin has nocturnal hypoglycaemia but awakes with high blood glucose. The problem may be helped by

- A. Injecting more insulin at night
- B. Checking that a bedtime snack is taken regularly
- C. Separating the evening dose and taking the intermediate insulin at bedtime rather than before supper
- D. Reducing the dose of soluble insulin before supper
- E. Changing the multiple injection regimen with soluble insulin to a rapid-acting insulin analogue

Q19.27

Intensive control of blood sugar in type 2 diabetes results in

- A. A reduction in overall risk of microvascular disease but causes a deterioration in albuminuria
- B. A reduction in the need for laser treatment but exacerbates microvascular disease

- C. A reduction in albuminuria
- D. A reduction in cardiovascular risk
- E. An increase in the level of glycosylated haemoglobin

Q19.28

An 18-year-old insulin-dependent diabetic wishes to work. He can pursue the following occupations

- A. Taxi driver
- B. Heavy goods vehicle driver
- C. Commercial pilot
- D. Nurse
- E. Police constable

Q19.29

A 17-year-old insulin-dependent diabetic presents with nausea, vomiting and abdominal pain. He is confused, hyperventilating and is dehydrated. Initial blood tests reveal Na 140 mmol/L, K 5 mmol/L, Cl 100 mmol/L, HCO₃ 5 mmol/L, urea 8 mmol/L, arterial pH 7.0 and blood glucose 30 mmol/L. The following processes could have contributed to his clinical condition

- A. Accelerated production of hepatic glucose
- B. Reduction in peripheral uptake of glucose
- C. Osmotic diuresis
- D. Rapid lipolysis
- E. Breakdown of free fatty acids to fatty acyl-CoA

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Q19.30

A 45-year-old diabetic has retinopathy and renal failure due to nephropathy. The following plans for further management are correct

- A. Aggressive treatment of blood pressure with a target below 135/85 mmHg
- B. Aggressive management of blood sugar with chlorpropamide or glibenclamide
- C. Drastic increases in insulin doses may be required
- D. Frequent ophthalmologist supervision
- E. Long-term antibiotic treatment to prevent infections

Q19.31

A 52-year-old diabetic seeks advice on foot care. The following advice is appropriate

- A. Inspect feet daily
- B. Check shoes inside and out for sharp bodies/areas before wearing
- C. Use lace-up shoes with plenty of room for the toes
- D. Keep feet away from sources of heat (hot sand, hot-water bottles, radiators, fires)
- E. Check the bath temperature before stepping in

Q19.32

A 45-year-old insulin-dependent diabetic is undergoing amputation of her right leg. The following statements are correct

- A. Long-acting insulin should be continued and in addition soluble insulin should be initiated
- B. Long-acting insulin should be stopped the day before surgery and soluble insulin should be substituted
- C. An infusion of glucose, insulin and potassium is given during surgery

- D. Preferably diabetic patients should be at the end of the theatre list
- E. Postoperatively the patient should be given an infusion of glucose, insulin and potassium until she is able to eat

Q19.33

A 22-year-old diabetic is pregnant and her HbA_{1c} is around 12 throughout her pregnancy. There is an increased risk of

- A. Stillbirth
- B. Fetal macrosomia
- C. Hydramnios
- D. Pre-eclampsia
- E. Gestational diabetes

Q19.34

A 23-year-old diabetic has recurrent ketoacidosis. The following could have resulted in unstable glycaemic control

- A. Poorly controlled hypertension
- B. Thyrotoxicosis
- C. Urinary tract infection
- D. Hypogonadism
- E. Tuberculosis

Q19.35

A 42-year-old nurse presents with confusion, diplopia, palpitations and grand mal seizures. Her blood glucose is low and her symptoms respond to 50% dextrose. After an overnight fast she has low glucose and elevated insulin levels. The following tests would rule out factitious hypoglycaemia

- A. A prolonged 72-hour supervised fast
- B. Measurement of C-peptide levels
- C. Plasma chromatography for sulphonylurea
- D. Fructose tolerance test
- E. Glucose tolerance test

A19.1

E

The brain is the major consumer of glucose. Its requirement is 1 mg/kg bodyweight per minute, or 100 g daily in a 70 kg man. Glucose uptake by the brain is obligatory and is not dependent on insulin, and the glucose used is oxidized to carbon dioxide and water. Other tissues, such as muscle and fat, are facultative glucose consumers.

A19.2

D

The liver combines 3-carbon molecules derived from breakdown of fat (glycerol), muscle glycogen (lactate) and protein (e.g. alanine) into the 6-carbon glucose molecule by the process of gluconeogenesis.

A19.3

B

Porphyria cutanea tarda (cutaneous hepatic porphyria), which has a genetic predisposition, presents with a bullous eruption on exposure to sunlight; the eruption heals with scarring. Alcohol is the most common aetiological agent. There is an abnormality in hepatic uroporphyrinogen decarboxylase. Evidence of biochemical or clinical liver disease may also be present.

A19.4

C

Acute intermittent porphyria is an autosomal dominant disorder. Presentation is in early adult life, usually around the age of 30 years, and women

are affected more than men. It may be precipitated by alcohol and drugs such as barbiturates and oral contraceptives, but a wide range of lipid-soluble drugs have also been incriminated. The abnormality lies at the level of porphobilinogen deaminase in the haem biosynthetic pathway.

A19.5

B

The diagnosis of severe hypoglycaemia resulting in confusion or coma is simple and can usually be made on clinical grounds, backed by a bedside blood test. Unconscious patients should be given intramuscular glucagon (1 mg). Glucagon acts by mobilizing hepatic glycogen, and works almost as rapidly as glucose. It is simple to administer and can be given at home by relatives. It does not work after a prolonged fast. Oral glucose is given to replenish glycogen reserves once the patient revives.

A19.6

E

Gaucher's disease is the most prevalent lysosomal storage disease and is due to a deficiency in glucocerebrosidase, a specialized lysosomal acid β -glucosidase. This results in accumulation of glucosylceramide in the lysosomes of the reticuloendothelial system, particularly the liver, bone marrow and spleen. Several mutations have been characterized in the glucocerebrosidase gene, the most common being a single base change causing the substitution of arginine for serine; this is seen in 70% of Jewish patients. The typical Gaucher cell, a glucocerebroside-containing reticuloendothelial histiocyte, is found in the bone marrow. There are three clinical

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types, the most common presenting in adult life with an insidious onset of hepatosplenomegaly. There is a high incidence in Ashkenazi Jews (1 in 3000 births), and patients have a characteristic pigmentation on exposed parts, particularly the forehead and hands. The clinical spectrum is variable, with patients developing anaemia, evidence of hypersplenism and pathological fractures that are due to bone involvement. Nevertheless, many have a normal life span.

A19.7

C

Osmolality is calculated from the formula $2(\text{Na} + \text{K}) + \text{glucose} + \text{urea}$. Therefore, $2(155+5) + 50 + 15 = 385 \text{ mOsm/kg}$.

A19.8

B

The normal anion gap is less than 17. It is calculated as $(\text{Na}^+ + \text{K}^+) - (\text{Cl}^- + \text{HCO}_3^-)$. The anion gap in the above example is 40.

A19.9

B

Lactic acidosis may occur in diabetic patients on biguanide therapy. The risk in patients taking metformin is extremely low provided that the therapeutic dose is not exceeded and the drug is withheld in patients with advanced hepatic or renal dysfunction. Patients present in severe metabolic acidosis with a large anion gap (calculated as $(\text{Na}^+ + \text{K}^+) - (\text{Cl}^- + \text{HCO}_3^-)$, normally less than 17 mmol/L), usually without significant hyperglycaemia or ketosis. Treatment is by rehydration and infusion of isotonic 1.26% bicarbonate.

A19.10

E

A therapeutic trial of sildenafil citrate, a phosphodiesterase type-5 inhibitor, which enhances the effects of nitric oxide on smooth muscle and increases penile blood flow, is warranted in most impotent diabetic patients who do not suffer from angina or previous myocardial infarction (contraindications). Patients can be trained by a clinician or impotence nurse specialist in the intracavernosal injection of alprostadil to cause erection. Papaverine (smooth muscle relaxant) and phentolamine and moxisylyte (thymoxamine) (alpha-adrenoceptor blockers) are sometimes also used.

A19.11

E

The earliest functional abnormality in the diabetic kidney is renal hypertrophy associated with a raised glomerular filtration rate. This appears soon after diagnosis and is related to poor glycaemic control.

A19.12

1) B 2) A 3) C 4) D

Cell membranes are not inherently permeable to glucose. A family of specialized glucose-transporter (GLUT) proteins carry glucose through the membrane into cells:

- GLUT-1 – enables basal non-insulin-stimulated glucose uptake into many cells
- GLUT-2 – transports glucose into the beta-cell: a prerequisite for glucose sensing

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- GLUT-3 – enables non-insulin-mediated glucose uptake into brain neurones
- GLUT-4 – enables much of the peripheral action of insulin. It is the channel through which glucose is taken up into muscle and adipose tissue cells following stimulation of the insulin receptor.

A19.13

- 1) A 2) B 3) D 4) E 5) C

Maturity-onset diabetes of the young (MODY)

	HNF-4a (MODY 1)	Glucokinase (MODY 2)	HNF-1a (MODY 3)	IPF-1 (MODY 4)	HNF-1b (MODY5)
Chromosomal location	20q	7p	12q	13q	17q
Proportion of all MODY cases	5%	15%	65%	<1% (MODY)	1%
Clinical features	Onset in teens/twenties Progressive hyperglycaemia	Present from birth Little deterioration with age	Onset in teens/twenties Progressive hyperglycaemia	?Early adulthood Progression unclear currently	?Early adulthood Progression unclear currently
Microvascular complications	Frequent	Rare	Frequent	Few data	Frequent
Non-diabetes-related features	None	Reduced birthweight	Low renal threshold for glucose and aminoaciduria	Pancreatic agenesis in homozygotes	Renal cysts Proteinuria Renal failure

The glucokinase gene is intimately involved in the glucose-sensing mechanism within the pancreatic beta-cell. The hepatic nuclear factor (HNF) genes and the insulin promoter factor-1 (IPF-1) gene control nuclear transcription in the beta-cell where they regulate its development and function. Abnormal nuclear transcription genes may cause pancreatic agenesis or more subtle progressive pancreatic damage

A19.14

- 1) D 2) A 3) D 4) B 5) D 6) C

The principal action of sulphonylureas is to promote insulin secretion in response to glucose and other secretagogues. The mechanism of action of metformin remains unclear but it reduces gluconeogenesis, thus suppressing hepatic glucose output, and it increases insulin sensitivity. Acarbose is a sham sugar that competitively inhibits alpha-glucosidase

enzymes situated on the brush border of the intestine. As a result, dietary carbohydrate is poorly absorbed, and the postprandial rise in blood glucose is reduced. The thiazolidinediones (more conveniently known as the 'glitazones') reduce insulin resistance by interaction with peroxisome proliferator-activated receptor-gamma (PPAR-gamma) a nuclear receptor which regulates genes involved in lipid metabolism and insulin action.

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A19.15

- 1) C 2) B 3) A 4) D 5) A

Tolbutamide is the safest drug in the very elderly because of its short duration of action. Gliclazide has a fairly long biological half life and is largely metabolized by the liver and can be used in renal impairment. Metformin is usually reserved for patients in middle or old age,

particularly for the overweight since it does not promote weight gain. It may be given in combination with sulphonylureas when a single agent has proved to be ineffective. Insulin is useful in diabetic ketoacidosis and should be considered in patients with type 2 diabetes if oral hypoglycaemic agents fail to provide adequate control of blood glucose.

A19.16

- 1) E 2) C 3) D 4) A 5) B

Guide to adjusting insulin dosage according to blood glucose test results

	Blood glucose persistently too high	Blood glucose persistently too low
Before breakfast	Increase evening long-acting insulin	Reduce evening long-acting insulin
Before lunch	Increase morning short-acting insulin	Reduce morning short-acting insulin or increase mid-morning snack
Before evening meal	Increase morning long-acting insulin or lunch short-acting insulin	Reduce morning long-acting insulin or lunch short-acting insulin or increase mid-afternoon snack
Before bed	Increase evening short-acting insulin	Reduce evening short-acting insulin

A19.17

- 1) B 2) B 3) B 4) A 5) A 6) A

Diabetes is usually irreversible and, although patients can have a reasonably normal lifestyle, its late complications result in reduced life expectancy and

major health costs. These include macrovascular disease, leading to an increased prevalence of coronary artery disease, peripheral vascular disease and stroke, and microvascular damage causing diabetic retinopathy and nephropathy, and contributing to diabetic neuropathy.

A19.18

1) C 2) A 3) B 4) B 5) A

	Fundoscopy/photography findings	Action needed
Background retinopathy	Microaneurysms (dot haemorrhages) Blot haemorrhages Hard exudates	Annual screening only
Pre-proliferative retinopathy	Cotton-wool spots Venous beading Venous loops Intraretinal microvascular abnormalities	Non-urgent referral to an ophthalmologist
Proliferative retinopathy	New blood vessel formation Preretinal (subhyaloid) haemorrhage Vitreous haemorrhage	Urgent referral to an ophthalmologist
Advanced retinopathy	Retinal fibrosis Traction retinal detachment	Urgent referral to an ophthalmologist – but much vision already lost

A19.19

1) C 2) B 3) A 4) D

In background retinopathy the first abnormality visible through the ophthalmoscope is the appearance of dot 'haemorrhages', which are actually due to capillary microaneurysms. Leakage of blood into the deeper layers of the retina produces the characteristic 'blot' haemorrhage, while exudation of fluid

rich in lipids and protein give rise to hard exudates. These have a bright yellowish white colour and are often irregular in outline with a sharply defined margin. Progressive retinal ischaemia will, in some patients, cause background retinopathy to progress to pre-proliferative, sight-threatening retinopathy. The earliest sign is the appearance of 'cotton-wool spots', representing oedema resulting from retinal infarcts.

A19.20

- 1) C 2) A 3) D 4) E 5) B

Drugs used in the management of hyperlipidaemia

Drug	Mechanism of action
Fibric acid derivatives e.g. Gemfibrozil Bezafibrate Fenofibrate Ciprofibrate	Complex and not fully understood 1. Limit substrate availability for hepatic triglyceride synthesis 2. Modulate LDL/ligand interaction 3. Promote action of lipoprotein lipase 4. Stimulate reverse transport of cholesterol
Cholesterol-binding resins e.g. Colestyramine Colestipol	Anion exchange resins Bind bile acids in the gut, preventing enterohepatic circulation This promotes liver to convert cholesterol to bile acids Also stimulates formation of hepatic LDL receptors which take up more cholesterol from the circulation
HMG-CoA reductase inhibitors ('statins') e.g. Simvastatin Pravastatin Atorvastatin Fluvastatin	Inhibit the rate-limiting step in cholesterol synthesis
Nicotinic acid and derivatives e.g. Nicotinic acid Acipimox	Unclear Probably inhibit lipid synthesis in the liver by reducing free fatty acid concentrations owing to an inhibitory effect on lipolysis in fat tissue
ω-3 marine triglycerides	Reduce hepatic VLDL secretion

VLDL, very low-density lipoprotein; LDL, low-density lipoprotein

A19.21

- 1) F 2) C 3) A 4) D 5) E

Drugs used in the management of hyperlipidaemia

Drug	Expected lipid-lowering effect
Fibric acid derivatives e.g. Gemfibrozil Bezafibrate Fenofibrate Ciprofibrate	Reduction of LDL cholesterol by 10–15% and triglycerides by 25–35% HDL cholesterol concentrations increase by 0–15% (newer agents often have greater beneficial effect on HDL)
Cholesterol-binding resins e.g. Colestyramine Colestipol	8–15% reduction in LDL Little or no effect on HDL cholesterol 5–15% rise in triglyceride concentration
HMG-CoA reductase inhibitors ('statins') e.g. Simvastatin Pravastatin Atorvastatin Fluvastatin	30–40% reduction in LDL cholesterol Moderate reduction in triglycerides or moderate elevation of HDL cholesterol
Nicotinic acid and derivatives e.g. Nicotinic acid Acipimox	Reduce LDL and triglycerides by 5–10% Modest HDL increase
ω-3 marine triglycerides	Reduce triglycerides in severe hypertriglyceridaemia No favourable change in other lipids, and may aggravate hypercholesterolaemia in a few patients

LDL, low-density lipoprotein; HDL, high-density lipoprotein

A19.22

- 1) B 2) A 3) E 4) C 5) D

The first patient has type V glycogen storage disease and the defect is in muscle phosphorylase. Typically adults develop muscle cramps and myoglobinuria after exercise. These patients have a normal life span and should avoid exercise. The second patient has type 1 homocystinuria which is due to a defect in cystathionine synthetase. Features include Marfan-like features, mental defect, thrombotic episodes and homocystine is excreted in

the urine. The third patient has albinism where the defect is in the enzyme tyrosinase. It is seen in 1 in 13 000 individuals and is characterized by amelanosis, whitish hair, pale-white skin and grey-blue eyes. The fourth patient has phenylketonuria where the defect is in the enzyme phenylalanine hydroxylase. The incidence is 1 in 20 000 and is characterized by brain damage with mental retardation and epilepsy. The urine contains phenylpyruvate and its derivatives. The treatment is a diet low in phenylalanine in the first few months of

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life to prevent damage. The prognosis is good but there remains some intellectual impairment. The fifth patient has alkaptonuria due a defect in the enzyme homogentisic acid oxidase. The incidence is 1 in 100 000. In these patients homogentisic acid polymerizes to produce a black-brown product that is deposited in cartilage and other tissues (ochronosis). These patients do not require treatment and prognosis is good.

A19.23

1) D 2) E 3) A 4) C 5) B

AL amyloidosis is a plasma cell dyscrasia, related to multiple myeloma, in which clonal plasma cells in the bone marrow produce immunoglobulins that are amyloidogenic. Familial amyloidoses are autosomally dominant transmitted diseases where the mutant protein forms amyloid fibrils, starting usually in middle

age. The most common form is due to a mutant – transthyretin – which is a tetrameric protein with four identical subunits. AA (reactive or secondary) amyloidosis depends on the nature of the disorder. Chronic inflammatory disorders include rheumatoid arthritis, inflammatory bowel disease, and untreated familial Mediterranean fever. In developing countries it is still associated with infectious diseases such as tuberculosis, bronchiectasis and osteomyelitis. Intracerebral and cerebrovascular amyloid deposits are seen in Alzheimer's disease. Amyloid deposits are frequently found in the elderly, particularly cerebral deposits of A4 protein. This is also seen in Down's syndrome.

Carpal tunnel syndrome due to β_2 -microglobulin deposition as amyloid fibrils is seen in patients on long-term haemodialysis.

A19.24

A) F B) T C) T D) F E) T

The glucose tolerance test – WHO criteria

	Normal	Impaired glucose tolerance	Diabetes mellitus
Fasting	Less than 7.0 mmol/L	Less than 7.0 mmol/L	More than 7.0 mmol/L
2 h after glucose	Less than 7.8 mmol/L	Between 7.8 and 11.0 mmol/L	11.1 mmol/L or more

The diagnosis of diabetes is usually simple. Blood glucose is so closely controlled by the body that even small deviations become important.

- In symptomatic patients, a single elevated plasma glucose ≥ 11 mmol/L, measured by a reliable method, indicates diabetes.
- In asymptomatic or mildly symptomatic patients, the diagnosis is made on:
 - (a) two fasting venous plasma glucose levels above 7.0 mmol/L (126 mg/dL); OR
 - (b) two random values ≥ 11.1 mmol/L (200 mg/dL) in venous plasma.
- A glucose tolerance test is only needed for borderline cases.

A19.25

A) T B) T C) T D) T E) F

Time has proved that insulin-treated patients still have a considerably reduced life expectancy. Those diagnosed before the age of 20 years in older studies had only a 50–60% chance of living past the age of 50 years, although there are indications of a steady improvement in survival. The excess deaths in early-onset patients are mainly related to diabetic nephropathy, but there is also a considerable excess cardiovascular mortality. Heart disease, peripheral vascular disease and stroke are the major causes of death in patients over the age of 50 years. The excess risk to diabetics compared with the general population increases as one moves down the body: a) stroke is twice as likely; b) myocardial infarction is 3–5 times as likely and women with diabetes lose their premenopausal protection from coronary artery disease; c) amputation of a foot for gangrene is 50 times as likely.

A19.26

A) F B) T C) T D) T E) T

Basal insulin requirements fall during the night but increase again from about 4 a.m. onwards, at a time when levels of injected insulin are falling. As a result many patients awake with high blood glucose levels, but find that injecting more insulin at night increases the risk of hypoglycaemia in the early hours of the morning. The problem may be helped by: a) checking that a bedtime snack is taken regularly; b) for patients taking twice-daily mixed insulin to separate their evening dose and take the intermediate insulin at bedtime rather than before supper; c) reducing the dose of soluble insulin before supper, since the effects of this persist well

into the night; d) changing patients on a multiple injection regimen with soluble insulin to a rapid-acting insulin analogue. The new longer-acting insulin analogues with a flatter profile of action overnight may also prove of value.

A19.27

A) F B) F C) T D) F E) F

The UK Prospective Diabetic Study (UKPDS) compared standard and intensive treatment in a large prospective controlled trial of type 2 diabetes patients. There was a 25% overall reduction in microvascular disease end points, a 33% reduction in albuminuria and a 30% reduction in the need for laser treatment for retinopathy in the more intensively treated patients. There appeared to be little difference in outcome between the tools used to achieve good metabolic control (metformin, sulphonylurea or insulin). A proportion of the total patients in the UKPDS were further randomized into standard and intensive blood pressure control groups. Cardiovascular risk was very considerably reduced in the intensive blood pressure treatment arm.

A19.28

A) F B) F C) F D) T E) F

On a practical level patients need to inform the driving and vehicle licensing authority and their insurance companies after diagnosis. They would also be wise to inform their family, friends and employers in case unexpected hypoglycaemia occurs. Insulin treatment can be undertaken by people in most walks of life; a few jobs are unsuitable. These include driving heavy goods or public service vehicles, working at heights, piloting aircraft or working close to dangerous machinery in motion.

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Certain professions such as the police and the armed forces are barred to all diabetic patients.

A19.29

A) T B) T C) T D) T E) T

In the absence of insulin, hepatic glucose production accelerates, and peripheral uptake by tissues such as muscle is reduced. Rising glucose levels lead to an osmotic diuresis, loss of fluid and electrolytes, and dehydration. Plasma osmolality rises and renal perfusion falls. In parallel, rapid lipolysis occurs, leading to elevated circulating free fatty-acid levels. The free fatty acids are broken down to fatty acyl-CoA within the liver cells, and this in turn is converted to ketone bodies within the mitochondria. Accumulation of ketone bodies produces a metabolic acidosis. Vomiting leads to further loss of fluid and electrolytes. The excess ketones are excreted in the urine but also appear in the breath, producing a distinctive smell similar to that of acetone. Respiratory compensation for the acidosis leads to hyperventilation, graphically described as 'air hunger'. Progressive dehydration impairs renal excretion of hydrogen ions and ketones, aggravating the acidosis.

A19.30

A) T B) F C) F D) T E) F

The management of diabetic nephropathy is similar to that of other causes of renal failure, with the following provisos: a) aggressive treatment of blood pressure with a target below 135/85 mmHg has been shown to slow the rate of deterioration of renal failure considerably. Angiotensin-converting enzyme inhibitors are the drugs of choice. Recent evidence suggests that these drugs should be

considered in normotensive patients with persistent microalbuminuria. b) Oral hypoglycaemic agents partially excreted via the kidney (e.g. chlorpropamide) must be avoided. c) Insulin sensitivity increases and drastic reductions in dosage may be needed. d) Associated diabetic retinopathy tends to progress rapidly, and frequent ophthalmic supervision is essential.

A19.31

A) T B) T C) T D) T E) T

Principles of diabetic foot care

Inspect feet daily
 Seek early advice for any damage
 Check shoes inside and out for sharp bodies/areas before wearing
 Use lace-up shoes with plenty of room for the toes
 Keep feet away from sources of heat (hot sand, hot-water bottles, radiators, fires)
 Check the bath temperature before stepping in

A19.32

A) F B) T C) T D) F E) T

The procedure for insulin-treated patients is simple: a) long-acting and/or intermediate insulin should be stopped the day before surgery, with soluble insulin substituted; b) whenever possible, diabetic patients should be first on the morning theatre list; c) an infusion of glucose, insulin and potassium is given during surgery. The insulin can be mixed into the glucose solution or administered separately by syringe pump. A standard combination is 16 U of soluble insulin with 10 mmol of KCl in 500 mL of 10% glucose, infused at 100 mL/h NS. d) Postoperatively, the infusion is maintained until the patient is able to eat. Other fluids needed in the perioperative period must be given through a separate intravenous line

and must not interrupt the glucose/insulin/potassium infusion. Glucose levels are checked every 2–4 hours and potassium levels are monitored. The amount of insulin and potassium in each infusion bag is adjusted either upwards or downwards according to the results of regular monitoring of the blood glucose and serum potassium concentrations.

A19.33

A) T B) T C) T D) T E) F

Poorly controlled diabetes is associated with stillbirth, mechanical problems in the birth canal owing to fetal macrosomia, hydramnios, and pre-eclampsia.

A19.34

A) F B) T C) T D) F E) T

Unsuspected infections, including urinary tract infections and tuberculosis, may be present. Thyrotoxicosis can also manifest as unstable glycaemic control.

A19.35

A) F B) T C) T D) F E) F

Factitious hypoglycaemia is a relatively common variant of self-induced disease and is much more common than an insulinoma. Hypoglycaemia is produced by surreptitious self-administration of insulin or sulphonylureas. Many patients in this category have been extensively investigated for an insulinoma. Measurement of C-peptide levels during hypoglycaemia should identify patients who are injecting insulin; sulphonylurea abuse can be detected by chromatography of plasma or urine.