ENDOCRINOLOGY AND DIABETES

Lecture Notes

Amir H. Sam
Karim Meeran
Neil Hill

2nd Edition

WILEY Blackwell

Endocrinology and Diabetes

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This edition first published 2023
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Edition History
Wiley-Blackwell (1e, 2009)

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Library of Congress Cataloging-in-Publication Data
Names: Sam, Amir H., author. | Meeran, Karim, author. | Hill, Neil (Neil Edward), author.
Title: Endocrinology and diabetes lecture notes / Amir Sam, Karim Meeran, Neil Hill.
Other titles: Lecture notes. Endocrinology and diabetes
Description: Second edition. | Hoboken, NJ : Wiley, 2023. | Preceded by Lecture note. Endocrinology and diabetes / Amir Sam, Karim Meeran. 2009.
Identifiers: LCCN 2022059957 (print) | LCCN 2022059958 (ebook) | ISBN 9781118682241 (paperback) | ISBN 9781118682234 (adobe pdf) | ISBN 9781118682227 (epub)
Subjects: MESH: Endocrine System Diseases | Diabetes Mellitus
Classification: LCC RC649 (print) | LCC RC649 (ebook) | NLM WK 140 | DDC 616.4—dc23/eng/20230323
LC record available at https://lccn.loc.gov/2022059957
LC ebook record available at https://lccn.loc.gov/2022059958

Cover Design: Wiley
Cover Image: © SCIEPRO/Getty Images

Set in 8.5/11pt Utopia by Straive, Pondicherry, India

A L G r a w a n y

Contents

Acknowledgements

We are grateful to Dr George Lam, Mr Alan Osborne, Mr Alexis Sudlow, Dr Saira Hameed, Professor Nick Oliver, Dr Rebecca Scott, Dr Chioma Izzi-Engbeaya, Dr Vassiliki Bravis, Professor Waljit Dhillo, Dr Vicky Salem, and Dr Sufyan Hussain for their helpful contributions, edits and advice.

We are also grateful to Professor Mark Gurnell, Dr Henry Tam, Professor Philip Gishen, Professor Fausto Palazzo, Dr Roberto Dina, Professor Pierre-Mac Bouloux, Dr John Frank, and Dr Owais Choudhri for kindly providing some of the images and illustrations used in this book. Additionally, we would like to express our thanks to Dr Kevin Shotliff and John Wiley & Sons for the diabetic retinopathy images used in Chapter 37, which were taken from *Practical Diabetes International*, Volume 23, pages 418–420.

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1

Thyroid anatomy and physiology

Anatomy

The thyroid gland consists of left and right *lobes* connected by a midline isthmus (Figure 1.1). The isthmus lies below the cricoid cartilage, and the lobes extend upward over the lower half of the thyroid cartilage. The thyroid is covered by the strap muscles of the neck and overlapped by the sternocleidomastoids. The pretracheal fascia encloses the thyroid gland and attaches it to the larynx and the trachea. This accounts for the upward movement of the thyroid gland on swallowing.

The thyroid gland develops from the floor of the pharynx in the position of the foramen caecum of the adult tongue as a downgrowth that descends into the neck. During this descent, the thyroid gland remains connected to the tongue by the thyroglossal duct, which later disappears. However, aberrant thyroid tissue or thyroglossal cysts (cystic remnants of the thyroglossal duct) may occur anywhere along the course of the duct (Figure 1.2). Such thyroid remnants move upward when the tongue is protruded.

The thyroid gland is composed of epithelial spheres called *follicles* (Figure 1.3), whose lumens are filled with a proteinaceous colloid containing *thyroglobulin*. Two basic cell types are present in the follicles. The follicular cells secrete thyroxine (T_4) and triiodothyronine (T_3) and originate from a downward growth of the endoderm of the floor of the pharynx (see above). The parafollicular or C cells secrete calcitonin and arise from neural crest cells that migrate into the developing thyroid gland. The follicles are surrounded by an extensive capillary network.

Physiology

Thyroid hormones act on many tissues. They regulate:

- organogenesis, growth, and development (central nervous system, bone)
- energy expenditure
- protein, carbohydrate, and fat metabolism
- gut motility
- bone turnover
- heart rate and contractility, and peripheral vascular resistance
- beta-adrenergic receptor expression
- muscle contraction and relaxation
- the menstrual cycle
- erythropoiesis.

Iodine is essential for normal thyroid function. It is obtained by the ingestion of foods such as seafood, seaweed, kelp, dairy products, some vegetables, and iodized salt. The recommended iodine intake for adults is 150 µg per day (250 µg per day for pregnant and lactating women). Dietary iodine is absorbed as iodide. Iodide is excreted in the urine.

Thyroid hormone synthesis

Figure 1.4 illustrates different steps in thyroid hormone synthesis.

- *Thyroglobulin* is synthesised in the rough endoplasmic reticulum and is transported into the follicular lumen by exocytosis.
- Iodide is transported into the thyroid follicular cells via a sodium–iodide symporter on the basolateral

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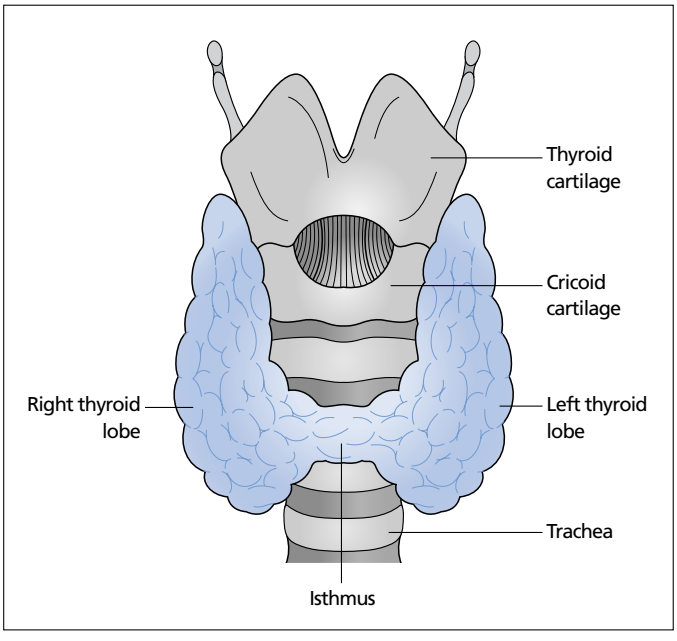

Figure 1.1 Thyroid gland.

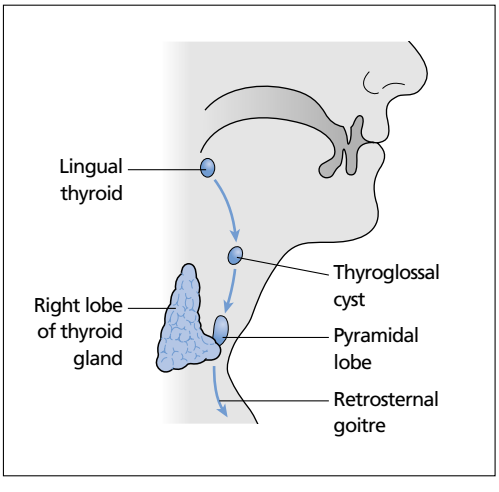

Figure 1.2 Possible sites of remnants of the thyroglossal duct.

membrane of the follicular cells. Iodide transport requires oxidative metabolism.

- Inside the follicular cells, iodide diffuses to the apical surface and is transported by pendrin (a membrane iodide–chloride transporter) into the follicular lumen.
- Within the colloid lumen, *thyroid peroxidase* (TPO) enzyme catalyses the process of oxidation of the iodide ($2I^-$) to iodine (I_2) and its binding (organification) to the tyrosine residues of thyroglobulin to form monoiodotyrosine (MIT) and diiodotyrosine (DIT).
- DIT and MIT molecules are linked by TPO to form *thyroxine* (T_4) and *triiodothyronine* (T_3) in a process known as coupling.
- Thyroglobulin containing T_4 and T_3 is resorbed into the follicular cells by endocytosis and is cleaved by lysosomal enzymes (proteases and peptidases) to release T_4 and T_3. T_4 and T_3 are then secreted into the circulation.
- Uncoupled MIT and DIT are deiodinated, and the free tyrosine and iodide are recycled.

The thyroid gland stores T_4 and T_3 incorporated in thyroglobulin, and can therefore secrete T_4 and T_3 more quickly than if they had to be synthesised.

Extrathyroidal T_3 production

T_4 is produced entirely by the thyroid gland. The production rate of T_4 is about 100 µg per day. However, only 20% of T_3 is produced directly by the thyroid gland (by coupling of MIT and DIT). Around 80% of T_3 is produced by the deiodination of T_4 in peripheral extrathyroidal tissues (mainly liver and kidney). The total daily production rate of T_3 is about 35 µg.

T_4 is converted to T_3 (the biologically active metabolite) by *5′-deiodination* (outer-ring deiodination),

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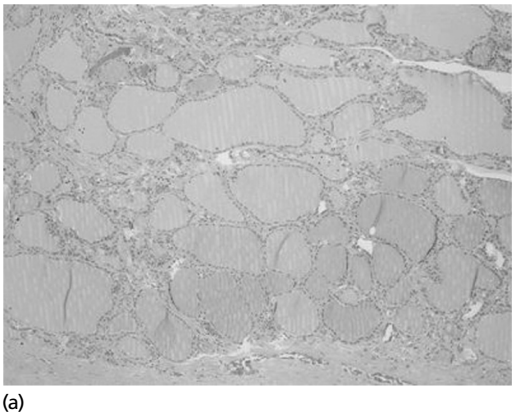
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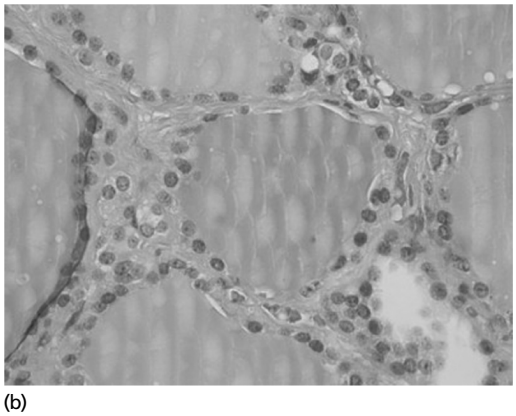
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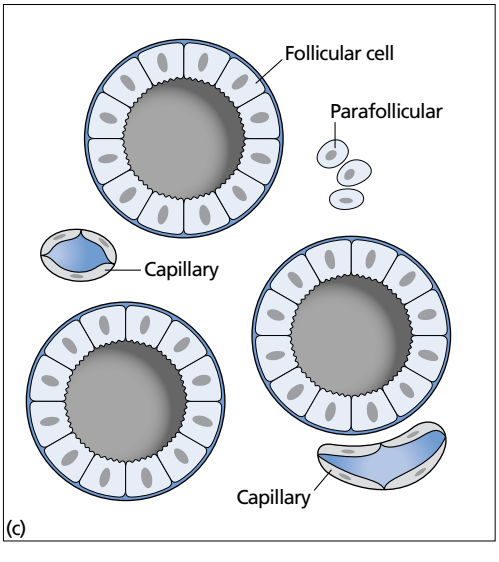

Figure 1.3 (a) A low-power histological image of thyroid tissue showing numerous follicles filled with colloid and lined by cuboidal epithelium. (b) A high-power view of follicles lined by cuboidal epithelium. (c) Thyroid follicles (lined by follicular cells), surrounding capillaries and parafollicular cells.

mediated by deiodinases type 1 (D1) and type 2 (D2). D1 is the predominant deiodination enzyme in the liver, kidney and thyroid. D2 is the predominant deiodination enzyme in muscle, brain, pituitary, skin, and placenta. Type 3 deiodinase (D3) catalyses the conversion of T_3 to reverse T_3 (the inactive metabolite) by *5-deiodination* (inner ring deiodination), as shown in Figure 1.5.

Changes in T_3 concentration may indicate a change in the rate of peripheral conversion and may not be an accurate measure of the change in thyroid hormone production. For example, the rate of T_3 production (by 5′-deiodination of T_4) is reduced in acute illness and starvation.

Total and free T_4 and T_3

Approximately 99.97% of circulating T_4 and 99.7% of circulating T_3 are bound to plasma proteins: *thyroid-binding globulin* (TBG), *transthyretin* (also known as thyroid-binding prealbumin), albumin, and lipoproteins.

Only the unbound thyroid hormone is available to the tissues. T_3 is less strongly bound and therefore has a more rapid onset and offset of action. The binding proteins have both storage and buffer functions. They help to maintain the serum free T_4 and T_3 levels within narrow limits, and also ensure

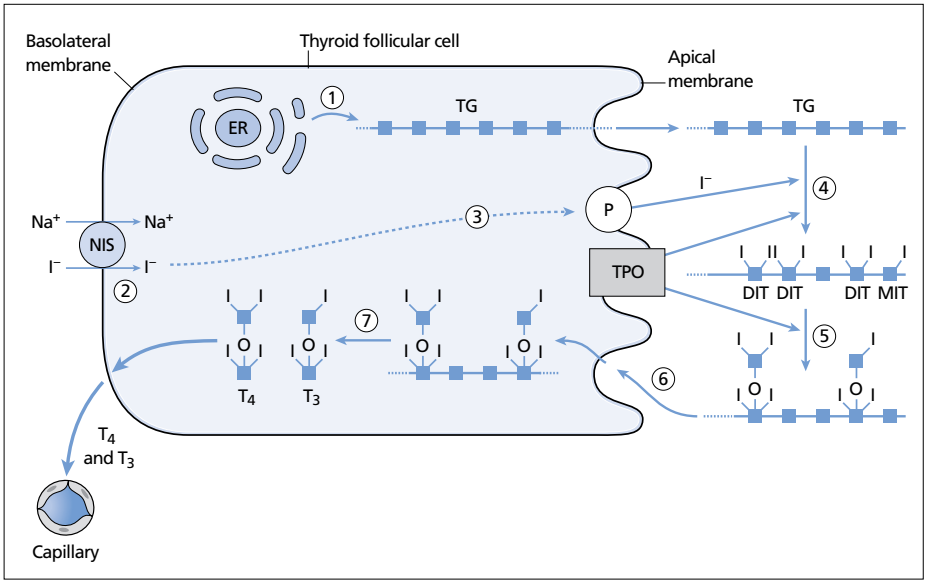

Figure 1.4 Steps in thyroid hormone synthesis. (1) Thyroglobulin (TG) is synthesised in the endoplasmic reticulum (ER) in the thyroid follicular cells and is transported into the follicular lumen. The small blue squares represent the amino acid residues comprising TG. (2) Iodide is transported into the follicular cell by the sodium–iodide (Na^+/I^-) symporter (NIS). (3) Iodide diffuses to the apical surface and is transported into the follicular lumen by pendrin (P). (4) Iodide is oxidised and linked to tyrosine residues in TG to form diiodotyrosine (DIT) and monoiodotyrosine (MIT) molecules. (5) Within the TG, T_4 is formed from two DIT molecules, and T_3 is formed from one DIT and one MIT molecule. (6) TG containing T_4 and T_3 is resorbed into the follicular cell by endocytosis. (7) TG is degraded by lysosomal enzymes to release T_4 and T_3 molecules, which move across the basolateral membrane of the follicular cell into the adjacent capillaries. TPO, thyroid peroxidase.

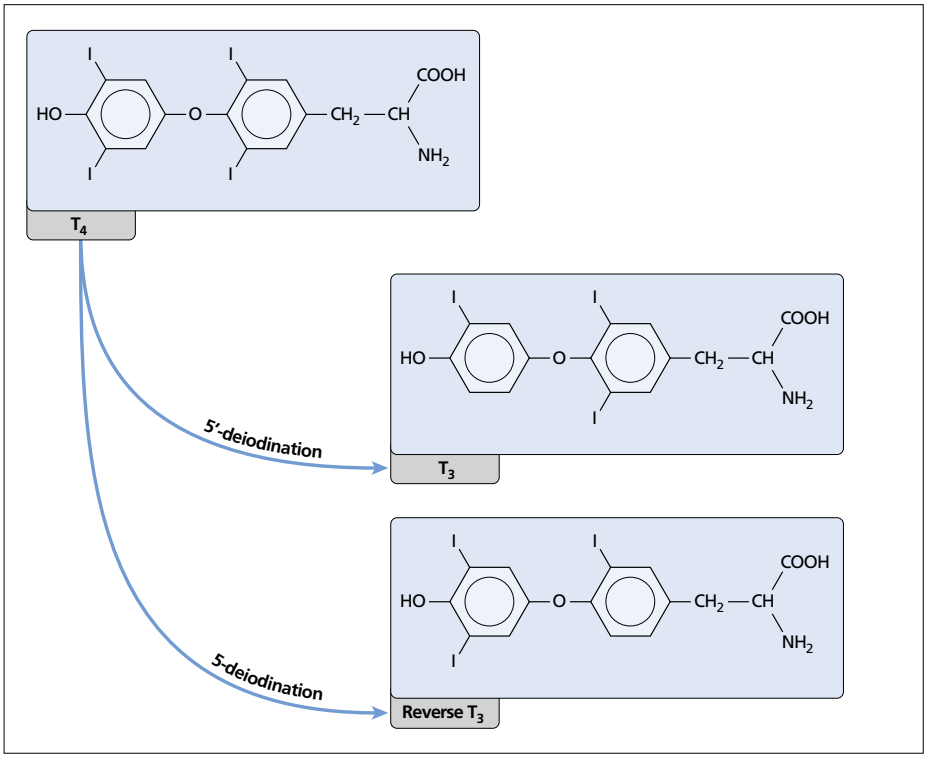

Figure 1.5 The conversion of T_4 to T_3 by 5′-deiodination and to reverse T_3 by 5-deiodination.

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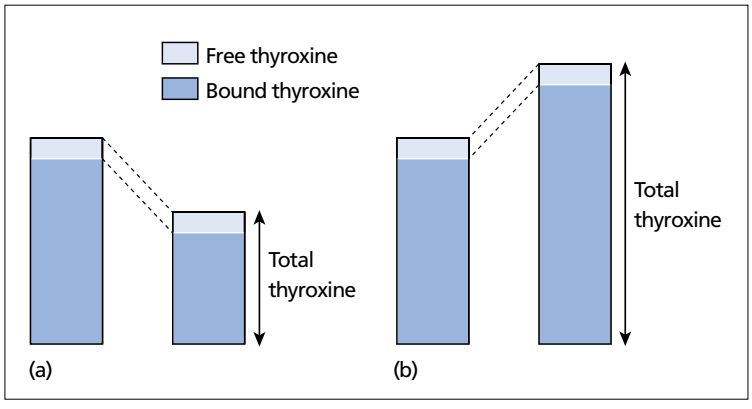

Figure 1.6 (a) If serum thyroid-binding globulin (TBG) levels are decreased, the level of thyroid hormone bound to TBG also decreases (the dark blue part of the bar). However, homeostatic mechanisms will maintain the free thyroid hormone levels (the light blue part of the bar). Note that although free hormone levels are unchanged, the 'total' hormone levels measured will be lower. (b) If TBG levels are increased, the level of thyroid hormone bound to TBG also increases (the dark blue part of the bar). However, homeostatic mechanisms will maintain the free hormone levels (the light blue part of the bar). Note that although free hormone levels are unchanged, the 'total' hormone levels measured will be higher.

continuous and rapid availability of the hormones to the tissues.

Free thyroid hormone concentrations are easier to interpret than total thyroid hormone levels. This is because the level of bound hormone alters with changes in the levels of thyroid-binding proteins, even though free T_4 (and T_3) concentrations do not change and the patient remains euthyroid (Figure 1.6). Box 1.1 summarises factors that may alter TBG levels.

Other causes of increased serum total T_4 and T_3 levels include familial dysalbuminaemic hyperthyroxinaemia (due to the presence of an abnormal albumin with a higher affinity for T_4) and the presence of anti-T_4 antibodies. Patients with these conditions are euthyroid, have normal serum thyroid-stimulating hormone (TSH) levels, and usually have normal serum free T_4 and T_3 levels when measured by appropriate methods.

Box 1.1 Factors that may alter thyroid-binding globulin (TBG) levels

↑ TBG

Hereditary TBG excess (X-linked dominant)
Pregnancy
Drugs, e.g. oestrogen, tamoxifen, opiates, phenothiazines, 5-fluorouracil, clofibrate
Hepatitis
Acute intermittent porphyria

↓ TBG

Genetically determined
Malnutrition
Chronic liver disease
Nephrotic syndrome
Drugs, e.g. androgens, corticosteroids, phenytoin
Cushing syndrome
Acromegaly

Thyroid hormone metabolism

T_4 has a half-life of ~7 days and is degraded at a rate of 10% per day. Around 40% of the T_4 is deiodinated to T_3 and 40% to reverse T_3. The remaining T_4 is conjugated with glucuronide and sulfate, deaminated and decarboxylated, or cleaved between the two rings.

T_3 is degraded (mostly by deiodination) at a rate of 75% per day ($t_{1/2}$ ~1 day). Reverse T_3 is degraded even more rapidly than T_3, mostly by deiodination ($t_{1/2}$ ~few hours).

Regulation of thyroid hormone production and release

T_3 and T_4 synthesis and secretion are stimulated by the TSH released from the anterior pituitary gland (Figure 1.7). TSH production and release are

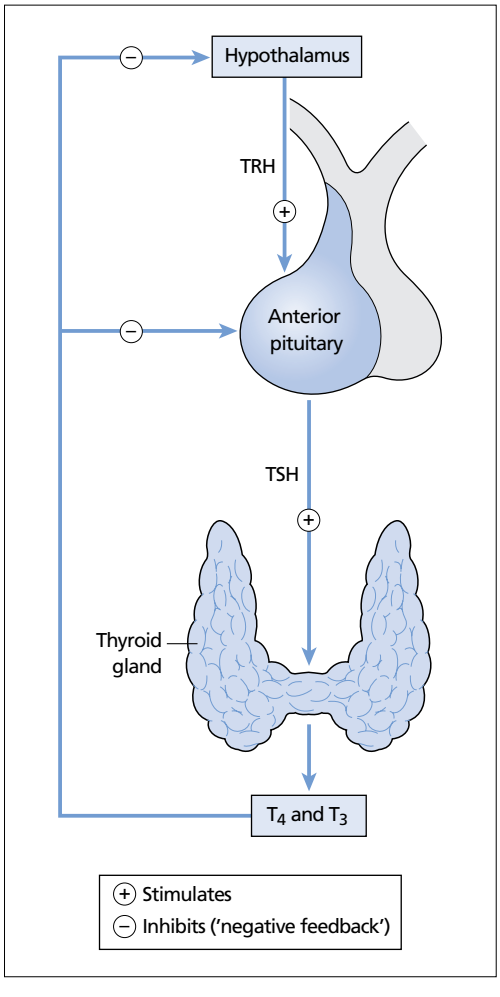

Figure 1.7 Hypothalamic–pituitary–thyroid axis. TRH, thyrotrophin-releasing hormone; TSH, thyroid-stimulating hormone.

increased by hypothalamic *thyrotrophin-releasing hormone* (TRH).

Thyrotrophin-releasing hormone

TRH is a tripeptide synthesised and released by the hypothalamus. TRH content is highest in the median eminence and paraventricular nuclei of the hypothalamus. TRH stimulates TSH secretion by activating a G-protein-coupled receptor and the phospholipase C-phosphoinositide pathway, resulting in mobilisation of calcium from intracellular storage sites.

Chronic TRH stimulation also increases the synthesis and glycosylation of TSH, which increases its biological activity.

Thyroid-stimulating hormone

TSH is a glycoprotein secreted by the thyrotroph cells of the anterior pituitary. TSH is composed of alpha and beta subunits that are non-covalently bound. The alpha subunit is the same as that of luteinising hormone, follicle-stimulating hormone, and human chorionic gonadotrophin. However, the beta subunit is unique to TSH. TSH binds to specific plasma membrane receptors and activates adenylyl cyclase. TSH also stimulates phospholipase C activity.

TSH stimulates every step in thyroid hormone synthesis and secretion. It also stimulates the expression of many genes in thyroid tissue and causes thyroid hyperplasia and hypertrophy.

T_4 and T_3 inhibit TSH synthesis and release both directly (by inhibiting transcription of the TSH subunit genes) and indirectly (by inhibiting TRH release). T_4 and T_3 also decrease the glycosylation and hence bioactivity of TSH.

TSH secretion is regulated by very small changes in serum T_4 and T_3 concentrations. However, an important exception is that the reduced T_3 levels in patients with non-thyroidal illness have little effect on TSH secretion. This may be due to a greater contribution of serum T_4 to the nuclear T_3 content of the pituitary than other tissues.

Box 1.2 shows a list of the causes of increased and decreased TSH concentration.

Box 1.2 Causes of increased and decreased thyroid-stimulating hormone (TSH) concentration

Increased TSH secretion

Primary/subclinical hypothyroidism
Secondary hyperthyroidism
Recovery from non-thyroidal illness
Thyroid hormone resistance
Primary adrenal insufficiency
Drugs: dopamine antagonists (metoclopramide, domperidone), amiodarone
Patients with antibodies to the murine immunoglobulins used in the assay

Decreased TSH secretion

Primary/subclinical hyperthyroidism
Secondary hypothyroidism
Non-thyroidal illness
Drugs: dopamine agonists, octreotide, phenytoin, steroids
Increased human chorionic gonadotrophin, e.g. early pregnancy, molar pregnancy, choriocarcinoma

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Mechanism of action of thyroid hormones

Thyroid hormones enter cells via active membrane transporter proteins (e.g. MCT8). Inside the cells, T_3 formed from the deiodination of T_4 and T_3 that enter the cells from the serum is transferred to the nucleus. The thyroid hormone receptors (TRs) heterodimerise with the retinoid X receptor and act as nuclear transcription factors. TRs bind thyroid hormone response elements in the promoter region of thyroid hormone-responsive genes. In the absence of T_3, TRs bind co-repressor proteins that repress transcription. On T_3 binding, co-repressors are displaced, and co-activator proteins bind the TRs, resulting in histone acetylation, generation of a permissive chromatin structure and induction of gene transcription.

There are two T_3 nuclear receptors – alpha and beta–encoded by separate genes located on chromosomes 17 and 3. Two forms of each TR are generated by alternative splicing. Only the beta-1, beta-2, and alpha-1 receptors bind T_3. Liver predominantly expresses beta receptors, whereas heart and bone express alpha receptors. The hypothalamus and pituitary express beta-2 receptors, which mediate the negative feedback regulation.

KEY POINTS

- Thyroid hormone synthesis involves the transport of iodide into follicular cells, iodide oxidation into iodine, binding of iodine to thyroglobulin tyrosine residues (organification) to form MIT and DIT, and coupling of DIT and MIT to form T_4 and T_3. The processes of iodide oxidation, organification and coupling are catalysed by the TPO enzyme.
- Thyroid hormone synthesis and secretion are stimulated by TSH released from the anterior pituitary gland. TSH production and release are increased by hypothalamic TRH.
- 80 percent of T_3 is produced by the 5′-deiodination of T_4 in peripheral extrathyroidal tissues (mainly liver and kidney).
- Free thyroid hormone concentrations are easier to interpret than total thyroid hormone levels as the level of bound hormone alters with changes in the levels of thyroid-binding proteins.
- T_4 is largely a prohormone, and almost the entire nuclear-bound hormone is T_3.

2

Hypothyroidism

Hypothyroidism results from insufficient secretion of thyroid hormones.

- *Primary* hypothyroidism is characterised by low serum free thyroxine (T_4) and high serum thyroid-stimulating hormone (TSH) levels (due to a reduced negative feedback effect of T_4 on TSH synthesis/secretion).
- *Subclinical* hypothyroidism (SCH) is defined as normal serum free T_4 and T_3 levels and a high serum TSH. This reflects the sensitivity of TSH secretion to very small decreases in thyroid hormone secretion.
- *Central* hypothyroidism is much less common and results from reduced TSH secretion from the anterior pituitary (secondary hypothyroidism) or reduced thyrotrophin-releasing hormone (TRH) secretion from the hypothalamus (tertiary hypothyroidism).

Epidemiology

The prevalence of congenital hypothyroidism in the UK is about 1 in 4000 of the population. The frequency of hypothyroidism varies from 0.1% to 2% of adults. Hypothyroidism is 5–8 times more common in females. Primary hypothyroidism accounts for more than 95% of cases of hypothyroidism. Around 5% of adults and 15% of women over the age of 60 have SCH.

Aetiology

Box 2.1 summarises the causes of hypothyroidism.

SCH (see above) may result from the same causes as primary hypothyroidism or from inadequate T_4 replacement in a patient with overt hypothyroidism.

Congenital hypothyroidism may be secondary to thyroid agenesis, dysgenesis, or inherited defects in thyroid hormone biosynthesis.

Acquired hypothyroidism may be primary or central as mentioned above. Primary hypothyroidism may be due to chronic autoimmune (Hashimoto) thyroiditis, iatrogenic causes (e.g. drugs, thyroidectomy, radioiodine), iodine deficiency/excess or thyroiditis.

Chronic autoimmune (Hashimoto) thyroiditis is caused by cellular and antibody-mediated injury to the thyroid tissue. There are two forms, goitrous and atrophic, which have similar pathophysiology and clinical management but are different in the extent of thyroid follicular cell hyperplasia, lymphocytic infiltration, and fibrosis. Chronic autoimmune thyroiditis is usually but not always permanent. People with chronic autoimmune thyroiditis are more likely to have a personal or family history of other autoimmune conditions, such as Addison disease and type 1 diabetes mellitus, vitiligo (Figure 2.1), pernicious anaemia, and premature ovarian failure. An increased incidence of Hashimoto thyroiditis is also found in those with Down or Turner syndrome.

Drugs such as the antithyroid drugs carbimazole and propylthiouracil (used to treat hyperthyroidism) may cause hypothyroidism. Amiodarone is an iodine-containing drug and may cause both hypothyroidism (see below) and thyrotoxicosis (see Chapter 3). Other drugs that may cause hypothyroidism include lithium, alpha-interferon and interleukin-2. Patients on these drugs should have their serum TSH checked every 6–12 months.

T_4 has a half-life of 7 days, and hypothyroidism occurs about 2–4 weeks following total *thyroidectomy*. After subtotal thyroidectomy for the treatment of Graves disease, hypothyroidism occurs within the first year in the majority of patients. The annual risk of hypothyroidism in those who are euthyroid at 1 year is 0.5–1%. Some patients become transiently hypothyroid after 4–8 weeks but recover several weeks or months later.

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Box 2.1 Causes of hypothyroidism

Congenital

Thyroid agenesis, dysgenesis or inherited defects in thyroid hormone biosynthesis

Acquired

Primary

Chronic autoimmune (Hashimoto) thyroiditis
Iatrogenic (drugs, thyroidectomy, radioiodine, neck radiotherapy)
Iodine deficiency/excess
Thyroiditis

Central

Pituitary/hypothalamic damage (e.g. due to tumours, trauma, radiotherapy, hypophysitis, infarction, infiltration)

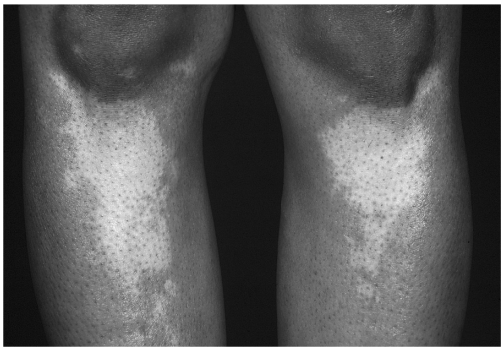

Figure 2.1 Vitiligo in a patient with Hashimoto thyroiditis.

Following *radioiodine therapy* for the treatment of Graves disease, the majority of patients become hypothyroid within the first year. The rest have a 0.5–2% annual risk of hypothyroidism. Some patients with toxic multinodular goitre or thyroid adenomas who receive radioiodine therapy also become hypothyroid.

External irradiation of the neck may result in hypothyroidism with a gradual onset. Many patients develop overt hypothyroidism after several years of SCH.

Iodine deficiency and excess can both cause hypothyroidism. Iodine deficiency is the most common worldwide cause of hypothyroidism and is more prevalent in mountainous areas. Iodine excess can also result in hypothyroidism by inhibiting iodine organification and T_4 and T_3 synthesis (Wolff–Chaikoff effect).

In *postpartum* and *subacute thyroiditis*, transient hypothyroidism (lasting weeks to a few months) may follow transient thyrotoxicosis.

Rarer causes include infiltrative diseases, for example fibrous (Reidel) thyroiditis, haemochromatosis, sarcoidosis, amyloidosis, leukaemia, and consumptive hypothyroidism due to an ectopic production of the type 3 deiodinase in vascular and fibrotic tumours, which metabolises T_4 to reverse T_3.

Clinical presentations

Hypothyroidism often has an insidious and non-specific onset. Patients may present with fatigue, lethargy and cold intolerance. Clinical presentations of thyroid hormone deficiency result from a generalised slowing of metabolic processes and an accumulation of hydrophilic glycosaminoglycans in the interstitial spaces of the tissues (*myxoedema*). Box 2.2 summarises the clinical presentations of hypothyroidism in adults and possible explanations for these manifestations.

In secondary hypothyroidism due to hypothalamic/pituitary disease, the symptoms are usually milder than in primary hypothyroidism and may be masked by symptoms of other hormone deficiencies (see Chapter 12). For example, hot flushes secondary to hypogonadism may make the cold intolerance caused by hypothyroidism less obvious.

Investigations

The diagnosis of hypothyroidism is made by measuring serum TSH and free T_4. In many developed countries, congenital hypothyroidism is diagnosed during the routine screening of all infants by measuring TSH or T_4 in blood obtained from a heel prick in the first week of life. Reference ranges for serum TSH are derived from populations without thyroid disease – there is some controversy regarding the level at which the upper limit of normal is set. Although thyroid peroxidase (TPO) antibodies are frequently positive in Hashimoto thyroiditis, they are neither sensitive nor specific and should not be used for diagnosis.

Table 2.1 shows the results of thyroid function tests in primary, subclinical and secondary hypothyroidism. In general, younger patients presenting with primary hypothyroidism have much higher TSH levels than older patients.

Other laboratory test abnormalities in hypothyroid patients include *hyperlipidaemia* and *hyponatraemia*.

Patients with central hypothyroidism should have pituitary function tests and a magnetic resonance imaging scan of the hypothalamus and pituitary. A TRH test may occasionally be done to differentiate

Box 2.2 Clinical presentations of hypothyroidism

General
Tiredness, cold intolerance, depression, goitre

Skin and hair
Skin: dry and coarse (decreased acinar gland secretion), pale (reduced blood flow), yellowish tinge (carotenaemia), oedematous (accumulation of glycosaminoglycans in the dermis with associated water retention)
Coarse hair, hair loss, and brittle nails

Cardiovascular

Bradycardia, exertional breathlessness, and reduced exercise tolerance (reduced heart rate and contractility as thyroid hormone regulates genes involved in myocardial contractility and relaxation), exacerbation of heart failure or angina, diastolic hypertension (increased systemic vascular resistance), pericardial effusion, hypercholesterolaemia, hypertriglyceridaemia (decreased lipid metabolism)

Respiratory

Exertional breathlessness, hypoventilation (respiratory muscle weakness, and reduced ventilatory responses to hypoxia and hypercapnia), obstructive sleep apnoea (macroglossia), pleural effusion

Gastrointestinal

Constipation (decreased gut motility), weight gain (reduced metabolic rate and accumulation of glycosaminoglycan-rich fluid), ascites (rare)

Reproductive

Hyperprolactinaemia (high TRH in primary hypothyroidism stimulates prolactin production)
Women: oligomenorrhoea/amenorrhoea or menorrhagia, early abortion
Men: reduced libido, erectile dysfunction, delayed ejaculation, reduced serum total testosterone due to low sex hormone-binding globulin levels

Neurological

Slowing of intellectual activities, movement and speech, impaired memory, delayed relaxation of deep tendon reflexes, carpal tunnel syndrome, peripheral neuropathy, cerebellar ataxia, encephalopathy, muscle abnormalities (asymptomatic rise in serum creatine kinase, muscle cramps, proximal muscle weakness, rarely rhabdomyolysis)

Myxoedema coma

May present with coma, hypothermia, hypercapnia, and hyponatraemia. Precipitating factors include infection, cold exposure, trauma, and drugs (hypnotics or opiates) in patients with severe hypothyroidism

Anaemia

Normocytic anaemia, macrocytic anaemia (in those with pernicious anaemia associated with autoimmune thyroiditis), microcytic anaemia (in female patients with menorrhagia)

Metabolic

Hyperlipidaemia, hyponatraemia (reduced cardiac output sensed by the carotid sinus baroreceptors can result in increased antidiuretic hormone release; also decreased glomerular filtration results in reduced free water excretion), hyperhomocysteinaemia

Table 2.1 Thyroid function tests in various forms of hypothyroidism

	Thyroid-stimulating hormone	Free thyroxine	Free triiodothyronine
Primary hypothyroidism	↑	↓	↓ or N
Subclinical hypothyroidism	↑	N	N
Central hypothyroidism	↓ or inappropriately N	↓	↓ or N

N, normal.

between pituitary and hypothalamic causes of TSH deficiency. A dose of 200 μg of TRH is given intravenously over 2 minutes. Blood samples are taken at 30 and 60 minutes. The 60-minute TSH value exceeds the 30-minute value in hypothalamic hypothyroidism.

Pituitary enlargement may occasionally be seen in severe primary hypothyroidism owing to hypertrophy and hyperplasia of the thyrotroph cells. It is important to distinguish this entity, which is reversible with T_4 replacement, from a pituitary adenoma.

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Treatment

Hypothyroidism usually requires lifelong treatment with synthetic levothyroxine. Exceptions include cases of transient hypothyroidism following subacute or postpartum thyroiditis, or reversible hypothyroidism due to a drug that can be stopped.

Treatment objectives are the resolution of symptoms, a normalisation of TSH and a reduction in the size of the goitre in patients with Hashimoto thyroiditis.

There is no proven benefit in using a combined T_3/T_4 replacement.

Dose and administration of levothyroxine

Younger patients (under 50 years) can be started on levothyroxine at a dose of 1.6 µg/kg body mass (typically 50–125 µg daily). Thyroid function tests are repeated after 6–8 weeks and the dose adjusted by 25 µg until the TSH is in the normal range.

Older patients or those with known ischaemic heart disease should be started on a lower dose (25 µg daily) as they may have ischaemic heart disease, and levothyroxine increases myocardial oxygen demand. The dose may be gradually increased but a suboptimal replacement may have to be accepted if an optimal dose causes cardiac symptoms.

The average dose of levothyroxine in hypothyroid adults is about 100 µg per day, but the range varies from 50 to 200 µg daily. It is important to advise patients on the potential adverse effects of levothyroxine over-replacement, such as arrhythmias and osteoporosis.

Levothyroxine should be taken on an empty stomach, and medications that interfere with its absorption (e.g. ferrous salts, cholestyramine) should be taken several hours after the levothyroxine dose. Some drugs (e.g. phenytoin, carbamazepine) may increase levothyroxine metabolism.

Patients with poor compliance with levothyroxine replacement may occasionally receive their total weekly dose of levothyroxine once per week. This should probably be avoided in coronary heart disease.

Follow-up and monitoring

Levothyroxine has a half-life of 1 week and it takes about 6 weeks (six half-lives) to reach a steady-state concentration. Serum T_4 increases first, and then TSH secretion starts to fall. Follow-up appointments for clinical assessment, measurements of thyroid function and adjustment of the dose should be arranged every 6 weeks. After stabilisation of TSH levels and establishment of the proper maintenance dose, clinical assessment and serum TSH measurements should be carried out annually.

When levothyroxine is commenced, TSH occasionally rises further initially before it starts to fall. This may be because the pituitary itself has begun to suffer from the profound hypothyroidism and has failed to make TSH. On commencement of the levothyroxine, the pituitary starts to recover.

It is worth noting that hair loss may initially be made worse by commencing levothyroxine. This is because new hair follicles start growing and push up the old hair follicles. It may take about 9 months before this stabilises.

Special circumstances

Myxoedema coma

Myxoedema coma should be treated aggressively as it has a high mortality of up to 80%. Patients should be monitored closely in an intensive care unit. Mechanical ventilation should be instituted for respiratory failure. Blood should be taken for culture, free T_4, T_3, TSH and cortisol before starting treatment. Treatment must be started before the diagnosis is established:

- No consensus has yet been reached about the optimal regimen of *thyroid hormone* replacement. An accepted regimen includes the administration of intravenous levothyroxine 300–500 µg (depending on the patient's age, weight and risk of myocardial ischaemia or arrhythmia) followed by daily intravenous doses of 50–100 µg until the patient can take oral levothyroxine. If there is no improvement within 24–48 hours, intravenous T_3 (2.5–10 µg 8-hourly) is added.
- Intravenous *hydrocortisone* (100 mg 6–8-hourly) must be given until co-existing adrenal insufficiency can be excluded.
- Treat possible *precipitating factors* such as infection with broad-spectrum antibiotics.
- Replace intravenous *fluids* (and glucose) appropriately.
- Correct *hypothermia* using a heating blanket. Aim for an hourly rise of 0.5 °C in core temperature. Rapid external warming can cause inappropriate vasodilation and cardiovascular collapse.

Suspected adrenal insufficiency

Levothyroxine replacement in patients with untreated adrenal insufficiency can precipitate an Addisonian crisis (see Chapter 6). A short Synacthen test should always be done prior to levothyroxine replacement if adrenal insufficiency or secondary hypothyroidism is suspected. Hydrocortisone must be given with the levothyroxine if adrenal insufficiency is confirmed.

Subclinical hypothyroidism

SCH is often transient (e.g. non-thyroidal illness). TSH >4.5 µmol/L is seen in up to 10% adults over 80 years. TSH has a circadian rhythm (rising in the evening) so it is helpful to measure at the same time of day when decisions regarding treatment initiation are concerned. Indications for levothyroxine replacement in SCH vary and include pregnancy, a serum TSH above 10 mU/L, goitre, symptoms of hypothyroidism such as fatigue, constipation or depression, or high serum antithyroid peroxidase (microsomal) antibody. People who are not treated should have periodic thyroid function tests to detect progression to overt hypothyroidism. There is some evidence from epidemiological studies that treatment of SCH in younger patients (under 65 years) with signs or symptoms of hypothyroidism may reduce fatigue. There is no evidence that treating SCH improves overall survival in adults under 70 years age; other studies have found the opposite – that high TSH and low (within the normal range) free T_4 concentrations lower the risk of adverse effects and mortality.

Oestrogen therapy

Oestrogens may increase the need for levothyroxine. In women receiving levothyroxine replacement, serum TSH should be measured about 12 weeks after starting oestrogen therapy to determine whether an increase in levothyroxine dose is needed.

Surgery

Patients on thyroxine replacement who are unable to eat or drink following surgery should receive intravenous levothyroxine (80% of oral dose) *only* if they have not resumed oral intake after 5–7 days.

Transient hypothyroidism

Transient hypothyroidism, for example following thyroiditis, can last from a few weeks to as long as 6 months. Patients with minimal symptoms may not require therapy. Symptomatic patients should receive levothyroxine for several months. A normal serum TSH level 6 weeks after stopping levothyroxine indicates a recovery of thyroid function.

Pregnancy

See Chapter 31.

KEY POINTS

- Primary hypothyroidism (low serum free T_4 and high serum TSH) may be due to chronic autoimmune (Hashimoto) thyroiditis, iatrogenic causes (antithyroid drugs, thyroidectomy, radioiodine), iodine deficiency/excess, or thyroiditis.
- Clinical presentations of thyroid hormone deficiency result from a generalised slowing of metabolic processes and an accumulation of hydrophilic glycosaminoglycans in the interstitial spaces of the tissues (myxoedema).
- Hypothyroidism usually requires lifelong treatment with synthetic thyroxine. Hypothyroid patients with a history of ischaemic heart disease should be started on a lower dose of levothyroxine.
- Levothyroxine replacement in patients with untreated adrenal insufficiency can precipitate an Addisonian crisis.

A L G r a w a n y

3

Thyrotoxicosis

Thyrotoxicosis is the syndrome resulting from an excess of circulating free thyroxine (T_4) and/or free triiodothyronine (T_3). Thyrotoxicosis may be due to either increased thyroid hormone synthesis (*hyperthyroidism*) or increased release of stored thyroid hormone from an inflamed thyroid gland (e.g. in subacute thyroiditis).

- *Primary* hyperthyroidism is characterised by raised free T_4 and/or T_3 and low thyroid-stimulating hormone (TSH). TSH is suppressed due to the negative feedback effect of thyroid hormones on TSH synthesis/secretion.
- *Secondary* hyperthyroidism is characterised by raised T_4 and T_3 due to increased TSH secretion from a pituitary tumour ('thyrotroph adenoma').

T_3 toxicosis (high free T_3, normal free T_4, low TSH) tends to occur early in the course of hyperthyroidism, when patients have relatively few symptoms. T_4 toxicosis (high free T_4, normal free T_3, low TSH) may be seen in hyperthyroid patients in whom a concurrent non-thyroidal illness reduces the conversion of T_4 to T_3.

Subclinical hyperthyroidism (SCH) is defined as suppressed TSH in the presence of normal free T_4 and T_3. These patients may have few or no symptoms or signs of hyperthyroidism.

Epidemiology

Thyrotoxicosis affects around 1% of females and 0.1% of males. Graves disease accounts for 70–80% of all cases of hyperthyroidism. Toxic multinodular goitre is the most common cause of hyperthyroidism in the elderly. Secondary hyperthyroidism is very rare.

Aetiology

Box 3.1 summarises the causes of thyrotoxicosis.

Graves disease

Graves disease is caused by autoantibodies that stimulate the TSH receptor and hence thyroid hormone synthesis and secretion, and thyroid growth (causing a diffuse goitre in about 80% people). Possible precipitating and predisposing factors include genetic susceptibility (suggested by an association with certain alleles of CTLA-4 and HLA and different concordances rates between mono- and dizygotic twins) and environmental factors such as stress, cigarette smoking, iodine, and infection (*Yersinia enterocolitica*), vitamin D and selenium deficiency.

The mechanisms that may be involved in the pathogenesis of Graves hyperthyroidism include molecular mimicry (similarity between some infectious/exogenous antigens and human proteins) and thyroid cell expression of HLA class II molecules (which may act as antigen-presenting cells to initiate an autoimmune response).

Patients with Graves disease may have a personal or family history of other autoimmune disorders such as vitiligo, alopecia areata, pernicious anaemia, type 1 diabetes mellitus, myasthenia gravis, or coeliac disease.

Toxic multinodular goitre and toxic adenoma

These are the result of focal and/or diffuse hyperplasia of thyroid follicular cells whose function is independent of regulation by TSH. Between 20% and 80% of toxic adenomas and some nodules of toxic multinodular goitres have somatic mutations of the TSH receptor gene that confer autonomous hyperactivity.

Thyroiditis

Thyroiditis (e.g. subacute viral, postpartum) can result in thyrotoxicosis by the release of preformed thyroid hormones from a damaged thyroid gland into the circulation.

Endocrinology and Diabetes: Lecture Notes, Second Edition. Amir H. Sam, Karim Meeran and Neil Hill.
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Box 3.1 Causes of thyrotoxicosis

Graves disease

Toxic multinodular goitre
Toxic adenoma
Thyroiditis (de Quervain and postpartum)
Secondary hyperthyroidism (due to a TSH-secreting pituitary adenoma)
Drugs: excessive exogenous thyroxine, amiodarone, interferon-alpha

Rarer causes

Metastatic thyroid cancer
McCune–Albright syndrome
Ectopic thyroid tissue (e.g. struma ovarii)
Gestational thyrotoxicosis
Human chorionic gonadotrophin-secreting gestational trophoblastic disease (including hydatidiform mole and choriocarcinoma)

Subacute (de Quervain) viral thyroiditis presents initially with thyrotoxicosis followed by hypothyroidism several weeks later. Recovery of normal thyroid function occurs 3–6 months later, but 10–30% of patients subsequently develop permanent hypothyroidism. A similar but painless thyroiditis may occur 3–6 months after delivery (postpartum thyroiditis), possibly due to the exacerbation of a previously subclinical autoimmune thyroiditis. The thyrotoxic phase lasts for about 1–4 weeks.

Secondary hyperthyroidism

Secondary hyperthyroidism due to a TSH-secreting pituitary tumour is very rare. A similar biochemical picture (high free T_4/T_3 and normal or high TSH) may be seen in the uncommon 'thyroid hormone resistance syndrome' (see below).

Amiodarone

Amiodarone (an iodine-containing antiarrhythmic drug) may affect thyroid function in several ways. Amiodarone inhibits the conversion of T_4 to T_3 and results in a high or high-normal free T_4, low-normal free T_3 and initially high TSH that normalises within 2–3 months. In addition, amiodarone may cause both hypothyroidism (see Chapter 2) and thyrotoxicosis.

Amiodarone-induced thyrotoxicosis (AIT) occurs in 6–10% people taking amiodarone. Clinical manifestations are often masked by the drug's beta-blocking activity. Patients may present with atrial arrhythmias, exacerbation of ischaemic heart disease or heart failure, unexplained weight loss, restlessness, or low-grade fever. There are two types of AIT. However, some patients may have a mixture of both types.

- *Type 1* thyrotoxicosis (10% AIT cases) is caused by amiodarone's high iodine content (the Jod–Basedow effect), which provides the substrate for excessive thyroid hormone synthesis in patients with a previously silent multinodular goitre.
- *Type 2* thyrotoxicosis (90% AIT cases) is due to a direct toxic effect of the drug on the thyroid gland, resulting in a destructive thyroiditis and the release of preformed T_4 and T_3.

Subclinical hyperthyroidism

This condition may be endogenous (due to the same conditions that cause overt hyperthyroidism) or due to excess exogenous T_4.

Clinical presentations

Clinical presentations of thyrotoxicosis are summarised in Box 3.2. Symptoms may be less pronounced in older patients.

Examination of the neck may reveal a diffusely enlarged goitre (90% of patients with Graves disease), a multinodular goitre or solitary nodule. A diffuse goitre may also be seen in painless thyroiditis and TSH-secreting pituitary tumours (TSHomas). Subacute (de Quervain) thyroiditis presents with a small tender goitre, and patients may have had a preceding flu-like illness and/or anterior neck pain.

Clinical signs specific to Graves disease include *orbitopathy*, *pretibial myxoedema* and *thyroid acropachy*. These are mediated by different autoantibodies that may co-exist in Graves disease.

Thyroid eye disease

Patients with thyrotoxicosis *due to any cause* may have *lid retraction* and *lid lag* (sclera visible above the iris as the patient looks downward) caused by sympathetic overactivity, possibly mediated by increased beta-adrenergic receptors.

Graves orbitopathy may be clinically obvious in 20–25% of patients with Graves hyperthyroidism at the time of diagnosis of the hyperthyroidism (Figure 3.1). It is more common in females. Many more (>90%) may have evidence of orbitopathy on computed tomography/magnetic resonance imaging (CT/MRI)

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Box 3.2 Clinical presentations of thyrotoxicosis

General

Heat intolerance, anxiety, irritability, hyperactivity, fatigue, insomnia

Skin, nails and hair

Increased sweating, warm moist skin (increased blood flow), palmar erythema, pruritus
Onycholysis (loosening of the nails from the nail bed)
Hair loss
Graves disease: pretibial myxoedema, acropachy
Alopecia areata, and vitiligo (associated with autoimmune disorders)

Ocular

Lid retraction and lid lag
Graves orbitopathy: periorbital oedema, grittiness, increased tear production, chemosis, proptosis (unilateral in 5–10%), ophthalmoplegia, optic nerve compression

Cardiovascular

Palpitations (sinus tachycardia, atrial fibrillation)
Widened pulse pressure (a combination of systolic hypertension and reduced peripheral vascular resistance), congestive heart failure, mitral valve prolapse/regurgitation

Respiratory

Exertional breathlessness (due to increased oxygen consumption and carbon dioxide production, and respiratory muscle weakness), tracheal obstruction secondary to large goitre

Gastrointestinal

Diarrhoea, increased appetite, weight loss, weight gain (10% of younger patients), dysphagia (due to a large goitre)

Neurological

Tremor, proximal muscle weakness, brisk tendon reflexes, inability to concentrate, chorea
Hypokalaemic (thyrotoxic) periodic paralysis: seen particularly in Asian men, characterised by intermittent weakness, usually after exercise or a high-carbohydrate meal

Psychiatric

Depression, apathetic thyrotoxicosis in the elderly, psychosis (rare)

Genitourinary

Females: oligomenorrhoea/amenorrhoea
Males: gynaecomastia, reduced libido, erectile dysfunction, abnormal or decreased spermatogenesis, polyuria (possibly due to primary polydipsia or hypercalciuria)

Musculoskeletal

Osteoporosis (thyroid hormone stimulates bone resorption), raised serum alkaline phosphatase (increased bone turnover), hypercalcaemia

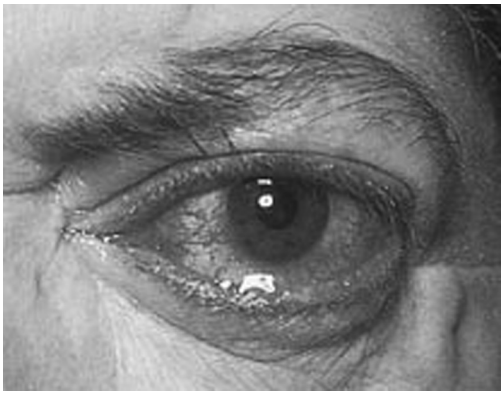

Figure 3.1 Graves orbitopathy.

of the orbits. Around 10% of patients with Graves orbitopathy do not have Graves disease; they may have autoimmune hypothyroidism or thyroid autoantibodies. Risk factors for Graves orbitopathy are shown in Box 3.3. Of note, 20% patients develop new Graves orbitopathy or have worsening of pre-existing GO after radioactive iodine (RAI) treatment and there is a 7% risk of severe Graves orbitopathy after RAI. The peak incidence of Graves orbitopathy is 6 months after RAI (range 1–24 months). There is good evidence that oral steroid cover and avoidance (or rapid treatment) of post-radioiodine hypothyroidism mitigate the risk of worsening Graves orbitopathy in patients at low risk of or with mild Graves orbitopathy.

Box 3.3 Risk factors for Graves orbitopathy

Smoker
Male
High TSH receptor antibody titre
High pretreatment T_3 levels
Prolonged hypothyroidism post RAI
Increasing age

Graves orbitopathy may present with periorbital oedema, conjunctival oedema (chemosis) and

Box 3.4 Vancouver orbitopathy rules

REFER IF:

Positive answer to Q1 and/or 2

1 Swelling or feeling of fullness in one or both of your upper eyelids?

2 Bags under the eyes?

Plus a positive answer to Q3–5

3 Do your eyes seem to be too wide open?

4 Is your vision blurry (even with glasses/contacts?)

5 Redness in your eyes or eyelids?

injection, grittiness, corneal ulceration, proptosis (60%), ophthalmoplegia, diplopia (40%), retrobulbar pain or pain on eye movement, and optic nerve compression (6%), which may result in impaired visual acuity or visual field defects. Graves orbitopathy may be unilateral in 15% of patients.

Pathogenesis involves activated T-cell cytokines and TSH receptor antibodies that activate TSH receptors on fibroblasts and adipocytes. This sets off an inflammatory process and causes the secretion of hydrophilic glycosaminoglycans, resulting in an increased retro-orbital volume.

There are several validated screening tools to assist clinician recognition of thyroid eye disease, including the DiaGo clinical assessment tool and the Vancouver orbitopathy rules (Box 3.4).

Pretibial myxoedema

Pretibial myxoedema (Figure 3.2) is an infiltrative dermopathy specific to Graves disease. It is seen in up to 2% of patients and results from an accumulation of hydrophilic glycosaminoglycans secreted by fibroblasts in the dermis. Almost all patients with pretibial myxoedema have co-existent Graves orbitopathy. Pretibial myxoedema is characterised by raised, pigmented, orange peel-textured nodules, or plaques on the anterior aspect of the leg or dorsum of the foot. They are usually asymptomatic but may be pruritic or painful.

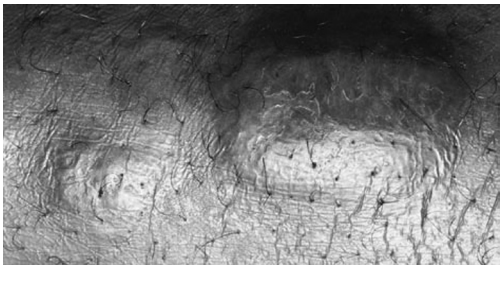

Figure 3.2 Pretibial myxoedema.

Thyroid acropachy

Thyroid acropachy (Figure 3.3) is seen in fewer than 1% of patients with Graves disease and resembles clubbing. It is due to periosteal new bone formation in the phalanges.

Thyroid storm

A thyroid storm ('thyrotoxic crisis') may present with:

- fever, sweating
- cardiovascular symptoms: tachyarrhythmias, cardiac failure
- neurological symptoms: agitation, delirium, seizure, coma
- gastrointestinal symptoms: diarrhoea, vomiting, jaundice.

It has an untreated mortality of 8–25%. It may be precipitated by thyroid surgery, radioiodine, iodinated contrast agents, withdrawal of thionamides (antithyroid drugs), and acute illnesses such as infection, stroke, diabetic ketoacidosis or trauma. Thyroid function tests will demonstrate thyrotoxicosis, but the levels of thyroid hormones may not be markedly elevated.

Investigations

Thyroid function tests

- In *primary hyperthyroidism*, thyroid function tests show suppressed serum TSH and high free T_4 and or free T_3.
- In *secondary hyperthyroidism*, TSH is either high or inappropriately normal in the presence of a raised free T_4/T_3. The differential diagnosis of this state includes thyroid hormone resistance (see below).
- In *T_3 toxicosis*, there is an isolated elevation in free T_3 with suppressed TSH, seen in thyroid nodular disease and in Graves disease.

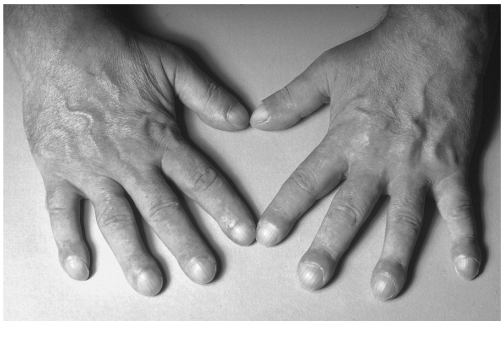

Figure 3.3 Thyroid acropachy.

- In *SCH*, TSH is low but free T_4 and free T_3 levels are normal. Therefore, free T_3 levels should always be measured when TSH is low in the presence of a normal T_4 to differentiate between SCH and T_3 thyrotoxicosis.
- *Heparin can displace bound thyroid hormone, increasing free T_4 levels, typically without affecting TSH.*
- Other patterns of unusual thyroid hormone results are listed in Figure 3.4.

Patients on amiodarone therapy should have their thyroid function checked before starting therapy, every 3–4 months during treatment and for at least 1 year after the drug has been stopped.

TSH receptor-stimulating antibodies

TSH receptor-stimulating antibodies (TSHRAb) can be measured in blood samples and are positive in Graves disease.

Some laboratories measure 'TBII' (TSH-binding inhibitor immunoglobulin). This test shows that there is an antibody that competes with TSH for the TSH receptor, but it does not differentiate between stimulating and blocking antibodies (some patients with Graves disease have a mixture of stimulating and blocking TSH receptor antibodies).

Antithyroglobulin and antithyroid peroxidase (microsomal) antibodies are present in up to 87% of patients with Graves disease. However, these have low specificity and are present in 15% of healthy females and 5% of males.

Radioisotope uptake scan

A radioisotope (intravenous [IV] ^{99}technetium pertechnetate or oral ^{123}iodine) uptake scan is helpful in differentiating between different causes of thyrotoxicosis (Figure 3.5).

- Graves disease is characterised by a diffuse increased uptake of the radioisotope. (Normal uptake is up to 3% of the administered dose.)
- Toxic multinodular goitre is characterised by multiple areas of increased radioisotope uptake ('hot' nodules) with suppression of uptake in the rest of the gland.

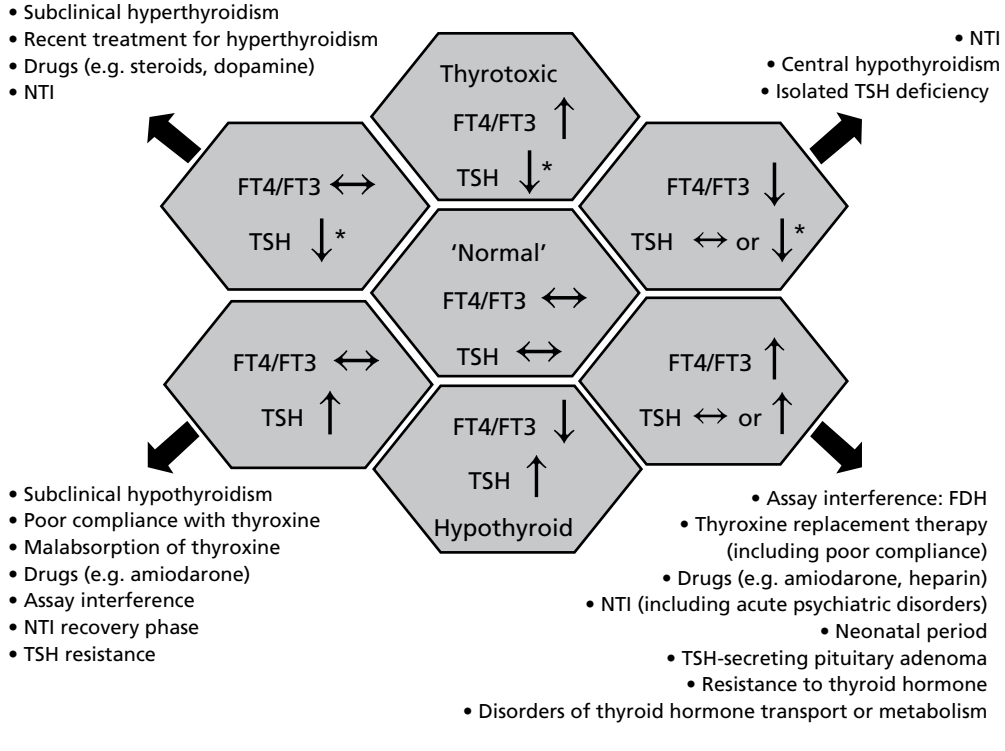

Figure 3.4 Pattern of thyroid function tests. FDH, familial dysalbuminaemic hyperthyroxinaemia; NTI, non-thyroidal illness; TSH, thyroid-stimulating hormone. Source: Gurnell, M., et al. 2011/John Wiley & Sons.

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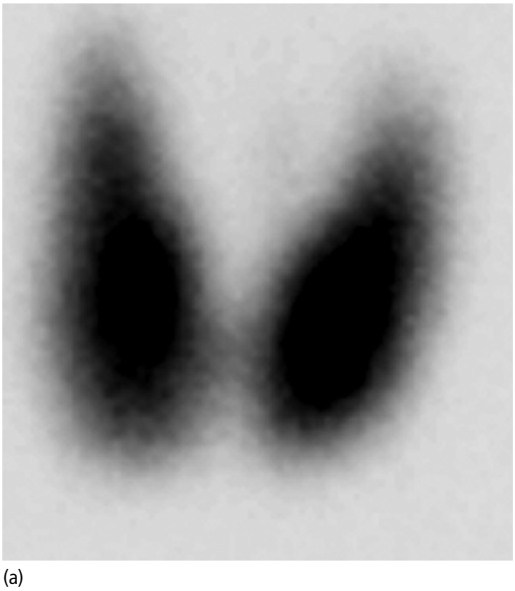
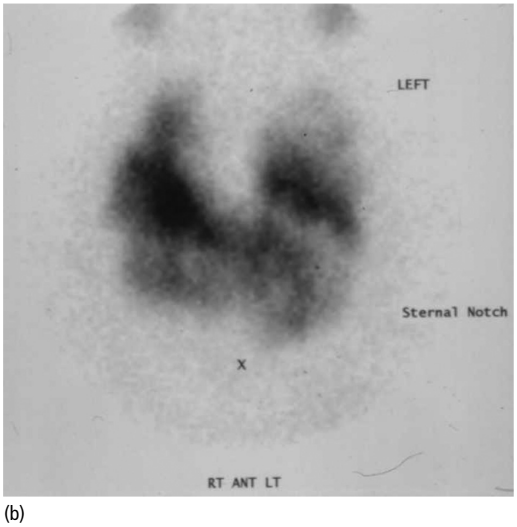


(a)



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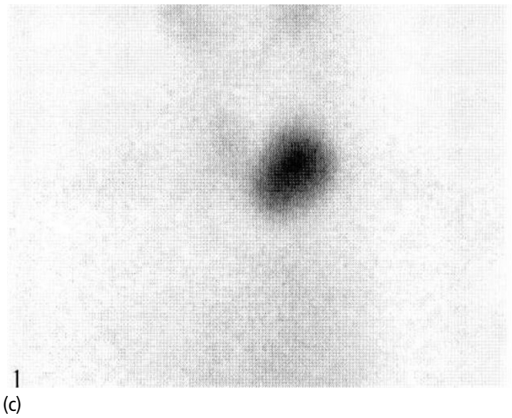

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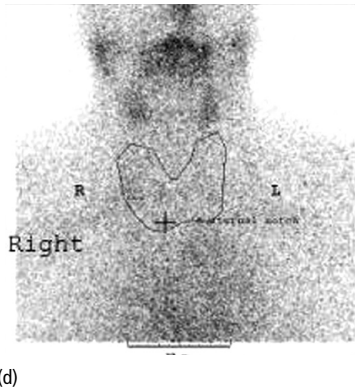

(d)

Figure 3.5 ^{99}Technetium pertechnetate uptake scan. (a) Graves disease, (b) toxic multinodular goitre, (c) solitary toxic adenoma, (d) thyroiditis.

- A solitary toxic adenoma is seen as a single area of increased radioisotope uptake ('hot nodule') with suppression of uptake in the rest of the gland.
- A low or absent radioisotope uptake indicates either thyroiditis (inflammation and destruction of thyroid tissue) or an extrathyroidal (e.g. exogenous) source of excess thyroid hormone.

The scanning time is earlier with ^{99}technetium pertechnetate (maximum thyroid uptake occurring within 30 minutes of IV injection), and there is no need to stop antithyroid drugs before the scan (technetium is transported into the thyroid follicular cells, but is not organified).

Patients must not have any iodine-containing medications, supplements or radiocontrast dyes before the radioisotope scan as they block radioisotope uptake. It is essential to make sure that the patient is not pregnant prior to the radioisotope scan.

Other investigations

Thyroiditis

Erythrocyte sedimentation rate (ESR) is elevated in patients with subacute viral de Quervain thyroiditis.

Graves orbitopathy

CT or MRI (STIR sequence) of the orbits may be used in the assessment and follow-up of patients with Graves orbitopathy.

Secondary hyperthyroidism

A pituitary MRI should be requested in cases of secondary hyperthyroidism. A differential diagnosis of secondary hyperthyroidism is thyroid hormone resistance (see below).

Amiodarone-induced thyrotoxicosis

A detectable uptake on a radioisotope uptake scan suggests type 1 AIT (see above). Low or absent uptake may be due to either type 2 AIT (i.e. thyroiditis) or the iodine content of amiodarone itself in those who have recently been taking the drug. Therefore, a radioisotope uptake scan is only useful in those who have not recently been on amiodarone, and even then it may be difficult to interpret given its very long half-life. Colour flow Doppler ultrasonography may distinguish type 1 (increased vascularity) from type 2 (reduced vascularity) AIT. However, this test requires an experienced sonographer.

Treatment

All patients with primary hyperthyroidism should be told about the three options available for treatment (Box 3.5). For the treatment of secondary hyperthyroidism, see Chapter 12.

In patients with severe thyrotoxic symptoms, *beta-blockers* such as propranolol (20–80 mg three times a day) may be used temporarily (initially, for 4–8 weeks) for symptomatic relief. Atenolol (100 mg daily) is an alternative. Alternatively, calcium channel blockers (e.g. verapamil) can be used when beta-blockers are contraindicated (unlicensed indication).

Graves disease

In Europe, most patients with Graves disease below the age of 50 years receive antithyroid drugs as initial treatment (see below). Radioiodine is more commonly used in North America. However, if thyrotoxicosis relapses, a second course of antithyroid drugs is unlikely to result in remission, and definitive treatment (radioiodine or surgery) is preferred. An alternative is the indefinite use of low-dose antithyroid drugs, with the risk of recurrence if drugs are inadvertently stopped.

In patients with Graves disease who are over 50 years of age, radioiodine should be encouraged as recurrent thyrotoxicosis may be dangerous in the presence of coincidental heart disease. A 12–18-month course of thionamides has a 50% relapse rate in women and a 95% relapse rate in men. Thus men tend to be offered radioiodine as primary treatment.

Pretreatment with antithyroid drugs prior to radioiodine or surgery may be required in those who do not tolerate the symptoms of hyperthyroidism. Symptoms are usually controlled in 4–8 weeks with antithyroid drugs. Pretreatment with antithyroid drugs may reduce the risk of thyroid storm and transient thyroiditis. However, pretreatment with antithyroid drugs is associated with a higher rate of failure, and a larger dose of radioiodine may be necessary.

Box 3.5 Treatment options in thyrotoxicosis

Antithyroid drugs (thionamides)
Radioiodine
Surgery (thyroidectomy)

Toxic multinodular goitre and toxic adenoma

People with multinodular goitre and toxic adenoma are ideally treated with radioiodine or surgery, depending on the patient's preference. Surgery is preferred in those with retrosternal extension or large goitres. However, long-term antithyroid drugs may be used in those who decline or cannot have radioiodine or surgery.

Antithyroid drugs

The antithyroid drugs *carbimazole*, *methimazole* and *propylthiouracil* (PTU) reduce T_4 and T_3 production by inhibiting thyroid peroxidase. Thionamides also lower TSHRAb and interleukin-6 levels, suggesting immune-modulating effects. PTU also inhibits the peripheral conversion of T_4 to T_3. Carbimazole has the advantage of once-daily dosing and is generally used as first-line treatment in the UK. PTU is preferred in the first trimester of pregnancy, during breast feeding, and in management of thyroid storm. Up to 50% of female patients with Graves disease show sustained remission after treatment with thionamides. This may possibly be secondary to a decrease in TSH-stimulating antibody levels by these drugs.

In the *titration regimen*, the initial doses of carbimazole (30–40 mg per day) or PTU (300–400 mg per day) are gradually reduced over 4–8 weeks (depending on thyroid function tests) to a maintenance dose of 5–15 mg per day of carbimazole or 50–150 mg per day of PTU. A higher initial dose of carbimazole (60 mg per day) or PTU (200 mg three times a day) is occasionally required in severely thyrotoxic patients.

The antithyroid drug dose is titrated down at regular (e.g. monthly) follow-up visits, using the free T_4/T_3 levels as a guide. It takes longer (up to several months) for suppressed TSH levels to increase. Treatment is continued for 12–18 months with regular monitoring of thyroid function tests. Good evidence for the duration of treatment (12 or 18 months) is lacking although 18 months is usually preferred.

In the *block and replacement* regimen, carbimazole 40 mg per day or PTU 400 mg per day is started, and levothyroxine (usually 100 µg/day) is added when free T_4 is in the normal range (usually after about 4 weeks). Levothyroxine can be adjusted by 25 µg/day according to the free thyroid hormone levels. This regimen is given for 12–18 months and requires fewer follow-up visits. The block and replacement regimen is contraindicated in pregnancy because levothyroxine crosses the placenta less well than antithyroid drugs, resulting in fetal hypothyroidism and goitre.

A *hybrid* regimen has been proposed in which carbimazole 40 mg per day is given for 6 weeks, then levothyroxine (usually 100 µg/day) is added. At 4 months, the levothyroxine dose is stopped and the carbimazole dose reduced to 5 mg.

The major drawback of using antithyroid drugs is the significant (>50%) chance of relapse following cessation of treatment. A rare but significant complication of antithyroid drugs is *agranulocytosis*, which happens in 0.1–0.5% of patients. Although idiosyncratic, this reaction usually occurs within the first 3 months of treatment, and in those on higher doses. Patients must be given written instructions to stop their antithyroid drug and tell their doctor immediately if they develop fever, a sore throat, mouth ulcers, or any signs of infection. Patients should have their full blood count checked the same day. Mild neutropenia ($1–1.5 \times 10^9$/L) is common in patients on antithyroid drugs. However, in patients with a neutrophil count of less than 1×10^9/L, antithyroid drugs should be discontinued. Such patients need radioiodine or urgent surgery. In the short term, beta-blockers may be used to control the symptoms. The cut-off for intervention is controversial. Patients with a neutrophil count of less than 0.5×10^9/L and a sore throat may require admission and treatment with granulocyte colony-stimulating factor and antibiotics.

Rashes and pruritus are common side-effects of antithyroid drugs and may be treated with antihistamines without stopping treatment. Occasionally, one antithyroid drug may need to be substituted with another. Other side-effects include macular rash (1–5%), nausea, vomiting, abnormal taste/smell, arthralgia, pruritus, lymphadenopathy, and deranged liver function tests (cholestatic or hepatitis). Rarely, PTU may cause fulminant liver failure (0.05%). PTU may also rarely be associated with antineutrophil cytoplasmic antibody (ANCA)-positive vasculitis. Measuring baseline full blood count and liver function tests prior to thionamide initiation are advisable.

People who are thyrotoxic and unable to have carbimazole or PTU can be offered lithium carbonate 800 mg once a day (blocks T_3/T_4 release) followed by radioiodine, or potassium iodide 60–65 mg three times a day (blocks T_3/T_4 release and reduces thyroid vascularity) with surgery after 10 days.

Follow-up

In both the regimens described above, drugs are discontinued after 18 months of treatment, and thyroid function tests are checked at intervals (e.g. 6-weekly for 6 months, 6-monthly for 2 years and then annually) or sooner if the patient develops symptoms suggestive of relapse. Around 70% of relapses occur in the first year; relapse is more likely in patients with a large goitre and high free T_3 levels at the time of diagnosis. Those who relapse (50% of females, 95% of males) need further definitive treatment in the form of radioiodine or surgery (thyroidectomy). Those who cannot have definitive treatment require lifelong antithyroid drug treatment. Autoimmune hypothyroidism may subsequently occur in 15% of patients with Graves disease.

Radioiodine

Radioiodine (^{131}I) is given orally as a capsule or solution. It is concentrated in the thyroid, and its beta-emissions result in cell damage and death over a period of 6–18 weeks. Antithyroid drugs should be discontinued (about 3 days) before radioiodine to allow uptake of the isotope by the thyroid gland.

Some centres use a fixed dose (370 or 555 MBq) to ablate the thyroid gland in Graves disease; others vary the dose (200–600 MBq) according to the size of the thyroid gland and the 24-hour radioiodine uptake result. Higher doses of radioiodine (e.g. 600–800 MBq) are used to treat toxic adenoma or toxic multinodular goitre. In patients with renal failure, doses of radioiodine must be significantly reduced.

Most endocrinologists prefer to delay radioiodine treatment in patients with moderate-to-severe

orbitopathy until their eye disease has been stable for at least 1 year. Radioiodine is occasionally given with prednisolone cover (25–30 mg per day withdrawn over 6–12 weeks).

Complications and advice for patients

Radioiodine destroys fetal thyroid and is contraindicated in pregnancy and breast feeding. Pregnancy is safe 6 months after radioiodine. Patients must avoid close contact with small children for several weeks depending on the radioiodine dose. Therefore radioiodine may not be an option for those patients who cannot comply with the restrictions.

Most studies suggest that radioiodine is associated with the appearance or exacerbation of Graves orbitopathy. Radioiodine therapy is followed by a transient increase in serum TSH receptor antibodies, which might be important in initiating or exacerbating orbitopathy.

Radioiodine may occasionally cause transient thyroiditis and sialoadenitis. Radioiodine therapy for hyperthyroidism has not been shown to increase the overall risk of malignancy, although one meta-analysis has demonstrated small increases in thyroid, stomach and renal cancer; however, it is important to emphasise that these are rare events.

Follow-up

Antithyroid drugs may need to be started shortly after radioiodine treatment in those who develop a transient thyroiditis. Restoration of normal thyroid function or hypothyroidism will occur in 80–95% patients after their first dose of RAI. The majority of people treated with RAI (90%) will go on to develop permanent hypothyroidism, in 10% of patients during the first year and 2–3% annually thereafter. Therefore, patients should be followed up with repeat thyroid function tests regularly in the first year and then annually. It is common practice to wait 4–6 months before repeating radioiodine treatment in patients with persistent thyrotoxicosis because remission commonly occurs during this period.

Surgery

Surgery may be selected when definitive cure is needed in people with Graves orbitopathy, women planning pregnancy, or who are unable to take antithyroid drugs or have radioactive iodine. Rarely, in people with very aggressive disease uncontrolled with oral medications (with or without thyrotoxic complications such as heart failure), urgent surgery is needed. The extent of surgery for Graves hyperthyroidism is controversial. More aggressive surgery (thyroid remnants <4 g) is associated with a higher rate of hypothyroidism. Less aggressive surgery is associated with a higher rate of recurrent overt/SCH. Surgery is more commonly used for patients with toxic multinodular goitre and toxic adenomas (see above).

Surgery should be undertaken by high-volume thyroid surgeons. Recurrence rates are about 2–4% in the best centres. The prevalence of hypothyroidism may be up to 80% several years after surgery. Other surgical complications (<1%) include hypoparathyroidism, recurrent laryngeal nerve damage, and laryngeal oedema (due to bleeding into the neck).

Preparation of thyrotoxic patients for thyroidectomy

Preparation includes administration of a beta-blocker, antithyroid drugs, and an excess of iodide/iodine, for example potassium iodide 60 mg three times a day or Lugol's iodine 0.3 mL three times a day. Iodide excess is given for 10 days before surgery to inhibit thyroid hormone synthesis (the Wolff–Chaikoff effect) and probably reduce perioperative blood loss. If the window at 10 days is missed, recurrent thyrotoxicosis occurs (again, the Jod–Basedow effect). PTU should be administered an hour before any iodide to prevent organification of the administered iodine.

Surgery is chosen over radioiodine in:

- patients with large goitres causing upper airway obstruction or dysphagia
- patients who cannot take antithyroid drugs (e.g. due to allergy/agranulocytosis) and are either pregnant or have moderate/severe Graves orbitopathy (which may be exacerbated by radioiodine).

Graves orbitopathy

Urgent ophthalmology review is needed in cases of visual impairment or corneal damage.

Patients should be reviewed by surgeons specialised in orbital, oculoplastic, and strabismus surgery, depending on their presentation. Patients must be advised to stop smoking. The treatment of Graves orbitopathy depends on the severity of symptoms.

- For mild symptoms:
  - artificial tears during the day and ointments at night
  - eye shades
  - elevation of the head of the bed
  - advice to avoid sleeping on the face.
- For congestive orbitopathy with visual impairment:
  - IV methylprednisolone (1 g daily for 3 days) or high-dose prednisolone

- decompression surgery
- radiotherapy.

Orbital radiotherapy is contraindicated in patients with diabetic retinopathy. Surgical correction may also be performed for cases of diplopia or cosmetic disability. Hypothyroidism (e.g. after radioactive iodine, overtreatment with drugs) is a risk factor for developing or worsening eye disease and must be promptly corrected.

Pretibial myxoedema

Pruritus or discomfort may be treated with topical steroid ointment such as fluocinolone covered by an occlusive dressing. Systemic corticosteroid therapy may occasionally be given for resistant cases.

Special circumstances

Thyroid storm (thyrotoxic crisis)

General supportive treatments include:

- close monitoring in the high-dependency or intensive therapy unit (level 2/3 care)
- IV fluids, paracetamol, and cooling. Avoid aspirin (as it displaces T_4 from thyroid-binding globulin)
- antiarrhythmics; when anticoagulation is given for atrial fibrillation, remember that thyrotoxic patients are very sensitive to warfarin
- treating the precipitating cause, for example antibiotics for infection
- chlorpromazine (50–100 mg intramuscularly) is useful for the treatment of agitation and hyperpyrexia
- monitoring glucose (as liver glycogen stores are depleted during thyroid storm).

Specific treatments include the following.

- *PTU:* a 600 mg loading dose, and then 200 mg 4-hourly orally or via a nasogastric tube.
- *Propranolol:* 60–80 mg 4-hourly orally. Care should be taken with complicating cardiac failure. Verapamil can be considered if beta-blockers are contraindicated.
- *Hydrocortisone:* 100 mg IV four times a day (inhibits the peripheral conversion of T_4 to T_3).
- *Potassium iodide:* 60 mg four times a day via a nasogastric tube (blocks thyroid hormone release). It must be commenced 6 hours after starting PTU. Alternatively, Lugol's iodine 1 mL four times daily may be given and should be started at least 1 hour after the first dose of PTU. Potassium iodide can be given for a maximum of 14 days followed by definitive treatment.
- *Cholestyramine:* 4 g three times a day orally or via a nasogastric tube; other medications must be given 1 hour before or 5 hours after cholestyramine (blocks enterohepatic circulation of T_4 and T_3).

Thyrotoxicosis and atrial fibrillation

Left atrial enlargement (a risk factor for thrombus formation) is seen in about 90% of hyperthyroid patients with atrial fibrillation; therefore, these patients should usually be anticoagulated. Around 60% of hyperthyroid patients with atrial fibrillation cardiovert back to sinus rhythm when the hyperthyroidism is treated.

Subclinical hyperthyroidism

In exogenous SCH caused by excessive levothyroxine, the dose should be reduced to maintain a normal serum TSH (except in those with previous thyroid cancer in whom suppressed TSH may be required).

There is no consensus about the management of endogenous SCH. An age-related reduction in median TSH is recognised, with stable free T_4 and below-median free T_3 concentrations. In people over 60 years of age with TSH 0.1–0.3 mIU/L (grade 1 SCH), 25–50% return to normal at 1 year. The risk of progression to overt hyperthyroidism is <1% with grade 1 SCH and 2–8% with SCH and TSH <0.1 mIU/L (grade 2 SCH). Atrial fibrillation, increased cardiovascular and overall mortality, heart failure, and reduced bone mineral density (and increased fracture risk) are associated with grade 2 SCH. Although there is no evidence that treating grade 2 SCH prevents these complications from occurring, it is recommended to treat people over 65 years age to potentially prevent these serious events.

The following recommendations are consistent with those of a clinical consensus group from the European Thyroid Association, Endocrine Society, American Thyroid Association and American Association of Clinical Endocrinologists (Figure 3.6).

- In patients >65 years, and postmenopausal women not on hormone replacement who have a high risk of complications of hyperthyroidism (i.e. osteoporosis or atrial fibrillation):

A L G r a w a n y

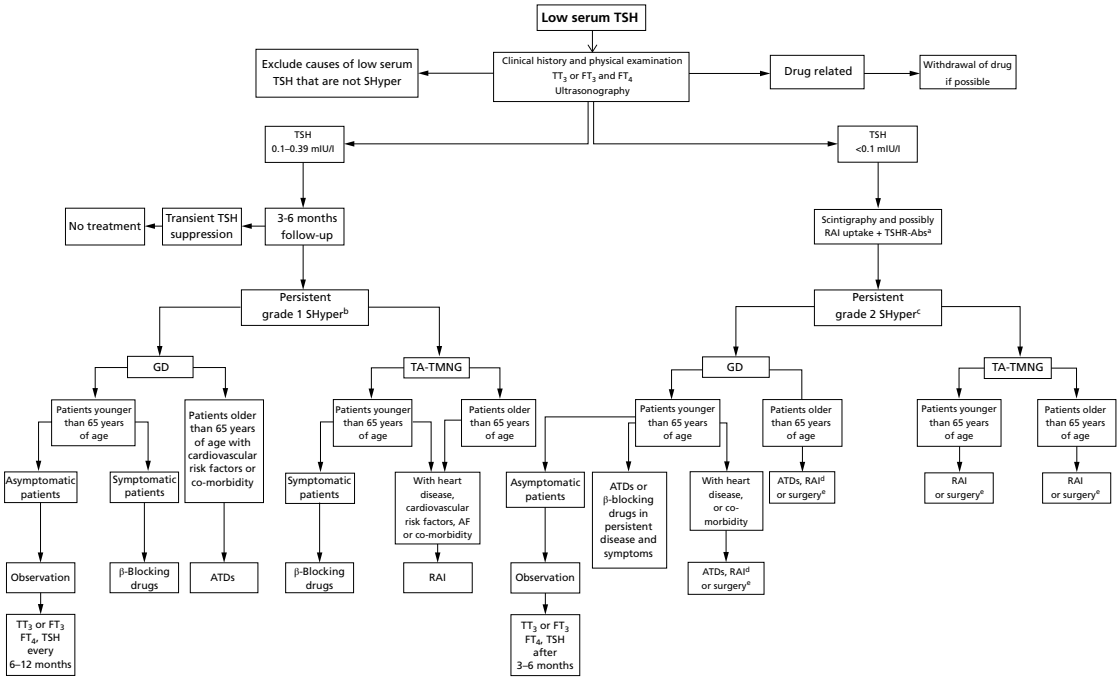

Figure 3.6 Algorithm for the management of subclinical hyperthyroidism. (a) TSHR-Abs = TSH receptor antibodies. (b) Grade 1 subclinical hyperthyroidism (TSH levels: 0.1–0.39 mIU/L). (c) Grade 2 subclinical hyperthyroidism (TSH levels <0.1 mIU/L). (d) RAI in patients with recurrences or if antithyroid drugs are not tolerated. (e) Surgery in patients with large goitre, symptoms of compression or thyroid malignancies. Source: Eur. Thyroid J. 2015;4: 149–163 (https://doi.org/10.1159/000438750). GD: Graves disease, TA: toxic adenoma, TMNG: toxic multinodular goitre.

  - If TSH is <0.1, treat for hyperthyroidism, for example with long-term low-dose carbimazole or radioiodine.
  - If TSH is 0.1–0.3, consider treatment if the thyroid radioisotope scan shows an area of high uptake or if bone density is low.
- In younger patients with a lower risk of complications of hyperthyroidism:
  - If TSH is <0.1, consider treatment if the thyroid radioisotope scan shows an area of high uptake or if the bone density is low.
  - If TSH is 0.1–0.3, follow up every 6 months.

Subacute and postpartum thyroiditis

Mild thyroiditis is treated with non-steroidal anti-inflammatory drugs. Moderate or severe thyroiditis may require steroids (prednisolone 40 mg per day for 1 week followed by gradual withdrawal over 4–6 weeks). The symptoms of patients with postpartum thyroiditis may be controlled with propranolol. Patients should be followed up as there is a risk of developing hypothyroidism.

Amiodarone-induced thyrotoxicosis

The decision to continue or stop amiodarone should be made by a cardiologist. Type 1 thyrotoxicosis usually responds to antithyroid drugs, and type 2 thyrotoxicosis responds to prednisolone (40 mg once daily continued for about 8 weeks before tapering). If the type of the hyperthyroidism is uncertain, prednisone (40 mg per day) and carbimazole (40 mg per day) are given initially. A rapid response suggests type 2 thyrotoxicosis, and carbimazole can then be tapered. A poor initial response suggests type 1 disease, and steroids can be tapered.

Thyroid hormone resistance

An important differential diagnosis of secondary hyperthyroidism is thyroid hormone resistance. Patients with this condition have a similar thyroid function profile to those with TSHomas, i.e. high free T_4/T_3 levels and an inappropriately normal or elevated serum TSH.

Thyroid hormone resistance is characterised by reduced responsiveness of the tissues to thyroid hormone. It results from mutations in the gene for the beta form of the thyroid hormone receptor in 90% of patients. The mutations may be inherited (mostly as autosomal dominant) or occur *de novo*. Thyroid hormone resistance has been detected in 1 in 50 000 live births, and affects males and females equally.

The severity of thyroid hormone resistance may vary in different tissues (pituitary and peripheral tissues) in the same patient and among different patients having the same mutation. Most patients have few or no symptoms and signs of thyroid dysfunction. However, patients may have some of the following features:

- goitre (65–95%)
- tachycardia (16–80%), probably due to unopposed activation of the alpha form of the thyroid hormone receptor
- attention deficit hyperactivity disorder, emotional disturbances, learning disability
- growth retardation, delayed bone maturation
- recurrent ear and throat infections, sensorineural hearing loss.

Table 3.1 summarises the features that help differentiate thyroid hormone resistance from TSHomas.

Table 3.1 Features that help differentiate thyroid hormone resistance from thyroid-stimulating hormone (TSH)-secreting adenomas

TSH-secreting adenomas	Thyroid hormone resistance
Often clinically thyrotoxic	Usually euthyroid (except those with selective pituitary resistance who are thyrotoxic)
High serum SHBG (85%)	Normal serum SHBG
High serum alpha subunit of TSH	Normal serum alpha subunit of TSH
TSH levels do not increase in response to TRH	TSH levels increase in response to TRH
TSH levels less likely to fall in response to T_3	TSH levels more likely (90%) to fall in response to T_3
Pituitary tumour may be seen on magnetic resonance imaging (but remember that a pituitary incidentaloma may be detected in up to 10% of normal subjects)	Identification of known mutations in the thyroid hormone receptor beta gene confirms the diagnosis

SHBG, sex hormone-binding globulin; TRH, thyrotrophin-releasing hormone.

In most patients with resistance to thyroid hormone, treatment is not required as the increase in thyroid hormone secretion compensates for the partial tissue resistance. However, levothyroxine replacement is required in those with prior destructive antithyroid therapy (i.e. radioiodine or surgery). Thyrotoxic patients with selective pituitary resistance to thyroid hormone may be treated with beta-blockers and triiodothyroacetic acid (TRIAC).

KEY POINTS

- 'Thyrotoxicosis' refers to an excess of circulating free T_4 and/or free T_3. Thyrotoxicosis may be due to either increased thyroid hormone synthesis (hyperthyroidism) or increased thyroid hormone release from an inflamed thyroid gland (thyroiditis).
- Primary hyperthyroidism is characterised by a raised free T_4 and/or T_3 and low TSH.
- Secondary hyperthyroidism is characterised by raised T_4 and T_3 due to increased TSH secretion from a pituitary tumour.
- Graves disease accounts for 70–80% of all cases of hyperthyroidism. Toxic multinodular goitre is the most common cause of hyperthyroidism in the elderly.
- Thyrotoxic patients may present with heat intolerance, anxiety, irritability, weakness, palpitations (atrial fibrillation or sinus tachycardia), exertional breathlessness, increased appetite, weight loss, oligomenorrhoea, and osteoporosis.
- Clinical signs specific to Graves disease include orbitopathy, pretibial myxoedema and thyroid acropachy.
- Treatment options for hyperthyroidism include antithyroid drugs, radioiodine, and surgery (thyroidectomy).
- A rare but significant complication of antithyroid drugs is agranulocytosis.

4

Goitre, thyroid nodules, and cancer

Goitre and thyroid nodules

A *goitre* is an enlarged thyroid gland and may be diffuse or nodular (consisting of a solitary or multiple nodules). Box 4.1 summarises the differential diagnosis of goitre. Goitre can be caused by both dietary iodine deficiency and excess. Certain medications (e.g. lithium carbonate) and foods (*Brassica* vegetables such as broccoli, cabbage, kale, and cauliflower) metabolise to the goitrogen thiocyanate.

Epidemiology

The prevalence of goitres and thyroid nodules was reported as 15% by the Whickham survey in North East England in the 1970s. In iodine-replete regions, goitres are clinically visible in 7% of the population (Figure 4.1) and are palpable (and not visible) in 8%. They are four times more common in females. Prevalence increases with age, iodine deficiency and previous exposure to ionising radiation. The Himalayas and the Andes are the most important goitrous areas in the world today. Iodine deficiency is also seen in central areas of Asia, Africa and Europe. Goitre is considered to be endemic if they occur in >5% children <12 years within a community or geographic area; otherwise they are referred to as sporadic goitre.

Fewer than 5% of thyroid nodules are cancerous. Thyroid nodules discovered incidentally on ultrasound (solitary or within a nodular goitre) have a very low prevalence of malignancy and are very common, occurring in 30–45% adults aged 55 years. The challenge for the endocrinologist is to identify those few patients who have cancerous thyroid nodules and to not operate on benign thyroid nodules.

Clinical presentations

A mass in the neck noticed by the physician, the patient or relatives may be the only presenting complaint.

Features in the history and examination that raise the suspicion of malignancy include:

- age <20 or >60 years
- recent rapid enlargement of a thyroid nodule
- local compressive symptoms: dysphagia, dyspnoea, hoarseness, stridor
- family history of thyroid cancer or multiple endocrine neoplasia (MEN)
- history of exposure to radiation (especially if occurring <14 years of age and associated with iodine deficiency)
- lymphadenopathy.

In addition, a history of Hashimoto thyroiditis raises the incidence of lymphoma. Papillary thyroid carcinoma may be associated with some rare inherited syndromes such as familial adenomatous polyposis, Gardner syndrome (autosomal dominant disease characterised by gastrointestinal polyps, multiple osteomas, skin, and soft tissue tumours) and Cowden disease (an autosomal dominant condition characterised by multiple hamartomas and an increased risk of early-onset breast and thyroid cancer).

Thyroid examination should include the following steps.

- *Inspection*: ask the patient to swallow (the goitre moves upward).
- *Palpation*: examine the goitre with the patient swallowing – the goitre moves upward. This may be lost in anaplastic carcinoma and Riedel.

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Box 4.1 Differential diagnosis of goitre

Thyrotoxic patients
Graves disease
Multinodular goitre
Solitary adenoma
Thyroiditis (subacute or painless)

Hypothyroid patients
Hashimoto thyroiditis

Euthyroid patients
Simple goitre (non-toxic)
Multinodular goitre
Solitary adenoma
Malignancy: thyroid carcinoma, lymphoma
Riedel thyroiditis (rare chronic inflammatory disease of the thyroid gland characterised by a dense fibrosis replacing normal thyroid parenchyma, which results in a 'woody' goitre)

Determine the size, whether the goitre is nodular or diffusely enlarged, soft or hard, or tender (e.g. in subacute thyroiditis or bleeding into a cyst) and the presence of firm, fixed, or tender lymph nodes.

- *Percussion* of the upper mediastinum (dull in retrosternal goitre).
- *Auscultation*: for a bruit (in hyperthyroidism) and inspiratory stridor (in cases of tracheal compression).
- *Determination of thyroid status* (look for features of hypothyroidism or thyrotoxicosis).

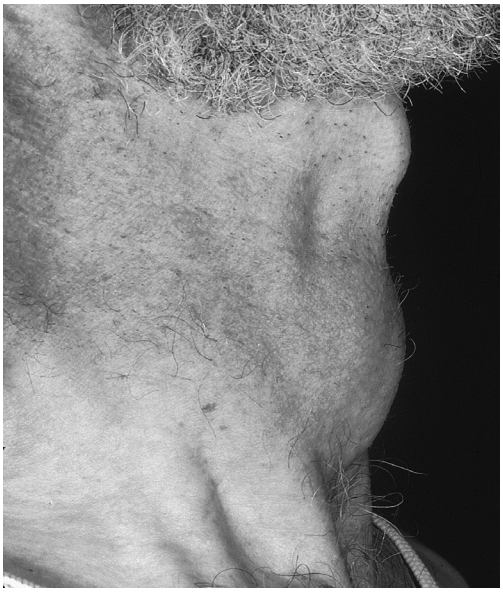


Figure 4.1 Goitre.

Investigations

Laboratory findings

Thyroid function tests (thyroid-stimulating hormone [TSH] and free thyroxine [T_4]) should be requested to exclude thyrotoxicosis and hypothyroidism. If the TSH is below the normal range, a thyroid uptake scan should be undertaken to evaluate for a hyperfunctioning nodule (see below); if the TSH is normal (or elevated), ultrasound ± fine needle aspiration (FNA) should be performed as described below. In people with thyroid cancer, higher TSH levels are associated with increased tumour aggressiveness. Serum thyroglobulin levels are increased in both benign and malignant nodules and should only be used in the follow-up of patients with treated differentiated (papillary and follicular) cancers. Calcitonin should be measured when medullary cell carcinoma is suspected (usually after FNA cytology results).

Patients with suspected tracheal obstruction should have respiratory flow–volume loop studies and cross-sectional imaging (e.g. CT scan of the neck).

Imaging

All patients with a palpable thyroid nodule, nodular goitre or thyroid nodule discovered incidentally on other imaging should have ultrasound assessment of their thyroid by an experienced sonographer. Ultrasonography enables thyroid cancer risk stratification. While there are no ultrasonographic findings that are specific for thyroid carcinoma, there are several features that raise suspicion of malignancy, including hypoechogenicity, irregular border, microcalcifications, and increased colour flow Doppler. Sonographic appearances can be utilised to select suspicious nodules for FNA biopsy (rather than the previous guidance to undertake FNA in all nodules >1 cm diameter).

The Thyroid Imaging Reporting and Data System (TIRADS) is used to systematically describe thyroid nodules and classifies them from 1 to 5 with increasing likelihood of malignancy (Table 4.1). Guidelines from different international thyroid societies and groups differ slightly in their sensitivities and specificities for the detection and exclusion of thyroid malignancy. A majority of thyroid nodules are TIRADS 2, and these should *not* have an FNA, but such patients should be reassured and discharged.

A radioisotope uptake scan can discriminate between a hot thyroid nodule, Graves disease (where

Table 4.1 EU-TIRADS

Category	Risk of thyroid malignancy (%)	Size for fine needle aspiration (mm)
1 Normal (no thyroid nodule found)	n/a	n/a
2 Benign	Close to 0	None unless compressive
3 Low risk	2–4	>20
4 Intermediate risk	6–17	>15
5 High risk	26–87	>10

Source: European Thyroid Association Guidelines for Ultrasound Malignancy Risk Stratification of Thyroid Nodules in Adults.

the whole gland is overactive) and viral thyroiditis (where there is no uptake) and can be performed in patients with suppressed TSH where the diagnosis is in doubt. ^{99}Technetium pertechnetate is more commonly used than ^{123}iodine as it is cheaper and more readily available.

Malignant nodules are more likely to be cold (i.e. not to take up radioisotope). However, most (80%) cold nodules are benign (e.g. colloid nodules, haemorrhage, cysts, or inflammatory lesions such as Hashimoto thyroiditis) (Figure 4.2). Hot nodules are associated with a low incidence of thyroid cancer.

If performing a contrast-enhanced CT scan of the neck to investigate thyroid cancer, radioiodine treatment should be delayed to 6 weeks following contrast to allow the urinary iodine concentration to return to baseline, as high iodine levels make the radioiodine less effective.

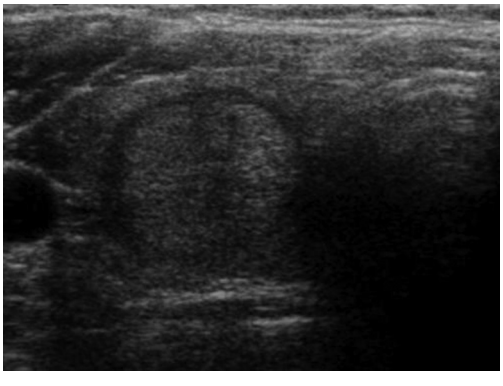


Figure 4.2 Neck ultrasound scan showing a benign thyroid nodule.

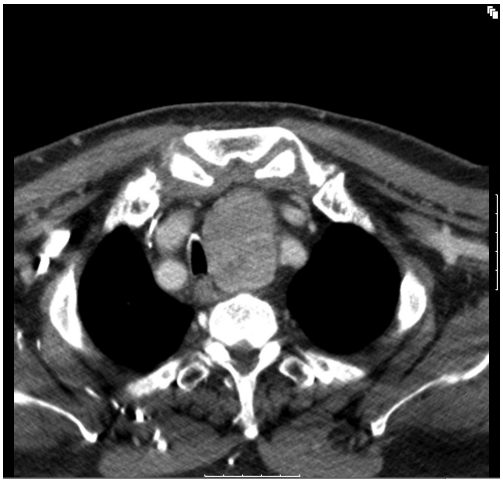


Figure 4.3 Computed tomography scan showing an enlarged left thyroid lobe extending into the mediastinum and indenting the trachea at the level of origin of the large vessels of the aortic arch.

Clinical suspicion of a retrosternal goitre causing tracheal compression may be confirmed by computed tomography (CT) or magnetic resonance imaging (MRI) of the neck and thoracic inlet (Figure 4.3).

Fine needle aspiration and cytology

Ultrasound-guided FNA of a thyroid nodule for cytological examination should be performed when there is high suspicion of malignancy (history of radiation, MEN type 2 [if they have not had a prophylactic thyroidectomy; see Chapter 32], suspicious ultrasound features, presence of cervical lymph nodes) (Figure 4.4).

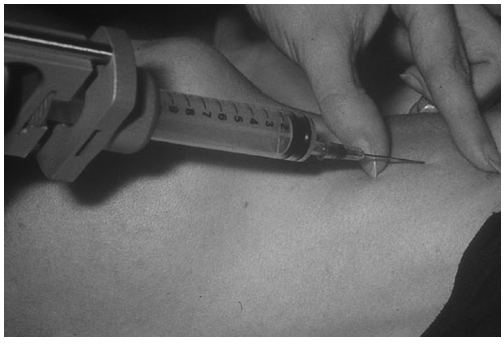


Figure 4.4 Fine needle aspiration of a thyroid nodule.

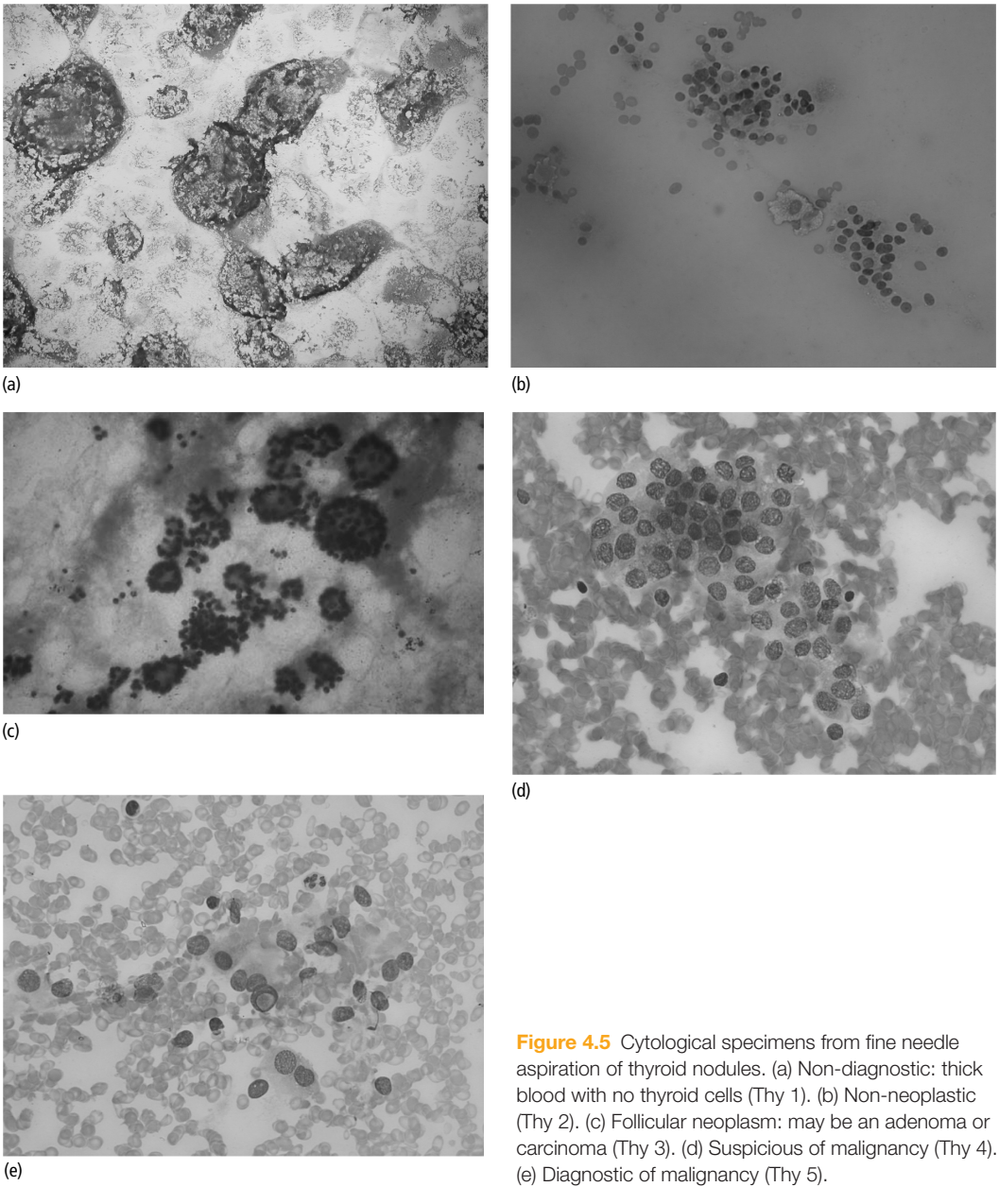


Figure 4.5 Cytological specimens from fine needle aspiration of thyroid nodules. (a) Non-diagnostic: thick blood with no thyroid cells (Thy 1). (b) Non-neoplastic (Thy 2). (c) Follicular neoplasm: may be an adenoma or carcinoma (Thy 3). (d) Suspicious of malignancy (Thy 4). (e) Diagnostic of malignancy (Thy 5).

The cytologist's report may be one of the following (Figure 4.5):

- non-diagnostic (histologically classified as Thy 1)
- non-neoplastic (abundant colloid, features compatible with multinodular goitre or thyroiditis; Thy 2)
- follicular lesions: adenoma or carcinoma (Thy 3)
- suspicious of malignancy (Thy 4)
- diagnostic for malignancy (Thy 5).

Molecular testing of indeterminate FNA results from thyroid nodules is beginning to be used clinically. Mutational analysis can be used to identify mutations in *BRAF*, *RAS*, *TERT*, and *TP53* genes associated with thyroid malignancy. Gene expression analysis is designed to identify nodules that do not

require surgery with a negative predictive value of ~95%. Neither of these modalities is in widespread use at the time of writing.

Treatment

Toxic multinodular goitre/solitary nodule

For a detailed discussion of the treatment of toxic multinodular goitre and solitary toxic nodules, see Chapter 3.

Non-toxic goitre/thyroid nodules

Following FNA of thyroid nodules and cytological examination, all patients should be discussed at a specialist thyroid multidisciplinary meeting.

- Patients with non-diagnostic cytology need repeat ultrasound-guided FNA immediately.
- Patients with suspicious or malignant cytology should be offered surgery.
- Patients who are biochemically euthyroid with asymptomatic multinodular goitre and benign cytology do not require treatment and should be discharged.

Surgery may also be offered in the presence of symptoms caused by local compression or significant cosmetic disfigurement.

Thyroid cancer

Epidemiology

Thyroid cancer (Box 4.2) is the most common endocrine malignancy, but it comprises fewer than 1% of all cancers and fewer than 0.5% of cancer deaths. The incidence of thyroid cancer has increased by 70% in the last 10 years. In spite of increasing diagnosis of thyroid cancer (due in part to greater public awareness and increased use of cross-sectional imaging leading to detection bias), the mortality has changed very little over the last 30 years, suggesting increased diagnosis is finding cases that would never have harmed the patient and surgery is thus increasing morbidity but not changing outcomes. This is being coupled with iatrogenic unnecessary hypothyroidism and, even worse, hypoparathyroidism, which is extremely unpleasant for the patient who will need calcium review for life.

Box 4.2 Classification of thyroid carcinoma

Papillary (70–80%)
Follicular (15%)
Anaplastic (5%)
Medullary (5–10%)
Lymphoma (5–10%)

Aetiology

Environmental factors

Exposure to ionising radiation, particularly at a young age, increases the risk of thyroid nodules (both benign and malignant). More than one-third of survivors of Hodgkin lymphoma had a thyroid abnormality. With radiotherapy affecting the neck there is a dose–response risk until around 30 gray, above which thyroid cells are killed and the risk decreases. The incidence of follicular carcinomas may have been reduced by iodine supplementation.

Genetic factors

Papillary thyroid carcinomas are associated with rearrangements of two genes – *RET* and *NTRK1* – and the formation of chimeric genes. The new 5′ end of the chimeric gene results in expression of the active tyrosine kinases in thyroid epithelial cells. This presumably activates growth pathways, causing papillary carcinomas in some patients. Mutations in *BRAF* (encoding a serine/threonine kinase) have also been implicated in the pathogenesis of papillary thyroid carcinoma. Activating point mutations of the *RAS* gene are found in follicular adenomas and carcinomas. *PPARG–PAX8* rearrangements are only found in follicular carcinomas. Inactivating point mutations of the *p53* gene are found in poorly differentiated and anaplastic thyroid carcinomas.

Papillary thyroid cancer

Papillary thyroid cancer (PTC) is the most common thyroid cancer (70–85%). It is more common in young women (30–50 years). Papillary thyroid carcinoma is often multifocal. In some patients, this may represent intraglandular metastases from the primary tumour. About 15–20% show local extrathyroidal invasion. Papillary carcinomas metastasise via the lymphatics to the regional lymph nodes (clinically evident in about one-third of patients at presentation) and distantly, for example to the lungs and bones (2–10% at diagnosis).

Papillary carcinomas are typically unencapsulated. They are characterised by papillae consisting of one or two layers of tumour cells surrounding a fibrovascular core. The cells and nuclei are large, and their cytoplasm has a 'ground glass' appearance. Nucleoli are prominent, and the nuclei have clefts, grooves, and 'holes' due to intranuclear cytoplasmic inclusions ('Orphan Annie eyes'). About 50% of papillary carcinomas contain calcified psammoma bodies, the scarred remnants of tumour papillae that presumably infarcted.

There are several variant forms of papillary carcinoma, including follicular, columnar cell, tall cell, and diffuse sclerosing.

Follicular thyroid carcinoma

This type of epithelium-derived thyroid carcinoma shows follicular differentiation and capsular or vascular invasion. The peak incidence of follicular carcinomas is between ages 40 and 60 years. FNA specimens may show microfollicles with varying nuclear atypia and little colloid. However, it is difficult to differentiate between benign follicular adenomas and malignant follicular carcinomas on cytology. The distinction between follicular adenoma and carcinoma can only be made through histological identification of capsule and/or vascular invasion (Figure 4.6), and therefore surgery is recommended. Follicular carcinomas may be minimally or widely invasive. Spread is more likely to be haematogenous (to lung and bones) than to regional lymph nodes.

Hurthle cell carcinoma is an uncommon variant of follicular thyroid carcinoma (FTC) and is characterised by the presence of oncocytic cells, which have an abundant oxyphillic cytoplasm (due to the accumulation of altered mitochondria) and round oval nuclei with prominent nucleoli. Hurthle cell carcinoma may behave more aggressively than FTC.

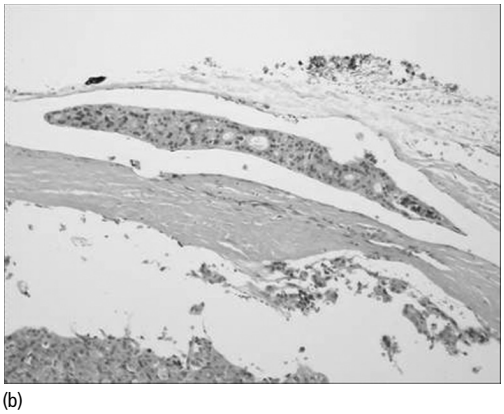
Medullary cell carcinoma

See Chapter 32.

Anaplastic carcinoma

Anaplastic thyroid carcinoma is an uncommon, undifferentiated malignancy that occurs more frequently in older patients (60–80 years of age). Patients usually present with a rapidly enlarging neck mass. The spread is haematogenous, and distant metastases are found in 15–50% of patients at initial disease presentation.

(a)



(b)

Figure 4.6 (a) Follicular adenoma. (b) Follicular carcinoma: a capsular blood vessel with tumour in the lumen is indicative of vascular invasion.

Thyroid lymphoma

Thyroid lymphoma may be part of a systemic disease or may primarily involve the thyroid gland. The risk of thyroid lymphoma is mostly in patients with autoimmune thyroiditis.

Treatment

Papillary and follicular carcinoma

Papillary and follicular neoplasms are differentiated. Treatment includes initial *thyroidectomy*, postoperative *TSH suppression* with thyroxine, and, in high-risk patients, postoperative *radioiodine ablation*.

Surgery

Surgery is the primary treatment and should be performed by an experienced thyroid surgeon to minimise the risk of hypoparathyroidism and recurrent

laryngeal nerve injury. Total thyroidectomy is appropriate when the primary tumour is 1.0 cm or more, or if there is extrathyroidal extension or metastasis.

Lobectomy plus isthmusectomy may be appropriate for tumours of less than 1.0 cm confined to one lobe of the gland. Lymph node status should be assessed by neck ultrasound scans, and regional neck dissection is carried out in cases of central or lateral nodal involvement.

Radioiodine

Thyroid follicular cells can take up radioiodine (^{131}I), which causes cell death by the emission of beta rays. Postoperatively (at about 4–6 weeks), radioiodine remnant ablation is given to all high-risk patients (those aged ≥45 years, tumours >3–4 cm, aggressive histological variants, extrathyroidal disease with direct invasion or metastases) to 'complete a total thyroidectomy'. The need for radioiodine ablation in low-risk patients is controversial.

Radioiodine remnant ablation destroys residual normal thyroid as well as microscopic malignant tissue and improves the specificity of subsequent radioiodine scans and serum thyroglobulin for detecting recurrent or metastatic cancer. Follow-up scanning with ^{123}I is done 6–12 months after initial radioiodine along with blood tests for thyroglobulin and thyroglobulin antibody levels. This is referred to as 'dynamic risk stratification' and determines the duration and degree of TSH suppression (see below). Further radioiodine treatment with ^{131}I in cases of positive uptake is done 6–12 months after initial radioiodine and is repeated until the patient has a negative scan.

Prior to the diagnostic or therapeutic use of radioiodine, TSH levels need to be high in order for the radioiodine to be taken up by any thyroid cells. This can either be achieved by the administration of recombinant TSH, which is now undertaken in most centres, or a protocol of thyroxine withdrawal can be undertaken. Thyroxine is stopped 6 weeks prior to radioiodine scan/ablation and is replaced with the shorter-acting triiodothyronine (T_3; 20 µg two or three times daily, or lower doses in elderly patients). T_3 has a shorter half-life and can be stopped 10 days before radioiodine scanning or treatment. This minimises the duration and symptoms of hypothyroidism. Patients are also advised to avoid foods with a high iodine content for at least 2 weeks before radioiodine scanning.

Patients who do not tolerate hypothyroidism (e.g. those with congestive cardiac failure or sleep apnoea) may be given recombinant TSH prior to radioiodine scanning. This obviates the need for thyroid hormone withdrawal.

Complications of radioiodine include radiation thyroiditis, painless neck oedema, sialoadenitis, tumour, haemorrhage or oedema, and nausea. An increased risk of secondary malignancies has been reported.

The radioiodine doses given in thyroid cancer are much higher than those given in hyperthyroidism, and patients may be isolated after treatment. However, some studies suggest that instructions to the patient to sleep alone, drink fluids liberally and avoid prolonged close personal contact with family members for 2 days after the treatment may be sufficient.

TSH suppression

After initial surgery, all patients should receive thyroxine to prevent hypothyroidism. In some cases, a suppressed TSH may reduce potential TSH stimulation of tumour growth but this also has side-effects. The decision as to whether patients should have a postoperative normal TSH or the aim of a suppressed TSH should be made by the thyroid MDT following review of the histology. Low-risk thyroid cancers do not need TSH suppression. TSH suppression is also associated with later atrial fibrillation and osteoporosis, so the balance of risks and benefits of TSH suppression in each patient needs to be carefully considered. The dose of levothyroxine should be adjusted by 25 µg every 6 weeks until the serum TSH is at target value, either normal or, in selected cases, below 0.1 mU/L. Most patients require 175–200 µg daily. The decision to suppress TSH also needs regular review, as the risk of recurrence falls with time, while the risk of side-effects increases with age.

Immunotherapy

The tyrosine kinase inhibitors sorafenib and lenvatinib have recently demonstrated improved progression-free survival in Phase 3 trials in people with radioiodine-refractory differentiated thyroid cancer. They are associated with significant toxicity, which may ultimately limit their clinical utility.

Hurthle cell carcinoma

These cancers take up radioiodine less avidly so should have total thyroidectomy and central compartment lymphadenectomy.

Anaplastic thyroid carcinoma

The treatment of anaplastic thyroid carcinoma includes total thyroidectomy with lymph node clearance, chemotherapy (e.g. doxorubicin and cisplatin), and external beam irradiation.

Thyroid lymphoma

Disease limited to the thyroid is treated with chemoradiotherapy.

Prognosis of thyroid cancer

PTC has a good prognosis. Poor prognostic factors in differentiated thyroid carcinomas include age (≥45 years), male gender, family history, tumour size, local extension, lymph node and distant metastases, and aggressive histological variants.

- *Papillary cancer* has a 10-year survival of 95% and a 10-year recurrence rate of 10%.
- *Follicular carcinomas* have a 10-year mortality of 15% (Hurthle cell carcinoma, which fails to concentrate radioiodine, has a 10-year mortality of 25%).
- *Anaplastic carcinoma* has a mean survival of 6 months.

Follow-up and monitoring

Most recurrences of differentiated thyroid carcinoma happen within the first 5 years after initial treatment. All patients should have periodic physical examinations and serum thyroglobulin (and thyroglobulin antibody) measurements. Metastatic lymph nodes typically occur in the jugular levels of the neck (II–IV). Surgery is the first choice of treatment; external beam irradiation may be used in irresectable disease, where there is no radioiodine uptake or for palliation.

Serum thyroglobulin

If initial surgery and thyroid remnant ablation are successful, the serum thyroglobulin concentration should be very low (<2 ng/mL). Serum thyroglobulin levels are elevated in 95% of patients with tumour recurrence. The laboratory should always test for antithyroglobulin antibodies. Antithyroglobulin antibodies interfere with the assay for thyroglobulin, so serum thyroglobulin cannot be used to monitor patients with these antibodies. These patients may need more frequent imaging studies during early follow-up.

Further imaging

If there is evidence of recurrence from clinical examination or tests, further imaging using radioiodine uptake scanning, ultrasonography, CT or MRI, skeletal X-rays or skeletal radionuclide imaging may be indicated to identify sites of disease. In patients with evidence of distant metastases, fluorodeoxyglucose positron emission tomography (PET) scanning may provide useful prognostic information.

KEY POINTS

- Goitre (enlargement of the thyroid gland) affects up to 15% of the population.
- Patients with goitre may be euthyroid, hypothyroid or thyrotoxic.
- Features that raise suspicion of malignancy in a thyroid nodule include rapid enlargement, symptoms of local compression, a family history of thyroid cancer, radiation exposure, and lymphadenopathy.
- Thyroid carcinoma is classified into papillary, follicular, anaplastic, medullary, and lymphoma.
- The treatment of differentiated thyroid carcinoma includes surgery, TSH suppression with thyroxine, and radioiodine ablation (in high-risk patients).
- Most patients with goitre do not need any intervention.

5

Adrenal anatomy and physiology

The adrenal glands are small Y-shaped glands located extraperitoneally at the upper poles of the kidneys (Figure 5.1). The arterial blood supply arises from the renal arteries, aorta and inferior phrenic artery. Venous drainage is via the central vein into the inferior vena cava on the right and into the left renal vein on the left.

The adrenal glands consist of an outer *cortex* (90%) surrounding an inner *medulla* (10%). The adrenal cortex is derived from mesodermal tissue, whereas the adrenal medulla is derived from neuroectodermal tissue (embryonic neural crest). The cortex has three layers or 'zones' (Figure 5.2):

- The *zona glomerulosa* secretes mineralocorticoids (aldosterone: 100–150 µg per day) (salt).
- The *zona fasciculata* secretes glucocorticoids (cortisol: 10–20 mg per day) (sugar).
- The *zona reticularis* secretes androgens (mainly dehydroepiandrosterone: DHEA) (sex).

The adrenal medulla is composed of *chromaffin cells*, which produce catecholamines (adrenaline, noradrenaline, dopamine) from the amino acid tyrosine. Chromaffin cells are so named because they can be visualised by staining with chromium salts. Catecholamine secretion is stimulated by preganglionic sympathetic nerves.

The pathways of steroid hormone biosynthesis in the adrenal glands are shown in Figure 5.3.

Aldosterone

Aldosterone secretion is stimulated by the *renin–angiotensin system* and elevated serum potassium. Renin is synthesised and stored in the juxtaglomerular apparatus in the kidney. Renin cleaves angiotensinogen (synthesised in the liver) to angiotensin I (a decapeptide); this is then converted to angiotensin II by angiotensin-converting enzyme on the luminal surface of capillaries in the lungs. Angiotensin II stimulates aldosterone secretion, resulting in sodium retention and potassium loss in the kidney. Renin release is stimulated by reduced renal perfusion pressure and blood flow, reduced sodium concentration in the renal tubules (sensed by macula densa cells) and increased renal sympathetic activity. To a lesser extent, adrenocorticotrophic hormone (ACTH) mediates aldosterone production (5–10% total).

Effects

Aldosterone is a lipid-soluble hormone that crosses plasma membranes and binds to intracellular receptors. The hormone–receptor complex increases the expression of certain genes and upregulates the synthesis of sodium channels and sodium/potassium (Na/K) ATPase in the distal renal tubular cells. Aldosterone increases sodium and water reabsorption and potassium secretion in the kidney. It also stimulates hydrogen ion secretion into the tubular lumen by cells in the collecting ducts.

Cortisol

Cortisol release is stimulated by ACTH released from the anterior pituitary (Figure 5.4). ACTH secretion is stimulated by hypothalamic *corticotrophin-releasing hormone* (CRH). Cortisol in turn inhibits ACTH and CRH production (negative feedback).

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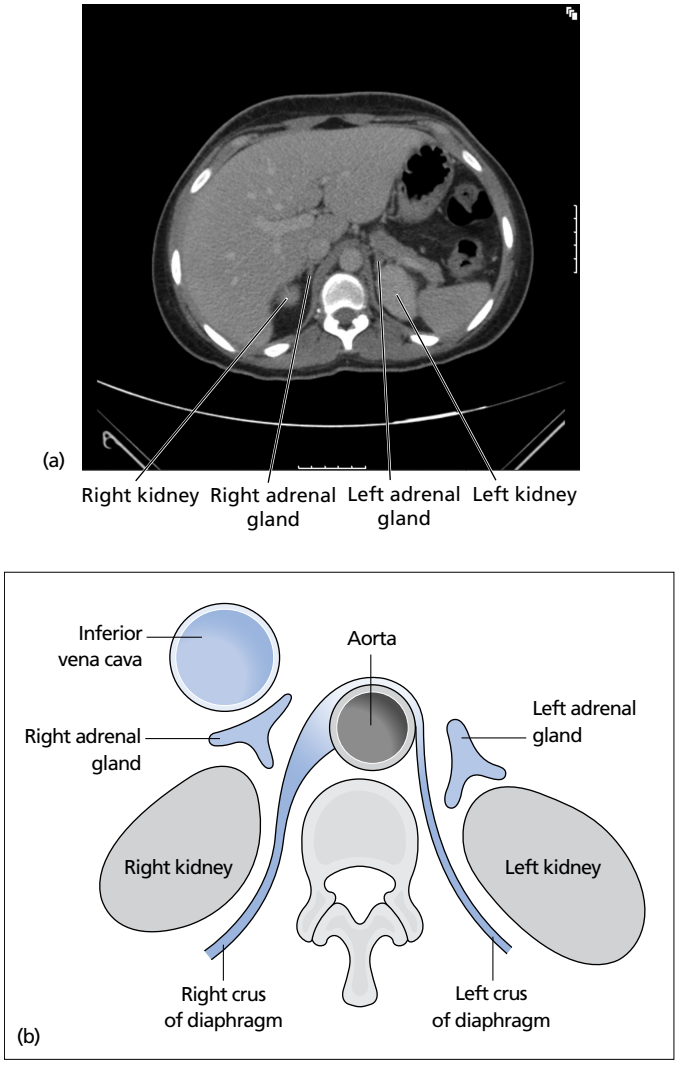

Figure 5.1 (a) Typical appearance of the adrenal glands on an abdominal computed tomography scan. (b) Diagram illustrating the cross-sectional anatomy of the adrenal glands.

Activation of the ACTH receptor on the plasma membrane of cells in the zona fasciculata results in the activation of adenylate cyclase and hence increased cyclic AMP levels. This leads to the stimulation of steroidogenic acute regulatory protein (StAR), which mediates the transport of cholesterol through the cytosol to the inner mitochondrial membrane, where it is converted to pregnenolone. This is the rate-limiting step in cortisol synthesis (see Figure 5.3). Activation of adenylate cyclase also results in upregulated gene expression of other enzymes involved in steroid synthesis.

Cortisol secretion normally reflects that of ACTH, and is therefore also pulsatile with a circadian rhythm.

Effects

Cortisol is a lipid-soluble hormone that crosses plasma membranes and binds to intracellular receptors, which in turn bind to specific DNA sequences and regulate the expression of certain genes. Cortisol increases hepatic *gluconeogenesis* by:

- enhancing the expression of enzymes involved in gluconeogenesis such as glucose-6-phosphatase and phosphoenolpyruvate carboxykinase (the rate-limiting enzyme in gluconeogenesis)
- increasing the availability of substrates, for example glucogenic amino acids and glycerol, by stimulating proteolysis (in skeletal muscle) and lipolysis, respectively.

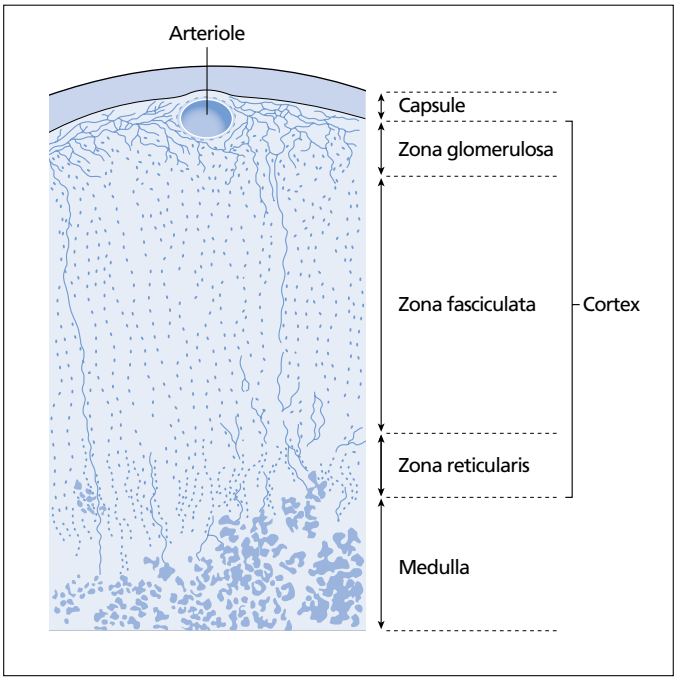

Figure 5.2 Adrenal histology.

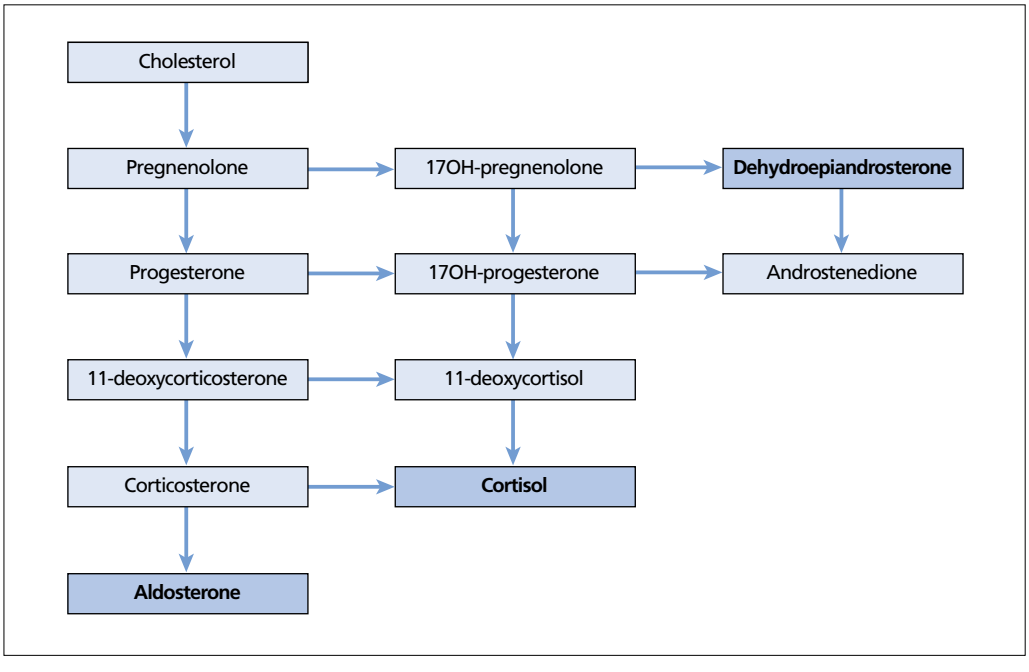

Figure 5.3 Biosynthesis of adrenal steroid hormones.

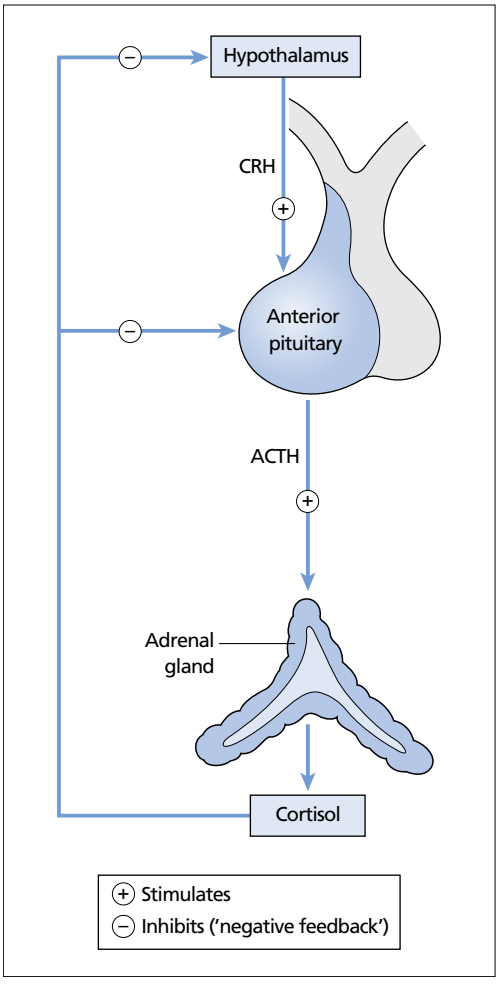

Figure 5.4 Hypothalamic–pituitary–adrenal axis.

Cortisol also has an important role in the maintenance of hepatic glycogen stores by activating the enzyme glycogen synthase and inactivating the glycogen-mobilising enzyme glycogen phosphorylase.

Glucocorticoids inhibit glucose uptake and utilisation by the peripheral tissues (adipocytes and skeletal muscle).

In humans with chronic cortisol excess, a redistribution of body fat occurs with relative sparing of the extremities and marked fat deposition in the dorsocervical and supraclavicular regions, trunk, anterior mediastinum and mesenteries. Cortisol also increases appetite.

Cortisol has inhibitory effects on T-cell- and B-cell-mediated immune responses as well as suppressive effects on monocytes and neutrophils. It also promotes the transcription of genes coding for *anti-inflammatory* products, and inhibits both the synthesis and secretion of inflammatory cytokines.

Adrenal androgens

Adrenal androgens are produced in the zona reticularis. Their synthesis is under the control of ACTH.

DHEA is converted to dehydroepiandrosterone sulfate (DHEA-S) in the adrenals and liver, both of which contain a sulfotransferase. In the adrenal glands and peripheral tissues, small amounts of DHEA and DHEA-S are converted to more active androgens such as androstenedione, testosterone and 5-dihydrotestosterone, and oestrogens such as oestradiol and oestrone.

These hormones exert their androgenic and oestrogenic effects via androgen and oestrogen receptors respectively. Androgen (and oestrogen) receptors are nuclear receptors that bind to specific DNA sequences and regulate the expression of certain genes.

In women, the adrenal production of DHEA and DHEA-S contributes substantially to overall androgen levels. In men, the adrenal contribution is very small compared with that of the testes.

KEY POINTS

- The adrenal glands are located at the upper poles of the kidneys.
- The adrenal glands consist of an outer cortex (90%) surrounding an inner medulla (10%).
- The adrenal cortex has three 'zones': the zona glomerulosa secretes aldosterone; the zona fasciculata secretes cortisol; and the zona reticularis secretes adrenal androgens.
- The adrenal medulla produces catecholamines: adrenaline (80%) and noradrenaline (20%).
- Aldosterone secretion is stimulated by the renin–angiotensin system and elevated serum potassium.
- Cortisol release is stimulated by ACTH from the anterior pituitary.
- Cortisol, aldosterone and adrenal androgens are lipid-soluble hormones. They cross the plasma membrane and bind to intracellular nuclear receptors that bind in turn to specific DNA sequences and regulate the expression of certain genes.

6

Adrenal insufficiency

Adrenal insufficiency refers to reduced production of the hormones secreted by the adrenal cortex. Adrenal insufficiency may be 'primary' due to disease affecting the adrenal cortex (Addison disease, named after Thomas Addison who described its features in 1855), or 'secondary' due to either pituitary/hypothalamic disease or long-term glucocorticoid use leading to suppression of the hypothalamic–pituitary–adrenal (HPA) axis. Some authors use the terms 'secondary adrenal failure' when the cause is pituitary failure and 'tertiary adrenal failure' when it is caused by exogenous glucocorticoid use. These patients have a preserved aldosterone axis, and so have a low risk of adrenal crisis. The terms 'primary adrenal insufficiency' (PAI) and Addison disease are often used interchangeably. Acute adrenal insufficiency is a life-threatening endocrine emergency, caused by a lack of both cortisol and aldosterone.

Epidemiology

The prevalence of Addison disease is about 120–140 per million. Historically, most cases were caused by tuberculosis. Now, isolated autoimmune adrenal insufficiency is the most common cause in the UK, occurring predominantly in males during the first two decades of life, equally in males and females in the third decade, and predominantly in females thereafter (80%). The reason for these sex differences is unknown. In contrast, 70% of patients with autoimmune adrenal insufficiency as part of one of the autoimmune polyglandular syndromes (APSs) are female.

Aetiology

The aetiology of PAI depends on geographical location. In developed countries, the most common cause of PAI is *autoimmune* adrenalitis (up to 80% of cases). In these patients, there is evidence of both humoral and cell-mediated immune mechanisms directed at all three zones of the adrenal cortex. Up to 75% of patients with autoimmune PAI have antibodies against steroidogenic enzymes (most often 21-hydroxylase) and all three zones of the adrenal cortex. The first evidence of autoimmune adrenal insufficiency is an increase in plasma renin activity (PRA), suggesting that the zona glomerulosa failure and reduction in aldosterone occur first. Zona fasciculata dysfunction becomes evident several months to years later.

About 50% of patients with autoimmune adrenal insufficiency have one or more other autoimmune endocrine disorders.

Autoimmune adrenal insufficiency may rarely be part of APSs.

- *APS type 1* is an autosomal recessive disorder caused by mutations in the *AIRE* gene, which encodes a nuclear transcription factor. APS type 1 occurs more commonly in males and is characterised by chronic mucocutaneous candidiasis and hypoparathyroidism (appearing by the early 20s, in 90%) followed by Addison disease (in 60–70%).
- *APS type 2* or Schmidt syndrome may be inherited in an autosomal recessive, dominant or polygenic manner. APS type 2 occurs more commonly in females and is characterised by Addison disease (100%), autoimmune thyroid disease, and type 1 diabetes. Pernicious anaemia is also described.

Primary hypogonadism occurs in both types of APS, and ovarian failure is more frequent than testicular failure.

Tuberculosis is the second most common cause of 'Addison disease'. Recently, an association between immune checkpoint inhibitors and autoimmune adrenal insufficiency has emerged (along with other endocrinopathies affecting the pituitary, thyroid and pancreas). Immune checkpoint inhibitors are monoclonal antibodies to proteins known as immune

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Box 6.1 Causes of primary adrenal insufficiency

Autoimmune

Isolated, APS types 1 and 2, immune checkpoint inhibitors

Infection

Tuberculosis, fungal (histoplasmosis, cryptococcosis), cytomegalovirus (in AIDS)

Infiltration

Metastases (lung, breast, kidney), lymphoma, amyloidosis, haemochromatosis

Infarction

Due to thrombosis caused by thrombophilia (e.g. antiphospholipid syndrome)

Haemorrhage

Waterhouse–Friderichsen syndrome due to meningococcal septicaemia, anticoagulants

Adrenoleukodystrophy

Adrenal dysgenesis

Congenital adrenal hypoplasia (due to mutations of the *NR0B1* gene on the X chromosome, encoding a nuclear receptor protein called DAX1), mutations in SF1 gene

Iatrogenic

Adrenal suppressors (ketoconazole, etomidate), immune checkpoint inhibitors (e.g. nivolumab, pembroluzimab), bilateral adrenalectomy

checkpoint regulators (cytotoxic T-lymphocyte-associated antigen-4, programmed cell death protein-1, and programmed death ligand 1 and 2), and are used to treat metastatic cancer, e.g. renal cancer, melanoma. Rarer causes of adrenal insufficiency are listed in Box 6.1.

The adrenal glands are a relatively common site of metastases. However, adrenal insufficiency with metastases is much less common.

Adrenoleukodystrophy is a rare X-linked disorder, caused by mutations in the *ABCD1* gene that prevent normal transport of very long chain fatty acids into peroxisomes (for beta-oxidation) and their accumulation in the central nervous system and adrenal cortex. Patients may present in childhood with cognitive and behavioural abnormalities which get worse, blindness and the development of quadriparesis.

Adrenoleukodystrophy consists of a spectrum of phenotypes that includes adrenomyeloneuropathy. Adrenomyeloneuropathy typically presents in adult males between 20 and 40 years of age with adrenal insufficiency, spastic paraparesis, abnormal sphincter control, or cerebellar signs.

For causes of secondary adrenal insufficiency, see Chapter 12.

Chronic glucocorticoid use and HPA axis suppression

It is important to note that aldosterone is preserved in patients who are taking oral glucocorticoids and so have a much lower risk of adrenal crisis than patients with PAI.

The following groups of patients are likely to have adrenal insufficiency secondary to HPA axis suppression by long-term glucocorticoid use:

- those who have received a glucocorticoid dose equivalent to or more than 5 mg of prednisolone per day for more than 4 weeks
- those who have received an evening or bedtime dose of prednisolone for more than a few weeks
- those who have a cushingoid appearance.

People who use long-term inhaler corticosteroids for asthma or chronic obstructive pulmonary disease, or those who have received intra-articular glucocorticoid injections, or those using topical steroid creams or bleachers may also develop adrenal insufficiency. It is important to ask about these when taking a medical history.

Clinical presentations of primary adrenal insufficiency

The insidious onset and non-specific symptoms often result in a delay in diagnosis. Adrenal insufficiency may therefore be undetected until an acute illness or other stress precipitates an adrenal crisis. Addison disease has been described as the 'unforgiving master of non-specificity and disguise'.

Patients may have symptoms and signs of glucocorticoid, mineralocorticoid and, in women, androgen deficiency. Patients with secondary adrenal insufficiency usually have normal mineralocorticoid

Box 6.2 Clinical presentations of primary adrenal insufficiency

Acute adrenal crisis
Hypotension/shock >90%
Abdominal pain 80–90%
Nausea and vomiting 50–60%
Fever 60–70%

General
Malaise, fatigue, weakness, anorexia, weight loss

Gastrointestinal
Nausea, vomiting, abdominal pain (which can mimic an acute abdomen), diarrhoea

Hypotension
Postural hypotension, improved blood pressure in hypertensive patients

Metabolic
Hyponatraemia, hyperkalaemia, hypoglycaemia, hypercalcaemia

Skin
Hyperpigmentation (generalised, palmar creases, nails, buccal, scars, nails), associated vitiligo

Musculoskeletal
Myalgia, arthralgia, flexion contractures of legs (rare), calcification of the auricular cartilages in men

Psychiatric
Impairment of memory, confusion, depression, psychosis

function as mineralocorticoids are regulated by the renin–angiotensin system rather than adrenocorticotrophic hormone (ACTH). This makes hypopituitarism even more non-specific, and the blood pressure is usually normal.

Clinical presentations of PAI are summarised in Box 6.2.

Acute adrenal insufficiency/ adrenal crisis

Adrenal crisis most commonly presents as *shock* with hypotension and/or tachycardia. Prompt identification can save lives. Acute adrenal crisis may be seen in patients with:

- previously undiagnosed adrenal insufficiency who have been subject to acute stress or illness, for example infection
- known adrenal insufficiency who have not increased their steroid dose during an infection or other illness, or have been vomiting
- HPA suppression caused by the long-term use of glucocorticoids (oral and occasionally inhaled) who suddenly stop their treatment, although such crises are rarely life-threatening. Cortisol is required to clear free water in the kidney, so such patients can present with hyponatraemia
- bilateral adrenal infarction or haemorrhage
- pituitary apoplexy (infarction) resulting in acute cortisol deficiency.

General

Patients with adrenal insufficiency often have non-specific symptoms such as malaise, fatigue, lethargy, weakness, anorexia and weight loss.

Gastrointestinal

Patients may complain of nausea, occasionally vomiting, abdominal pain and diarrhoea that may alternate with constipation. The cause of gastrointestinal symptoms in adrenal insufficiency is not fully understood but may be related to electrolyte abnormalities.

Hypotension

Adrenal insufficiency can present with *postural hypotension* (causing postural dizziness), low blood pressure or improved blood pressure in patients with pre-existing hypertension. This is mainly due to volume depletion resulting from aldosterone deficiency. Glucocorticoid deficiency can contribute to hypotension by causing decreased vascular responsiveness to the vasoconstrictor effect of noradrenaline and angiotensin II, but patients with preserved aldosterone may not be hypotensive.

Skin

In PAI, lack of cortisol negative feedback causes an increase in the hypothalamic precursor protein pro-opiomelanocortin (POMC) and its cleavage products, including ACTH and alpha-melanocyte-stimulating hormone. The latter increases the melanin content of the skin, resulting in *hyperpigmentation*, which may be generalised, particularly in areas exposed to light or pressure (e.g. elbows, knees, spine, knuckles, brassiere straps). It may also be seen in the palmar creases, nails (longitudinal bands of darkening), buccal

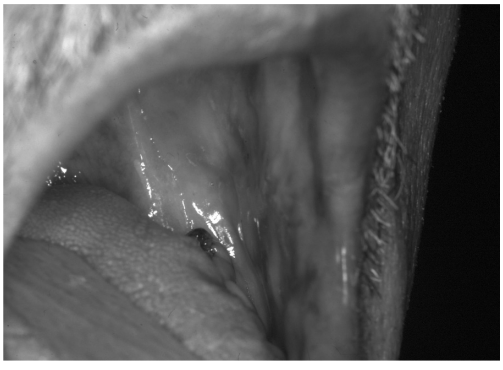

Figure 6.1 Buccal pigmentation in a patient with Addison disease.

mucosa (Figure 6.1) and scars acquired when PAI is present and untreated. The hyperpigmentation usually disappears after a few months of treatment with glucocorticoids. However, scars do not fade because the melanin is trapped in fibrous connective tissue.

Associated vitiligo (areas of depigmented skin) is seen in 10–20% of patients with Addison disease. Vitiligo results from autoimmune destruction of dermal melanocytes.

Electrolyte abnormalities

Hyponatraemia is seen in 90% of patients and is due to sodium loss caused by mineralocorticoid deficiency, and increased antidiuretic hormone secretion caused by cortisol deficiency (resulting in reduced renal water clearance). Patients may present with salt craving.

Hyperkalaemia occurs in 60% of patients. It is associated with mild hyperchloraemic acidosis and is due to mineralocorticoid deficiency.

Patients may have an elevated urea (and possibly creatinine) due to dehydration. Hypercalcaemia may rarely occur in Addison disease.

Hypoglycaemia

Hypoglycaemia is rare in adults in the absence of infection or alcohol ingestion. It may occur after prolonged fasting or, rarely, several hours after a high-carbohydrate meal. It is more common in patients with secondary adrenal insufficiency caused by isolated ACTH deficiency.

Addison disease should be suspected in patients with type 1 diabetes mellitus in whom insulin requirements decrease or with new, frequent, unexplained hypoglycaemia.

Reduced adrenal androgens in women

In women, the adrenal cortex is the primary source of androgens in the form of dehydroepiandrosterone (DHEA) and DHEA sulfate. Women with adrenal insufficiency may have decreased pubic and axillary hair and loss of libido due to reduced adrenal androgens.

Clinical presentations of secondary adrenal insufficiency

Many of the symptoms such as weakness, fatigue, myalgia and arthralgia are the same as those for PAI. The major exceptions are that in secondary adrenal insufficiency, the following are observed:

- There is no hyperpigmentation (due to ACTH deficiency).
- There is no dehydration or hyperkalaemia (reflecting the presence of aldosterone).
- Gastrointestinal symptoms are less common (suggesting that electrolyte disturbances may be involved in their aetiology).
- Hypoglycaemia is more common (possibly because of co-existent growth hormone deficiency).
- There may be clinical manifestations of a pituitary or hypothalamic tumour, such as a headache, visual field defects or symptoms and signs of deficiency of other anterior pituitary hormones.

Investigations

Initial blood tests at presentation may show:

- hyponatraemia
- hyperkalaemia
- acidosis (normal anion gap)
- high urea
- mild hypercalcaemia
- normocytic anaemia
- eosinophilia
- hypoglycaemia (rare in adults)
- high renin and low aldosterone.

Patients with Addison disease may have low free thyroid hormone levels and elevated thyroid-stimulating hormone. This may either be a direct effect of glucocorticoid deficiency or due to associated primary autoimmune hypothyroidism. Thus,

thyroid function tests must be rechecked after adrenal insufficiency has been treated.

Early morning cortisol and short ACTH stimulation test

Taken between 7 and 9 a.m., a serum cortisol level of less than 100 nmol/L suggests adrenal insufficiency. Adrenal insufficiency is unlikely if the early morning cortisol is more than 350 nmol/L. The circadian rhythm results in a normal cortisol falling during the morning, provided the patient has a normal sleep pattern. These ranges are inaccurate in patients who work night shifts.

Patients with features of adrenal insufficiency and a 7–9 a.m. cortisol of below 350 nmol/L should have a *short ACTH stimulation test*. In this test, 250 µg of synthetic ACTH (amino acids 1–24) is given intramuscularly or intravenously and serum cortisol is measured at time 0 (just before the injection) and 30 and 60 minutes after the synthetic ACTH has been given. A normal response to the short ACTH stimulation test is a peak cortisol of over 550 nmol/L or an incremental rise of more than 170 nmol/L. These values may vary according to local guidelines and laboratories. An abnormal response is consistent with primary or secondary adrenal failure and should be investigated further (see below).

If the patient is already on hydrocortisone, this should be omitted on the morning of the short ACTH stimulation test. This is because the exogenous hydrocortisone may be measured by the assay. The previous practice of administering dexamethasone instead of hydrocortisone results in profound adrenal suppression, as dexamethasone is 50 times more potent than hydrocortisone. Delaying a single dose of hydrocortisone for an hour is always safe, and there is never an indication to switch to dexamethasone.

Oestrogens should be discontinued for 6 weeks before the test. This is because the assay measures total cortisol level, and oestrogens increase cortisol-binding globulin (CBG) and result in higher total cortisol level measurements.

False-negative results may be seen in acutely unwell patients, in whom levels of CBG may be low. Thus, total cortisol levels measured following the ACTH stimulation test may be misleadingly low (due to low CBG) even though free cortisol levels may be normal or even high.

A normal response does not exclude the diagnosis of secondary adrenal insufficiency, particularly if the secondary adrenal insufficiency is recent (e.g. within 2 weeks after pituitary surgery). This is because the adrenals have not yet become completely atrophic, and are still capable of responding to ACTH stimulation. In these patients, an insulin tolerance test (i.e. stimulation of ACTH and subsequently cortisol release by insulin-induced hypoglycaemia) is the preferred test.

Chronic glucocorticoid use and HPA axis suppression

In patients who have been on long-term glucocorticoids, a short ACTH stimulation test should be performed if:

- abrupt discontinuation is required
- the patient is facing an acute stress, for example surgery
- there is difficulty in reducing the prednisolone dose below 3 mg per day because of non-disease-related symptoms.

Determining the level of defect

Once adrenal insufficiency has been diagnosed, it should be determined whether it is primary or secondary.

Basal plasma ACTH

Basal plasma ACTH levels should be measured at the beginning of the short ACTH stimulation test (i.e. before synthetic ACTH is given). ACTH is unstable in blood at room temperature. Thus, the specimen for plasma ACTH is collected in an EDTA tube and sent to the laboratory on ice immediately. Raised ACTH (>200 ng/L) in the presence of an impaired cortisol response is consistent with PAI. ACTH levels less than 10 ng/L are consistent with a diagnosis of secondary adrenal insufficiency.

ACTH secretion is suppressed by glucocorticoid therapy. Thus, blood samples for ACTH must be drawn before starting glucocorticoids. In patients who are already on hydrocortisone, the test should be done at least 24 hours after the last dose of hydrocortisone, and longer after long-acting glucocorticoids such as dexamethasone if this is thought to be safe clinically.

Prolonged ACTH stimulation test

This test is no longer performed as it does not add useful information.

Metyrapone test

The metyrapone test may occasionally be used if partial ACTH deficiency is suspected. Metyrapone

blocks the final step in cortisol biosynthesis, resulting in reductions in cortisol concentration and stimulation of ACTH secretion due to reduced negative feedback. Hypocortisolaemia is a weaker stimulus to ACTH secretion than hypoglycaemia, and thus the metyrapone test will detect partial ACTH deficiency that may be missed by the insulin tolerance test. It can also be used in patients where insulin-induced hypoglycaemia is contraindicated as in patients with ischaemic heart disease or epilepsy.

Determining the aetiology

The investigations for determining the aetiology of PAI are discussed below. Patients with secondary adrenal insufficiency should have a pituitary magnetic resonance imaging scan to exclude a tumour or other mass lesion, and further pituitary function tests (see Chapter 12).

Adrenal antibodies

Antibodies to enzymes of the adrenal cortex are found in more than 90% of patients with recent-onset adrenal autoimmunity. 21-Hydroxylase antibodies are the major component of adrenal cortex antibodies. Adrenal antibodies are not good for screening as only 20% of people with positive antibodies subsequently develop Addison disease.

Imaging

If there is clinical suspicion of tuberculosis, chest and abdominal radiographs should be performed to look for apical shadowing and adrenal calcification respectively. Abdominal computed tomography (CT) may show adrenal enlargement with or without calcification in patients with tuberculosis, infiltration or metastatic disease. In autoimmune adrenalitis, the adrenal glands are often small and atrophic.

Other tests

Other tests may be done depending on the suspected causes of adrenal insufficiency. These may include, for example, serological or microbiological investigations for infections (e.g. urine culture for *Mycobacterium tuberculosis*, tuberculin skin testing, complement fixation titres for *Histoplasma capsulatum*), thrombophilia screen (including antiphospholipid antibodies), plasma concentration of very long chain fatty acids (elevated in adrenoleukodystrophy) and percutaneous CT-guided biopsy.

Detecting other autoimmune diseases

Patients with autoimmune adrenal failure should be investigated for:

- diabetes mellitus: fasting glucose
- thyroid disease: free thyroxine/triiodothyronine and thyroid-stimulating hormone
- parathyroid dysfunction: calcium and phosphate (and parathyroid hormone if hypocalcaemic)
- pernicious anaemia: parietal cell antibodies
- primary gonadal failure: luteinising hormone, follicle-stimulating hormone, testosterone (in men), oestradiol (in women).

Treatment

Management of addisonian crisis

Adrenal crisis is a life-threatening emergency and requires immediate treatment. Blood for serum cortisol, ACTH, renin and serum urea and electrolytes should be drawn and therapy should be started immediately.

- *Fluids*: 1–3 L of 0.9% saline should be infused intravenously within the first 12–24 hours based on an assessment of volume status and urine output. Hypoglycaemia (if present) must be corrected with intravenous dextrose.
- *Glucocorticoids*: patients with known adrenal insufficiency should be treated with hydrocortisone 100 mg intramuscularly which should be given immediately, followed by either 200 mg intravenous infusion over 24 hours or 50 mg IV 6-hourly. Mineralocorticoid replacement is not required acutely because adequate sodium replacement can be achieved by intravenous saline alone and cortisol at these high doses also binds to the aldosterone receptor in the kidney. Unless there is a major complicating illness, parenteral glucocorticoid therapy can be tapered over 1–3 days and changed to an oral maintenance dose.
- The *precipitating cause* of the adrenal crisis (e.g. bacterial infection or viral gastroenteritis) should be treated appropriately.

Once the patient's condition is stable, the diagnosis can be confirmed in patients not known to have adrenal insufficiency with a short ACTH stimulation test.

Long-term treatment

It cannot be emphasised enough that patient education is vital. As with diabetes mellitus and vasopressin insufficiency, daily treatment is life-sustaining and illness and possibly mortality will ensue rapidly if treatment is delayed or missed. The standardised mortality ratio is doubled in people with Addison disease, predominantly due to infectious and cardiovascular disease, which may be due to chronic glucocorticoid excess.

Glucocorticoid replacement

Prednisolone 3–4 mg once daily taken first thing on waking mimics the circadian rhythm well.

Hydrocortisone can be used in a regimen of 10 mg in the morning, 5 mg at noon, and 2.5 mg in the afternoon as a 'best-guess' starting dose. The aim will be to replicate the circadian rhythm. Late doses of hydrocortisone are not physiological.

Over-replacement may result in Cushing syndrome. Thus, the total daily dose should not exceed 20 mg (except at times of intercurrent illness).

It is essential that patients are provided with:

- information regarding the doubling of glucocorticoid (steroid) dose at times of intercurrent illness
- an emergency intramuscular hydrocortisone supply (to be given at times of vomiting o*n their way to hospital – it is important that patients and family/carers are aware that IM hydrocortisone should only be used as a bridge to emergency hospital admission*)
- a steroid emergency card and/or MedicAlert bracelet.

It must be remembered that glucocorticoid replacement may unmask underlying central vasopressin insufficiency, leading to marked polyuria.

Mineralocorticoid replacement

Fludrocortisone is given orally in a usual dose of 100 µg per day with the aim of achieving normal sodium homeostasis. Patients receiving hydrocortisone (which has some mineralocorticoid activity) may require a lower dose of fludrocortisone (e.g. 50 µg per day). However, patients receiving prednisolone or dexamethasone (which have no mineralocorticoid activity) may require up to 200 µg per day of fludrocortisone. The mineralocorticoid dose may have to be increased in the summer, when salt loss in perspiration increases.

Patients with essential hypertension and PAI should be treated by dietary sodium restriction and a lower dose of fludrocortisone. Fludrocortisone cannot usually be discontinued without risking sodium depletion. If an antihypertensive drug is needed, diuretic drugs and spironolactone should not be used, as they simply counteract the action of fludrocortisone.

Mineralocorticoid replacement is not required in patients with secondary adrenal insufficiency as ACTH is not an important regulator of aldosterone release.

Androgen replacement

Clinical trial data suggest that DHEA replacement in women may be beneficial for mood and psychological well-being. However, there is insufficient evidence to recommend therapy in all patients with adrenal insufficiency, particularly in men. In women with adrenal insufficiency (primary or secondary), DHEA therapy (25–50 mg daily) may be tried in those who have a significantly impaired sense of well-being or mood despite optimal glucocorticoid and mineralocorticoid replacement. If no obvious benefit has been seen after 6 months, or if adverse effects such as acne occur, DHEA should be discontinued.

Treatment of the underlying disorder

Patients with causes other than autoimmune adrenalitis (e.g. adrenal tuberculosis or adrenoleukodystrophy) should be referred to the appropriate specialists.

HPA axis suppression

Patients who are likely to have HPA axis suppression due to the chronic use of glucocorticoids (e.g. for inflammatory diseases), should wear a MedicAlert bracelet and carry a 'steroid card' and arguably a hydrocortisone ampoule.

If withdrawal from glucocorticoids is indicated, the dose must be reduced *gradually*. The goal of tapering is to prevent both recurrent activity of the underlying disease and symptoms of cortisol deficiency. If patients are on more than 3 mg of prednisolone, the rate of reduction will be decided by the physician treating their primary autoimmune disease. The dose will be slowly reduced to ensure that the primary disease does not reactivate. If the dose gets down to 3 mg daily and the primary condition is thought to be in remission, then further reduction in steroid dose is made more difficult by the suppressed adrenal. Tiredness may ensue if the glucocorticoid levels are lower than normal. A very slow reduction below 3 mg can help. A suggested protocol for very gradual reduction of prednisolone is given on the next page.

- For prednisone doses of 20–60 mg per day: reduce by 5 mg per day every 1–2 weeks.
- For prednisone doses of 10–19 mg per day: reduce by 2.5 mg per day every 1–2 weeks.
- For prednisone doses of 5–9 mg per day: reduce by 1 mg per day every 1–2 weeks.
- For prednisone doses below 5 mg per day: reduce by 0.5 mg per day every 1–2 weeks.

Specific situations

In certain situations, additional glucocorticoid cover will be required, described in Box 6.3.

Follow-up and monitoring

Glucocorticoid replacement

The adequacy of treatment is monitored by *clinical assessment* and laboratory tests. The glucocorticoid dose should be increased if symptoms of cortisol deficiency are present. However, if increasing the dose does not promptly ameliorate the symptoms, an alternative cause should be sought and the lower steroid dosage should be resumed. The glucocorticoid dose may be high if the patient develops excessive weight gain, facial plethora, osteoporosis or other symptoms or signs of Cushing syndrome.

Some endocrinologists use prednisolone levels or *hydrocortisone day curves* to adjust the dose and timing of hydrocortisone replacement therapy. Blood is taken in the morning then before and 1 hour after the lunchtime and evening doses. With hydrocortisone replacement, the aim is to achieve adequate cortisol levels throughout the day (peak <900 nmol/L and trough >50–100 nmol/L). Once adequate levels have been achieved, this rarely needs to be repeated. All oestrogens should be stopped 6 weeks prior to the test as they increase CBG levels and result in misleadingly high measured total cortisol levels. ACTH levels are not useful for monitoring the efficacy of glucocorticoid replacement (levels will be high before taking steroids and low afterwards). Likewise, random cortisol levels should not be taken.

Mineralocorticoid replacement

The adequacy of mineralocorticoid replacement should be monitored by asking about symptoms of postural hypotension and measuring *lying and standing blood pressure* and serum urea and electrolytes. Postural hypotension suggests under-replacement. Hypertension, oedema and hypokalaemia suggest over-replacement.

PRA is difficult to interpret. In asymptomatic patients with normal serum electrolytes but a high PRA, the dose of fludrocortisone should not be raised to normalise PRA as patients may develop hypokalaemia and oedema. The best markers of adequacy of fludrocortisone dose are plasma potassium and blood pressure.

Box 6.3 Management of PAI in specific situations

Home management of illness with fever
Glucocorticoid replacement doses doubled until recovery
Increased consumption of electrolyte-containing fluids as tolerated

Unable to tolerate oral medication due to gastroenteritis or trauma
Hydrocortisone 100 mg IM or IV

Minor to moderate surgical stress
Steroid replacement doses doubled until recovery

Major surgery with general anaesthesia, trauma, delivery or disease that requires intensive care
Hydrocortisone, 100 mg per IV injection followed by 50 mg every 6 hours IV or IM (alternatively continuous IV infusion of 200 mg hydrocortisone/24 h)
Weight-appropriate continuous IV fluids
Rapid tapering and switch to oral regimen depending on clinical state

KEY POINTS

- The most common cause of PAI is autoimmune adrenalitis.
- The insidious onset and non-specific symptoms usually result in a delay in diagnosis.
- Physical signs of Addison disease include postural hypotension and hyperpigmentation.
- Laboratory tests in Addison disease may show hyponatraemia and hyperkalaemia.

- Patients with suspected Addison disease should have a short ACTH stimulation test.
- Addisonian crisis is treated with IV fluids (0.9% saline) and intramuscular/intravenous hydrocortisone.
- The long-term treatment of Addison disease includes oral prednisolone (3–4 mg) and fludrocortisone (50–100 mcg) once daily.
- Patients must be advised to carry a steroid card and a MedicAlert bracelet, and to double their glucocorticoid dose at times of intercurrent illness.
- If withdrawal from glucocorticoids is indicated in patients who are likely to have HPA axis suppression due to long-term glucocorticoid use, the dose must be reduced gradually.

7

Primary hyperaldosteronism

Primary hyperaldosteronism (PH) is characterised by an excessive autonomous secretion of aldosterone resulting in suppression of plasma renin activity. The two main causes of primary hyperaldosteronism are a *unilateral adrenal adenoma* secreting excess aldosterone and *bilateral hyperplasia* of the adrenal cortex.

Secondary hyperaldosteronism is due to increased plasma renin activity and may be seen in conditions associated with reduced renal perfusion such as renal artery stenosis, congestive cardiac failure and cirrhosis or rare metabolic conditions such as Barrter syndrome.

Epidemiology

The prevalence of primary hyperaldosteronism in hypertensive patients is 8–13%, but this may increase to 20% people with 'resistant' hypertension. The high prevalence of PH is further strengthened by improvements in resistant hypertension by the administration of spironolactone. Aldosterone-producing adenomas occur more commonly in women (2:1 ratio) and in younger patients (<50 years). Bilateral adrenal hyperplasia occurs more commonly in men and usually presents at an older age.

Aetiology

Primary hyperaldosteronism may be due to bilateral hyperplasia of the adrenal cortex (60–70%) or a unilateral aldosterone-producing adenoma (30–40%). Rarely, hyperaldosteronism may be secondary to glucocorticoid-suppressible hyperaldosteronism (1–3%) or an aldosterone-producing adrenal carcinoma.

Aldosterone stimulates sodium reabsorption and potassium and hydrogen loss by acting on the distal renal tubules. Excessive aldosterone secretion results in sodium and water retention leading to hypertension, hypokalaemia and metabolic alkalosis.

In *bilateral adrenal hyperplasia* (BAH, also known as idiopathic hyperaldosteronism), the adrenal zona glomerulosa (which produces aldosterone) becomes more sensitive to angiotensin II. The hyperplasia may be macro- or micronodular. Hypokalaemia is typically milder (compared to APAs).

Aldosterone-producing adenomas (APAs, also called Conn syndrome) are usually 0.5–2 cm in size and have a yellow colour due to their high cholesterol content (Figure 7.1). These adenomas express very high levels of aldosterone synthase and usually produce greater levels of aldosterone than bilateral adrenal hyperplasia.

Somatic mutations may lead to aldosterone hypersecretion in up to 90% of patients with APAs. Mutations in the following genes affecting ion channel function in glomerulosa cells result in increased intracellular calcium, aldosterone production and cell proliferation.

- *KCNJ5* (encoding potassium channel Kir3.4): loss of K^+ selectivity, increased Na^+ conductance and membrane depolarisation (seen in approximately 40% of patients with APAs)
- *CACNA1D* (encoding a voltage-gated calcium channel): increased Ca^{2+} influx
- *ATP1A1* (encoding a Na^+/K^+ ATPase alpha subunit): inappropriate depolarisation
- *ATP2B3* (encoding a Ca^{2+} ATPase): decreased intracellular calcium clearance

Mutations in *CTNNB1* (beta-catenin, the Wnt signalling pathway) genes have also been identified in APAs.

Glucocorticoid-suppressible hyperaldosteronism is a rare autosomal dominant condition caused by a mutation that results in a chimeric gene containing the promoter region of the gene encoding 11-beta-hydroxylase (which catalyses the conversion of 11-deoxycortisol to cortisol) and the coding sequences of the gene for aldosterone synthase.

Endocrinology and Diabetes: Lecture Notes, Second Edition. Amir H. Sam, Karim Meeran and Neil Hill.
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Figure 7.1 Bisected Conn adenoma.

This results in an adrenocorticotrophic hormone (ACTH)-dependent activation of aldosterone synthase, which is expressed in the zona fasciculata as well as zona glomerulosa. Thus, glucocorticoids suppress ACTH secretion and, hence, aldosterone production. Glucocorticoid-suppressible hyperaldosteronism is usually associated with bilateral adrenal hyperplasia.

Aldosterone-producing carcinomas (rare) are often over 4 cm in diameter at presentation. They are usually associated with the hypersecretion of cortisol, androgens and oestrogens, as well as very high levels of aldosterone. Hypokalaemia may be profound.

Clinical presentations

Patients usually present with *hypertension* and *hypokalaemia*. Cardiovascular morbidity (including stroke, ischaemic heart disease and atrial fibrillation) is at least doubled in people with PH compared to people with essential hypertension.

Hypertension is often asymptomatic. Hypokalaemia may cause fatigue, muscle weakness, cramps, tetany, polydipsia and polyuria (especially nocturia, due to hypokalaemia-induced nephrogenic diabetes insipidus). Serum potassium may be normal in 50% of patients. A low-sodium diet may mask hypokalaemia as reduced sodium delivery to the distal nephron diminishes aldosterone-induced potassium loss. Oedema is not prominent in response to high aldosterone levels; extracellular fluid volume rarely increases by more than 15%. This is because of escape mechanisms which include increased renal perfusion with subsequent hypertension, reduced sodium reabsorption in the proximal convoluted tubule and the effects of natriuretic hormones.

Early (childhood) haemorrhagic strokes are characteristic in patients with glucocorticoid-suppressible hyperaldosteronism.

Investigations

Investigations for PH should firstly confirm hyperaldosteronism. There are many potential causes of false-positive readings which should be sought. Only when hyperaldosteronism has been unequivocally demonstrated should the focus switch to identifying the cause and localising the source. This avoids unnecessary imaging, which may lead to identification of incidental adrenal adenomas wrongly suspected of causing hyperaldosteronism. As well as appropriate management of hypertension and low potassium caused by PH, a secondary goal is to avoid removing normal adrenal glands with incidental nodules.

There are no protocols to inform screening for PH. Case detection for primary hyperaldosteronism should be undertaken in the following groups:

- early-onset hypertension (<35 years)
- early-onset stroke (<40 years)
- severe hypertension >160/110 mmHg
- resistant hypertension (e.g. three or more antihypertensive medications)
- hypokalaemia (spontaneous or diuretic-induced hypokalaemia that does not respond to potassium replacement)
- family history of APA
- discovery of adrenal incidentaloma (see Chapter 10).

Screening tests

Only 10–40% of patients with primary hyperaldosteronism are hypokalaemic. Serum sodium levels usually remain normal because of the parallel increase in the water content of the blood.

The initial screening test is measurement of *plasma aldosterone concentration* and *plasma renin activity*. A raised plasma aldosterone concentration to renin activity ratio suggests primary hyperaldosteronism. The cut-off for a 'high' ratio is dependent on the plasma renin activity assay and is therefore laboratory dependent. It is important to note the limitations of these assays; there are no independent reference standards and results are dependent on posture, timing, other medications and sodium status. Expert advice from the laboratory scientists is often invaluable.

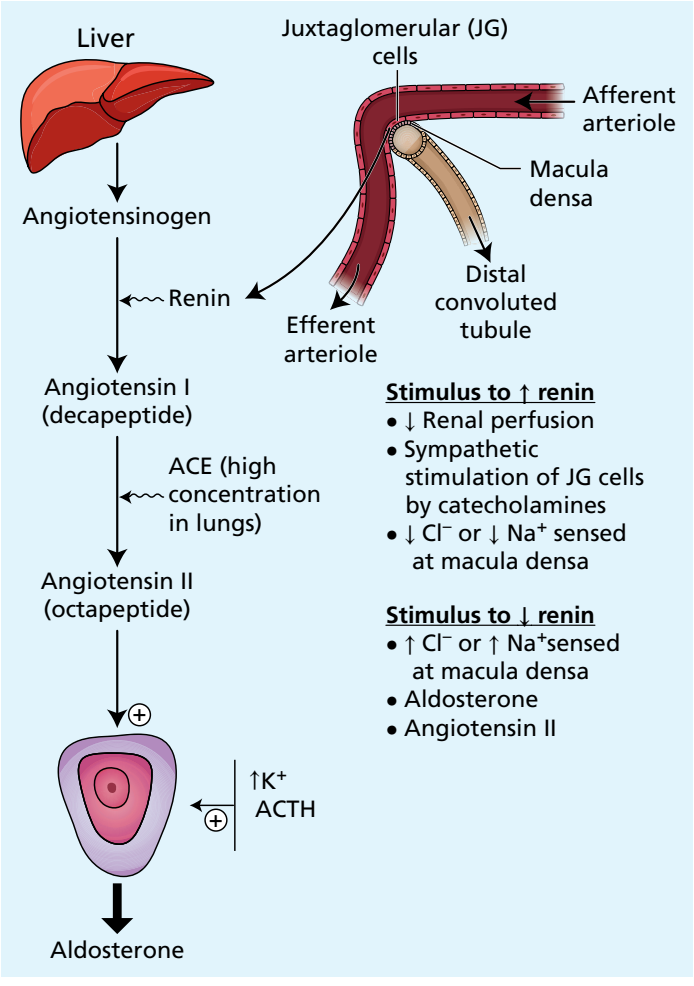

Figure 7.2 The Renin-Angiotensin-Aldosterone System.

To better understand the effect of various antihypertensives on renin/aldosterone levels, it is worth revisiting the stimuli for renin and aldosterone release (Figure 7.2). Spironolactone, eplerenone, angiotensin-converting enzyme (ACE) inhibitors, angiotensin receptor blockers and diuretics increase plasma renin activity. Beta-blockers suppress renin release, and calcium channel blockers may reduce aldosterone levels. The duration of wash-out is 6 weeks for spironolactone and 2 weeks for most other antihypertensives. If antihypertensive therapy is required, an alpha-blocker (e.g. doxazosin) and/or verapamil may be used.

Hypokalaemia should be corrected (with oral potassium chloride supplementation, aiming for potassium >4.0 mmol/L) as it reduces aldosterone secretion.

A false-negative result may be seen in chronic renal failure.

Confirmatory tests

Salt loading

The response in normal people following a sodium load is aldosterone suppression. Failure of aldosterone suppression following a sodium load confirms primary hyperaldosteronism.

Oral sodium chloride (two 1 g sodium chloride tablets taken three times a day with food) is given. On the third day, a 24-hour urine specimen is collected for measurement of aldosterone, sodium and creatinine. The 24-hour urine sodium excretion should exceed 200 mmol to document adequate sodium loading.

Urine creatinine is measured to ensure adequate urine collection. Remember that sodium loading causes increased urinary potassium loss and hypokalaemia. Therefore serum potassium should be measured daily, and hypokalaemia must be corrected.

Alternatively, intravenous 0.9% sodium chloride (2 L over 4 hours) may be given (not in patients with heart failure). A plasma aldosterone level of over 280 pmol/L is consistent with primary hyperaldosteronism. Plasma aldosterone of less than 140 pmol/L excludes the diagnosis, and levels between 140 and 280 pmol/L need further investigation.

Captopril suppression test

Rarely performed now, this test involves the oral administration of 25–50 mg of captopril (an ACE inhibitor), which suppresses aldosterone levels in normal people. An inability to reduce plasma aldosterone levels after administration of captopril suggests primary hyperaldosteronism.

Determining the cause

The cause must be determined because of significant treatment implications. Unilateral adenomas can be surgically cured, whereas bilateral adrenal hyperplasia requires lifelong pharmacotherapy with aldosterone antagonists. The specific pitfalls of different biochemical and radiological tests need to be considered.

Imaging

Imaging should be done only after biochemical confirmation of primary hyperaldosteronism since non-functioning adrenal 'incidentalomas' are common. High-resolution computed tomography (CT) or magnetic resonance imaging may show a unilateral adenoma (and rarely carcinomas, which are usually >4 cm in size) with a normal contralateral adrenal gland. It is important to note that APAs are often small and may go undetected by CT imaging. In bilateral hyperplasia, the adrenal glands may be enlarged or of normal size. Adrenal imaging identifies most adenomas of over 0.5 cm. It should be noted that patients with primary hyperaldosteronism and a normal CT scan or bilateral adrenal nodules on CT may be found to have a unilateral source of aldosterone following adrenal vein sampling. A unilateral adenoma seen on CT may be found to be a non-functioning adenoma in a patient with bilateral hyperplasia. Positron emission tomography-computed tomography with metomidate may improve detection of APAs; studies are under way.

Adrenal vein sampling

In patients for whom surgery is practical and feasible, adrenal vein sampling should be performed to differentiate between a unilateral aldosterone-producing adenoma and bilateral hyperplasia. This is a technically challenging procedure and not offered in all centres.

Although modern-day radiological techniques offer excellent resolution, it is still possible for a small adenoma to be missed and, conversely, for a unilateral adrenal lesion seen on CT to be a non-functioning 'incidentaloma' in a patient with bilateral hyperplasia.

The current 'gold standard' test to distinguish between an adenoma and hyperplasia is adrenal vein sampling by an experienced radiologist. A bolus of tetracosactrin (250 µg) may be given 20 minutes prior to sampling. Aldosterone and cortisol levels are measured from the right and left adrenal veins and inferior vena cava. During the procedure, cortisol is measured to ensure correct catheterisation of the adrenal veins (an adrenal vein to inferior vena cava cortisol ratio of 3:1 ensures proper placement of the catheter into the adrenal vein). A unilateral aldosterone-producing adenoma produces a ratio of aldosterone to cortisol that is 4–5 times greater than that of the opposite side.

With successful adrenal vein catheterisation, the procedure is 95% successful in correctly distinguishing between bilateral hyperplasia and an adenoma. However, even in the best hands, correct placement of the cannula is achieved in only 75% of patients. The right adrenal vein in particular can be difficult to cannulate as it is short and enters the inferior vena cava at an acute angle. Other complications (groin haematoma, adrenal haemorrhage, adrenal vein dissection) are rare.

Other investigations

Genetic testing for glucocorticoid-suppressible hyperaldosteronism should be done in patients with an onset of primary hyperaldosteronism at age less than 20 years, a history of stroke at age below 40 years or a family history of primary hyperaldosteronism.

Treatment

Bilateral adrenal hyperplasia

In bilateral adrenal hyperplasia, *spironolactone* (200–400 mg per day) is usually the first choice for

treatment of hypertension and hypokalaemia. The side-effects of spironolactone include gynaecomastia, impotence, menstrual irregularities, muscle cramps and gastrointestinal upset. Spironolactone may be changed to eplerenone (a selective aldosterone receptor antagonist) if it causes intolerable side-effects. Patients who do not tolerate eplerenone may be started on amiloride (a potassium-sparing diuretic). Serum potassium, creatinine and blood pressure should be monitored frequently during the first 4–6 weeks of treatment. The clinical course and circumstances dictate the frequency of monitoring thereafter.

Other antihypertensives (e.g. ACE inhibitors and calcium channel blockers) may need to be added. It can take 4–8 weeks for the hypertension to respond to the treatments.

Aldosterone-producing adenomas

Aldosterone-producing adenomas are treated with *adrenalectomy* by an experienced endocrine surgeon. Laparoscopic adrenalectomy is now established as the standard of care as it is associated with reductions in postoperative morbidity, length of hospital stay and expense compared with open laparotomy.

Surgery may either cure hypertension (in about 50%) or make it more amenable to antihypertensive therapy in those who are not cured (usually the elderly or those with longstanding hypertension). Spironolactone given before surgery helps in correcting hypokalaemia. However, it should be stopped 2 days before the surgery to prevent mineralocorticoid deficiency after adrenalectomy. People with APA who do not want or cannot have surgery can be managed medically, and radiofrequency ablation may provide an alternative option for treatment, although not currently in widespread use. Patients with bilateral adrenal hyperplasia should not undergo adrenalectomy as the risks associated with bilateral adrenalectomy (including the need for lifelong glucocorticoid and mineralocorticoid replacement) outweigh the potential benefits. Blood pressure control is often inadequate with subtotal adrenalectomy.

Glucocorticoid-suppressible hyperaldosteronism is treated with dexamethasone (0.25 mg in the morning and 0.5 mg at night). However, side-effects of dexamethasone often limit its use. Spironolactone may be used if dexamethasone is not tolerated due to side-effects, and may reduce the risk of stroke.

Adrenal carcinoma is treated with surgery and postoperative mitotane (which may cause hypoadrenalism). The prognosis is usually poor.

Other causes of endocrine hypertension

The causes of endocrine hypertension are summarised in Box 7.1. Cushing syndrome, phaeochromocytoma, acromegaly, primary hyperparathyroidism and congenital adrenal hyperplasia are discussed in separate chapters.

11-Beta-hydroxysteroid dehydrogenase type 2 hypofunction (due to autosomal recessive mutations) or inhibition (by liquorice or carbenoxolone) causes hypertension, hypokalaemia and metabolic alkalosis. 11-Beta-hydroxysteroid dehydrogenase type 2 converts cortisol to cortisone, which does not bind to the mineralocorticoid receptor. Mutations in the gene encoding this enzyme result in a failure of conversion of cortisol to cortisone. Cortisol can therefore activate the mineralocorticoid receptor causing an 'apparent mineralocorticoid excess'. Patients typically have low levels of renin and aldosterone with elevated cortisol levels. This condition may be treated with dexamethasone to suppress endogenous cortisol, or with high-dose spironolactone/amiloride.

Liddle syndrome is a rare autosomal dominant condition caused by mutations in the beta or gamma subunits of the renal epithelial sodium channels, resulting in a constitutive activation of sodium reabsorption in the collecting tubules. Amiloride (or triamterene) is the treatment of choice.

Box 7.1 Causes of endocrine hypertension

Primary hyperaldosteronism
Cushing syndrome
Phaeochromocytoma
Acromegaly
Primary hyperparathyroidism
Low plasma renin activity and low plasma aldosterone levels occur in:

- congenital adrenal hyperplasia (11-beta-hydroxylase and 17-alpha-hydroxylase deficiency)
- 11-beta-hydroxysteroid dehydrogenase type 2 defect (due to autosomal recessive mutations) or inhibition by liquorice or carbenoxolone

Liddle syndrome

KEY POINTS

- Primary hyperaldosteronism is characterised by an excessive autonomous secretion of aldosterone, resulting in a suppression of plasma renin activity.
- Primary hyperaldosteronism may be due to bilateral hyperplasia of the adrenal cortex (70%) or a unilateral aldosterone-producing adenoma (30%).
- Patients may present with hypertension and hypokalaemia (10–40%).
- The initial screening test is measurement of plasma aldosterone concentration and plasma renin activity (after stopping interfering medications). Failure of suppression of aldosterone following salt loading confirms the diagnosis.
- The cause must be determined because of significant treatment implications.
- Adrenal vein sampling by an experienced radiologist is the 'gold standard' test to distinguish between an adenoma and hyperplasia.
- Bilateral adrenal hyperplasia is treated with mineralocorticoid antagonist (e.g. spironolactone). Aldosterone-producing adenomas are treated with adrenalectomy by an experienced endocrine surgeon.

ALGrawany

8

Phaeochromocytomas and paragangliomas

Phaeochromocytomas are catecholamine-producing tumours that usually arise from the chromaffin cells of the adrenal medulla but are located extra-adrenally in about 10% of cases. Extra-adrenal phaeochromocytomas are referred to as *paragangliomas*. However, the term 'paraganglioma' is also used to describe non-catecholamine-secreting tumours that are derived from parasympathetic paraganglia (e.g. carotid body chemodectomas).

The pattern of catecholamine secretion from phaeochromocytoma/paragangliomas (PPGLs) differs from that of normal adrenal medulla: phaeochromocytomas mainly secrete noradrenaline, whereas the normal adrenal medulla predominantly secretes adrenaline. Familial phaeochromocytomas are an exception and secrete large amounts of adrenaline.

Catecholamine-secreting tumours are rare and occur in fewer than 0.2% of hypertensive patients. Around 10% of phaeochromocytomas are malignant, and 10% are bilateral.

Genetics

Phaeochromocytomas may be familial in up to 40% of patients. Susceptibility genes where variants predispose to phaeochromocytoma/paraganglioma can be grouped in two clusters.

- Cluster 1 genes (e.g. *SDHB*, *SDHC*, *SDHD*, *SDHAF2*, *SDHA*, *VHL*, *HIF2A*, *FH* gene encoding fumarate hydratase): encode proteins involved in the cellular response to hypoxia. Cluster 1 tumours are mostly *extra-adrenal* paragangliomas (except in VHL where most tumours are localised to the adrenal), with a *noradrenergic* biochemical phenotype.
- Cluster 2 genes (e.g. *RET*, *NF1*, *MAX*, and *TMEM12*): encode proteins that activate kinase signalling. Cluster 2 tumours are usually *adrenal* pheochromocytomas with an *adrenergic* biochemical phenotype.

There are several clinical syndromes causing dominantly inherited cases of PPGL:

- Multiple endocrine neoplasia (MEN) type 2a (associated with medullary thyroid carcinoma and hyperparathyroidism) and MEN type 2b (associated with medullary thyroid carcinoma and mucosal neuromas) with mutations in the RET proto-oncogene.
- Von Hippel–Lindau (VHL) syndrome (associated with cerebellar or retinal haemangioblastomas, renal cell carcinoma and pancreatic tumours).
- Paraganglioma syndromes 1–5 (PGL1–5) caused by mutations in the genes encoding subunits of the mitochondrial enzyme succinate dehydrogenase: *SDHA* (PGL5), *SDHAF2* (PGL2), *SDHB* (PGL4), *SDHC* (PGL3), *SDHD* (PGL1). These are often seen in paragangliomas of the skull base or neck.
- Neurofibromatosis type 1 (NF-1).

The approximate frequency of phaeochromocytoma in these disorders is 50% in MEN type 2, 10–20% in VHL syndrome and 2% in neurofibromatosis type 1. Both *SDHD* and *SDHAF2* are maternally imprinted (meaning the gene is not expressed from the maternal allele and PPGL development is rare when the mutation is inherited from the mother, which may lead to skipped generations).

Mutations in *VHL*, *SDHB* and *SDHD* may contribute to the pathogenesis of tumours via dysregulation of the hypoxia-inducible factor-1 (HIF-1) and HIF-2 transcription factors.

Decisional algorithms support targeted genetic testing depending on the location of PPGL, whether it

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is metastatic and the predominant catecholamine secreted. Bilateral PPGLs are more common in *VHL* and *RET* mutations. *SDHB* mutations have the highest risk of metastatic PPGL.

Clinical presentations

Patients with phaeochromocytomas usually have *paroxysmal* symptoms. The most common symptoms in patients with phaeochromocytomas are episodic:

- headache (80%)
- sweating (70%)
- palpitations (70%).

Other presenting symptoms include:

- *cardiorespiratory*: chest pain and dyspnoea (20%), which may be due to myocardial ischaemia or heart failure
- *gastrointestinal*: nausea (40%), epigastric pain (20%), constipation (10%)
- *neuropsychiatric*: tremor (30%), weakness (30%), anxiety, and panic attacks (20%)
- *metabolic*: hypercalcaemia, hypokalaemia.

Clinical signs in patients with phaeochromocytomas include:

- pallor (40%)
- tachycardia
- hypertension (paroxysmal in ~50%; sustained or normal in the rest)
- postural hypotension (due to reduced plasma volume).

Patients with PPGL may also have no symptoms. People with head and neck paragangliomas may present with painless, slowly growing masses but may subsequently develop lower cranial nerve palsies. Conductive hearing loss and tinnitus may herald jugulotympanic paraganglioma.

Investigations

24-Hour urinary catecholamines and metanephrines

Patients with suspected phaeochromocytoma should be investigated with two or three measurements of 24-hour *urinary catecholamines*, i.e. adrenaline, noradrenaline and dopamine (sensitivity and specificity of 85%) and, if available, 24-hour urinary fractionated *metanephrines* (sensitivity 97%, specificity 91–98%). Although measurement of catecholamines is less sensitive, clearly elevated values (>2 times the upper limit of the normal range) make the diagnostis of phaeochromocytoma very likely.

The term 'metanephrines' describes two catecholamine metabolites produced by catechol-*O*-methyltransferase: normetanephrine and metanephrine. 'Fractionated metanephrines' refers to the measurement of normetanephrine and metanephrine separately. In addition, 3-methoxytyramine is a breakdown product of dopamine, and may also be secreted by PPGLs.

Some phaeochromocytomas produce modest amounts of catecholamines and may not produce positive urine catecholamine test results. Also, many phaeochromocytomas secrete catecholamines episodically so the urinary excretion of catecholamines may be normal between episodes. However, normetanephrine and metanephrine are produced continuously and independently of catecholamine release. Therefore, their measurement may be a more sensitive test to diagnose phaeochromocytomas.

Urinary creatinine should be measured in the 24-hour collection to verify an adequate collection. Because catecholamines are more stable at low pH, urine should be collected in acid-containing bottles.

Urinary vanillylmandelic acid (a catecholamine metabolite) is now rarely measured as it has a low sensitivity (around 62%).

Plasma free metanephrines

In patients who are at high risk of phaeochromocytoma (i.e. familial syndromes or a previously surgically cured phaeochromocytoma or paraganglioma), plasma free metanephrine and normetanephrine should be measured if available. This test has a sensitivity of 97% and specificity of 93%.,

Free metanephrines are produced in the phaeochromocytoma tumour cells. Sulfate-conjugated metanephrines are formed predominantly in the gastrointestinal tissues.

Urinary free metanephrines are measured following a sulfate deconjugation step. Therefore, the free metanephrines measured in urine are the sum of free metanephrines and (previously) conjugated metanephrines. This may explain the higher sensitivity of plasma free metanephrine compared with urinary metanephrines.

False-positive results

Slight elevations in urinary and plasma catecholamine and metanephrine levels can be seen in

Box 8.1 Medications that may increase measured catecholamines and metanephrines

Tricyclic antidepressants
Levodopa
Adrenergic receptor agonists (e.g. decongestants)
Amphetamines
Buspirone and most psychoactive agents (not selective serotonin reuptake inhibitors)
Phenoxybenzamine
Prochlorperazine
Ethanol
Caffeine, nicotine
Calcium channel blockers (may increase urinary catecholamines)
Paracetamol (may increase measured levels of fractionated plasma metanephrines in some assays)
Labetalol and methyldopa (may cause analytical interferences with high-performance liquid chromatography assays)

people who do not have phaeochromocytoma or paraganglioma and it is important that these people are identified and do not have unnecessary investigations and/or treatment. Certain drugs should be tapered and discontinued at least 2 weeks before any biochemical tests (Box 8.1). If it is contraindicated to discontinue certain medications (e.g. antipsychotics) and the biochemical tests are abnormal, imaging may be helpful to exclude a catecholamine-secreting tumour, although an adrenal incidentaloma is an important pitfall.

The clinical circumstances in which catecholamines and metanephrines are measured must be assessed in each case. Catecholamine secretion may be appropriately increased in stress or illness (e.g. stroke, myocardial infarction, congestive cardiac failure, obstructive sleep apnoea, head injury).

Imaging

If the biochemical results are abnormal, imaging with computed tomography (CT) or magnetic resonance imaging (MRI) of the abdomen and pelvis is required to locate the tumour. Furthermore, dedicated imaging should be performed in those with incidentally detected adrenal or retroperitoneal masses and those with a confirmed germline mutation and associated syndrome. Either test detects almost all sporadic tumours as most are 3 cm or larger. Around 90% of tumours will be visualised in the abdomen. If the tumour is not localised in the adrenals, whole-body imaging should be performed.

Both CT and MRI are sensitive (98–100%) but are only about 70% specific.

Computed tomography

Radiological features of the phaeochromocytomas on CT (Figure 8.1a) include:

- size >3 cm
- irregular/heterogeneous
- high (>20) Hounsfield unit (unit of X-ray attenuation) reading in a non-contrast scan as they contain less fat.

The historical risk of intravenous contrast agent exacerbating hypertension by causing catecholamine release was prevented by pretreatment with alpha-adrenergic blockade and is now obviated by the use of non-ionic contrast media. If incidentally detected and CT attenuation of an adrenal mass is less than 20 Hounsfield units, the lesion is lipid-rich and PPGL can be excluded without the need for biochemical testing.

Magnetic resonance imaging

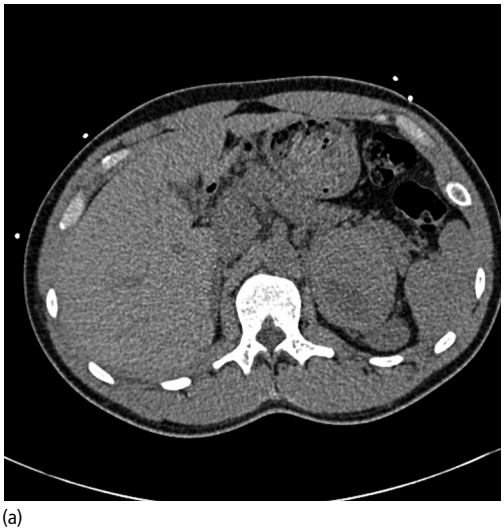
Phaeochromocytomas appear hyperintense (compared with the liver) on *T2-weighted imaging*. With MRI, there is neither radiation nor dye. However, it is more expensive than CT.

Functional imaging

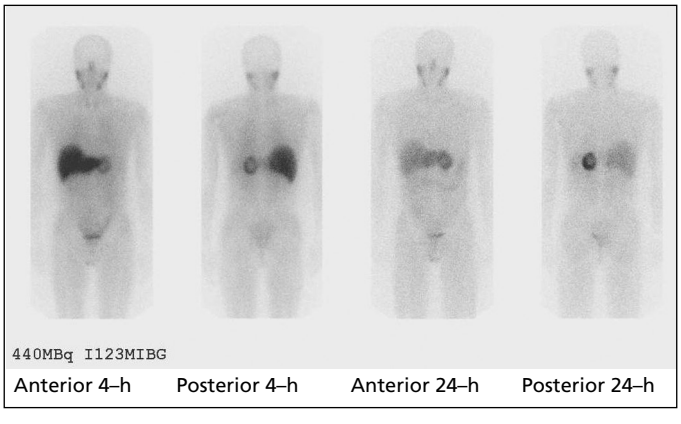
^{123}Iodine-metaiodobenzylguanidine (MIBG) is a compound resembling noradrenaline that is taken up by adrenergic tissue (Figure 8.1b). An MIBG scan can detect tumours not detected by CT or MRI, or multiple tumours when CT or MRI is positive. MIBG scintigraphy is indicated in patients with large (>10 cm) adrenal phaeochromocytomas (increased risk of malignancy) or paragangliomas (increased risk of multiple tumours and malignancy).

MIBG scintigraphy may also be done if CT or MRI is negative and the diagnosis is still considered likely owing to clinical and biochemical evidence of phaeochromocytoma.

^{68}Gallium Dotatate PET-CT scanning may be superior to MIBG, especially for identifying phaeochromocytoma metastases, but these scans are not widely available. Fluorodeoxyglucose positron emission tomography (FDG PET) maps glucose metabolism and can differentiate between benign and metastatic phaeochromocytoma.



(a)



(b)

Figure 8.1 (a) Computed tomography scan showing a left-sided phaeochromocytoma. (b) Radio-iodine-labelled MIBG scans in the same patient: anterior and posterior views 4 hours and 24 hours after injection. There is reduced uptake in the middle of the tumour due to necrosis.

Screening for associated conditions

All patients with confirmed phaeochromocytomas should have screening tests/examinations for:

- *MEN type 2*: measure serum calcium and calcitonin
- *VHL disease*: ophthalmoscopy, MRI of the posterior fossa and renal ultrasound
- *neurofibromatosis type 1*: a thorough clinical examination for neurofibromas, café-au-lait spots and axillary freckling.

Genetic testing

Genetic testing and counselling for mutations in *VHL*, *SDHB*, *SDHD*, *RET*, *MAX*, and *TMEM127* genes should be considered (in a stepwise manner) in patients with:

- onset at a young age (<20 years)
- a family history of phaeochromocytoma or paraganglioma
- clinical findings suggestive of one of the familial disorders mentioned above
- bilateral adrenal phaeochromocytoma
- paraganglioma.

Furthermore, genetic counselling (and testing) should be offered to all first-degree relatives of a confirmed mutation carrier. Asymptomatic mutation carriers identified in this way will need age-appropriate clinical surveillance to identify and treat developing neoplasia according to the clinical syndrome and disease penetrance.

Treatment

Surgery

Surgical resection of the phaeochromocytoma (Figure 8.2) may result in a resolution of hypertension in 75% of patients. Elective surgery has a mortality of less than 2%.

Phaeochromocytomas may be resected via an open adrenalectomy or a laparoscopic approach for patients with solitary intra-adrenal tumours less than 8 cm in diameter. For adrenal phaeochromocytomas, laparoscopic adrenalectomy by an experienced high-volume endocrine surgeon is preferred because of the reduction in postoperative morbidity, hospital stay and expense compared with open laparotomy. Adrenal cortex-sparing surgery for bilateral adrenal phaeochromocytomas may prevent iatrogenic primary adrenal insufficiency.

An anterior midline abdominal surgical approach is indicated for abdominal paragangliomas. Paragangliomas of the neck, chest (Figure 8.3), and urinary bladder require specialised approaches.

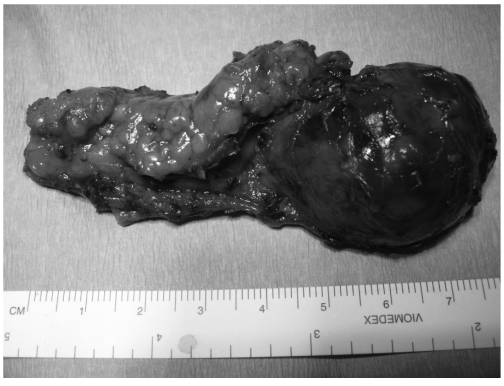


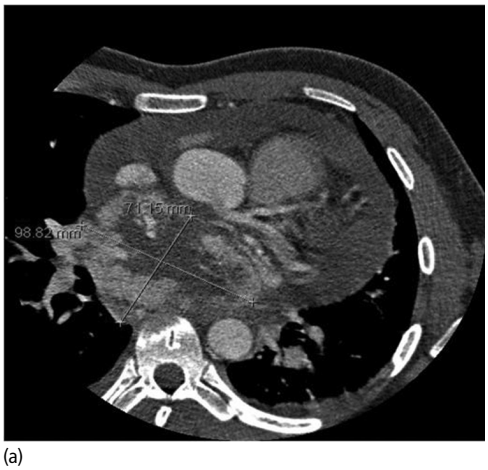
Figure 8.2 Resected phaeochromocytoma.

Preoperative preparation

Inadequate preparation before surgery can cause hypertension during the surgery and hypotension postoperatively. All patients should receive an *alpha-blocker* (phenoxybenzamine) followed by a *beta-blocker* (propranolol) for at least 2–3 weeks before surgery. Patients should be warned of the side-effects of alpha-blockers, including postural hypotension and nasal stuffiness. The beta-blocker should be started 2–3 days *after* the alpha-blocker. Patients should be rehydrated (1 L of 0.9% saline) before alpha-blockade to prevent sudden hypotension on receiving the first dose of the alpha-blocker.

Treatment should be commenced in hospital, and pulse, blood pressure, and haematocrit should be monitored closely as haemodilution may be caused by reversal of alpha-mediated vasoconstriction. Patients should also be adequately alpha- and beta-blocked prior to receiving any intravenous contrast.

Recently, a prospective study of more than 150 patients who did not receive preoperative alpha-blockade showed no major differences in blood pressure or complications compared to those who were



(a)

(b)

Figure 8.3 (a) Computed tomography scan showing a mediastinal paraganglioma. (b) Resected mediastinal paraganglioma.

alpha-blocked. The current consensus and clinical guidelines, however, all support the preoperative use of alpha-adrenergic blockade.

Phenoxybenzamine (non-selective alpha-adrenergic blockade)

Phenoxybenzamine is started at 10 mg twice a day orally. The dose is increased by 10 mg daily. The usual dose is 1–2 mg/kg daily in two divided doses. Intravenous phenoxybenzamine (0.5 mg/kg in 250 mL 5% dextrose over 2 hours) may be given for the 3 days prior to surgery to ensure complete preoperative alpha-blockade if available.

Doxazocin (selective alpha-1-adrenergic blockade)

Starting with 1 mg once a day orally and increased up to 8 mg twice daily.

Propranolol

Propranolol is started at 40 mg three times a day 2–3 days after starting phenoxybenzamine. The dose may be increased to 80 mg three times a day as necessary to control the tachycardia (the goal being a heart rate of 60–80 beats per minute).

A calcium channel blocker (nicardipine) may be used to supplement the combined alpha- and beta-adrenergic blockade protocol when blood pressure control is inadequate, or to replace the adrenergic blockade protocol in patients with intolerable side-effects.

Perioperative hypertension and arrhythmias

Acute hypertensive crises may occur during an operation due to tumour handling. They should be treated with intravenous sodium nitroprusside started at a rate of 0.5 µg/kg per minute and adjusted every few minutes according to the blood pressure. Intravenous phentolamine and nicardipine are alternatives.

Perioperative cardiac arrhythmias are treated with lidocaine (50–100 mg intravenously) or esmolol.

Tumour devascularisation may result in hypotension. This often responds to intravenous fluids but may require inotropes. Hypoglycaemia can occur in 10–15% of patients due to the removal of catecholamine suppression of insulin secretion and is treated by intravenous dextrose.

Malignant phaeochromocytomas

A total of 10% of phaeochromocytomas are malignant. Diagnosing malignant PPGL is challenging because they are histologically and biochemically similar to benign ones and can only be confirmed by the presence of metastases. *SDHB* mutation carriers are more likely to develop malignant paragangliomas.

Surgical removal of the tumour to improve symptoms and survival is the primary treatment. Metastatic lesions should be resected if possible. Patients with malignant phaeochromocytomas need long-term alpha- and beta-blockade.

Chemotherapy (with dacarbazine, cyclophosphamide and vincristine) may control the symptoms. Radiotherapy may be helpful in those with bony metastases. In initial studies, local tumour irradiation with ^{131}I-MIBG has been found to be of limited therapeutic value.

Malignant PPGLs are associated with local invasion or distant metastases (often to bone and lymphatics in phaeochromocytoma; liver in paraganglioma), which may occur as long as 20 years after resection. Therefore, patients should be followed up life-long to detect recurrence or metastases. Five-year survival for malignant phaeochromocytomas is about 44% and disease-specific survival is 34 years.

Follow-up and monitoring

Twenty-four-hour urinary catecholamines should be measured about 2 weeks after surgery to assess cure (catecholamines may be elevated in the first 7–10 days postoperatively). Patients should be followed up life-long to detect recurrence. Chromogranin A can be used as a postoperative tumour marker. The recurrence rate of phaeochromocytomas is less than 10%. Five-year survival for benign tumours is about 96% and many patients are cured.

KEY POINTS

- Phaeochromocytomas are catecholamine-secreting tumours of the adrenal medulla.
- Patients may present with the triad of headache, sweating, and palpitations.
- Patients with suspected phaeochromocytoma should have measurement of 24-hour urinary catecholamines and, if available, fractionated plasma metanephrines.
- Those with abnormal biochemical tests should be further investigated with imaging (CT, MRI) to locate the tumour.
- All patients should receive an alpha-blocker (e.g. phenoxybenzamine) followed by a beta-blocker (propranolol) for at least 2–3 weeks before surgery. Preparation is critical and must include rehydration.
- Phaeochromocytomas are familial in up to 30% of patients.

9

Congenital adrenal hyperplasia

Congenital adrenal hyperplasia (CAH) encompasses a group of autosomal recessive disorders caused by a deficiency of enzymes involved in the synthesis of adrenal steroids (Figure 9.1).

The most common form of CAH is due to *21-hydroxylase deficiency* ('classic CAH').

Epidemiology

The incidence of classic CAH in the general population is 1 in 10 000–15 000. The incidence of the milder 'non-classic' (late-onset) form may be as high as 1 in 1000. The prevalence of the disorder is higher in Hispanic and Eastern European Jewish women than in other ethnic groups. The other forms of CAH are very rare.

Aetiology

Classic CAH is caused by 21-hydroxylase enzyme deficiency (mutations in the CYP21A2 gene) and is an autosomal recessive condition. It is the most common form of CAH and accounts for 95% of cases of CAH. 21-hydroxylase deficiency causes:

- reduced aldosterone production
- reduced cortisol production resulting in increased adrenocorticotrophic hormone (ACTH) secretion (due to reduced negative feedback), which further stimulates the steroid synthesis pathway leading to increased production of adrenal androgens (dehydroepiandrosterone [DHEA] and androstenedione) and the substrate for the defective enzyme, i.e. 17-hydroxyprogesterone. Androstenedione is converted to testosterone in the peripheral tissues (e.g. liver). There is minimal synthesis of testosterone in the adrenal gland.

The non-classic form of CAH is due to reduced 21-hydroxylase activity caused by a classic mutation and a variant allele, or by two variant alleles.

Clinical presentations

In patients with 21-hydroxylase deficiency, three main clinical phenotypes have been described.

- Classic salt losing (caused by complete enzyme deficiency)
- Classic simple virilising (caused by partial enzyme deficiency)
- Non-classic (late onset) (caused by a very mild enzyme deficiency)

Presentation in infancy/childhood

Classic salt losing

Male and female infants present with failure to thrive, dehydration, hyponatraemia and hyperkalaemia due to aldosterone deficiency.

Girls have ambiguous genitalia (enlargement of the clitoris and labial fusion) caused by the effects of androgen excess on the development of the external genitalia *in utero* (female pseudohermaphroditism).

Boys may have hyperpigmented scrotal skin and develop testicular masses ('adrenal rests') due to ectopic adrenal cells stimulated by ACTH hypersecretion. They are typically bilateral and may be diagnosed as early as 5 years, but usually present between the ages of 10 and 20 years (see 'Effects of classic CAH on adolescents and adulthood' below).

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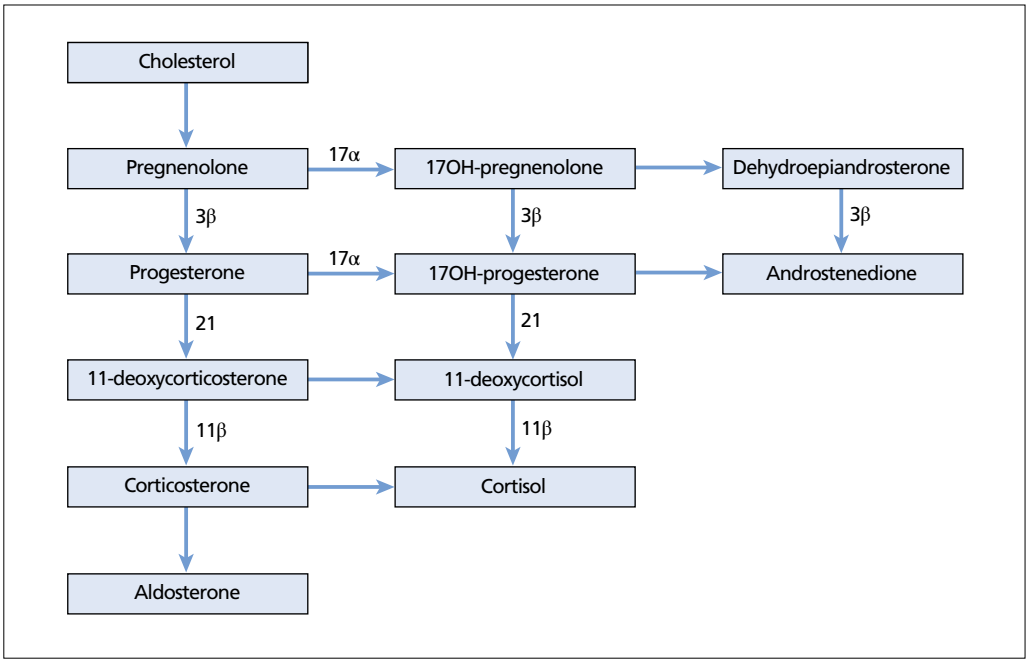

Figure 9.1 The adrenal steroid synthesis pathway and some of the enzymes involved. 3β, 3-beta-hydroxysteroid dehydrogenase; 17α, 17-alpha-hydroxylase; 21, 21-hydroxylase (CYP21A2); 11β, 11-beta-hydroxylase.

Classic simple virilising

In this form of CAH, aldosterone secretion is adequate but cortisol is not synthesised efficiently.

Girls present with ambiguous genitalia (see above).
Boys present at 2–4 years of age with early virilisation and signs of puberty (pubic hair, growth spurt, adult body odour). Boys may also develop testicular adrenal rests (see below).

Effects of classic CAH on adolescents and adulthood (Table 9.1)

Reproduction

In *females,* fertility rates may be reduced by hyperandrogenaemia due to inadequate glucocorticoid therapy (resulting in menstrual irregularity) and/or structural abnormalities due to androgen excess *in utero* or suboptimal surgical reconstruction. In women with simple virilising and salt-losing CAH, respective fertility rates of up to 80% and up to 60% may be achieved with treatment.

In *males,* high levels of adrenal androgens (if poorly controlled) suppress gonadotrophins and therefore testicular function and spermatogenesis. Boys or young men may develop testicular masses composed of ectopic adrenal tissue ('adrenal rests') that is stimulated by the increased ACTH. They are more common in the salt-losing form as they tend to have poorer control and higher ACTH levels. They are benign but may lead to obstruction of the seminiferous tubules, gonadal dysfunction and infertility.

Table 9.1 Clinical presentation of CAH

Age	Sex	Presentation
Infancy	F	Atypical genitalia
	M/F	Salt loss
Early childhood	M	Virilisation, rapid growth
Late childhood	F	Early pubic hair, rapid growth
Adolescence/ young adult	F	Delayed menarche, irregular menses, acne, hirsutism, infertility
	M	Testicular masses, infertility

F, female; M, male.
Source: Simpson H, Hughes I. Congenital adrenal hyperplasia. Medicine 2021; 49(8): 507–511.

Stature

Exposure to high levels of sex hormones leads to accelerated growth in childhood but induces premature epiphyseal closure, resulting in a short final adult stature. Excess glucocorticoid therapy may also suppress growth and contribute to adult short stature.

Non-classic CAH (late onset)

Young women with non-classic or late-onset CAH may present with hirsutism (roughly 6% women with hirsutism have CAH), acne and menstrual irregularity. Early pubarche or sexual precocity in school-age children may occur, or there may be no symptoms.

Rarer forms of CAH

11-Beta-hydroxylase deficiency (~5% cases)

Increased 11-deoxycorticosterone (Figure 9.1) (which has mineralocorticoid activity) results in hypertension, which may be severe and is often detected in late childhood/adolescence. Hypokalaemia occurs frequently. Increased androgens result in the virilisation of female fetuses, causing ambiguous genitalia (female pseudohermaphroditism).

3-Beta-hydroxysteroid dehydrogenase deficiency

Mineralocorticoid (see Figure 9.1) deficiency results in salt wasting and hyperkalaemia. Reduced androgens in men result in ambiguous genitalia (male pseudohermaphroditism) ranging from hypospadias to nearly normal female external genitalia. Increased DHEA in women may result in mild virilisation of the external genitalia.

17-Alpha-hydroxylase deficiency

Increased mineralocorticoids (see Figure 9.1) result in hypertension and frequently hypokalaemia. Reduced adrenal and gonadal sex steroids result in ambiguous genitalia in men (male pseudohermaphroditism), and in females a blind vagina, no uterus or fallopian tubes, intra-abdominal testes and absent puberty/primary amenorrhoea.

Investigations

Classic CAH

Most patients with classic CAH are diagnosed in infancy. An elevated level of *17-hydroxyprogesterone* indicates 21-hydroxylase deficiency. 17-Hydroxyprogesterone is a precursor steroid that accumulates upstream of the enzyme defect (see 'Aetiology'). However, the test should be repeated (along with 11-deoxycortisol measurement) after 48 hours of age to distinguish CAH from the physiological hormonal surge in the first 2 days of life. Hyponatraemia and hyperkalaemia indicate a salt-losing crisis. Plasma renin level is useful in confirming salt wasting.

Genetic analysis may be performed to identify specific *CYP21* mutations.

In infants with ambiguous genitalia, *karyotyping* should be carried out as soon as possible; *gender assignment* should be done in conjunction with the family. The initial evaluation should include pelvic ultrasonography of the internal genitalia (uterus).

Because of the high prevalence of testicular adrenal rests and their association with infertility in male patients, they should be monitored by testicular ultrasonography in adolescence or early adulthood.

Men who desire future fertility should be evaluated with serum testosterone level, semen analysis, and testicular ultrasound.

Non-classic CAH

17-Hydroxyprogesterone should be measured at 9 a.m. (because of the diurnal variation in adrenal hormone secretion) and in the follicular phase of the menstrual cycle. False-positive results may occur if 17-hydroxyprogesterone is measured in the luteal phase, as it is also produced by the corpus luteum and there may be some cross-reaction with progesterone.

17-Hydroxyprogesterone levels of less than 5 nmol/L are normal, and levels of over 15 nmol/L are consistent with CAH. However, in patients with levels of between 5 and 15 nmol/L, an ACTH stimulation test should be done. 17-Hydroxyprogesterone is measured 60 minutes after 250 µg of tetracosactrin (synthetic ACTH) is given intramuscularly or intravenously. In patients with CAH, the 17-hydroxyprogesterone values at 60 minutes vary according to the degree of enzyme deficiency, and

A L G r a w a n y

range between 30 and 300 nmol/L. Cortisol response to ACTH is usually low normal.

Other tests

Serum testosterone and androstenedione levels are elevated. There is a great overlap with levels in polycystic ovary syndrome, and therefore serum androgen levels cannot distinguish between the two disorders.

A proportion of women with non-classic CAH may have mildly raised plasma renin levels.

Treatment

Salt-losing form

Infants/children

Infants are initially treated with intravenous saline and hydrocortisone. Thereafter, *glucocorticoid* and *mineralocorticoid* replacement are given as oral hydrocortisone and fludrocortisone. The short half-life of hydrocortisone necessitates several doses daily. Balancing the suppression of androgens with the cushingoid side-effects of glucocorticoids is a particular challenge, and many different regimens are used; at present, there is no evidence in favour of any of the suggested options, but they all have risks and benefits. One has to also consider the effects of reverse circadian treatment on such patients.

Older adolescents/adults

It is important to plan for the transition from paediatric to adult care. The initial management challenge is to use glucocorticoid replacement to prevent the effects of androgen excess while limiting growth suppression from excess glucocorticoids, followed by normal puberty and, in girls, regular menses. Later, avoidance of osteoporosis and other adverse metabolic sequelae of glucocorticoid over-replacement while maintaining reproductive potential become the focus.

Glucocorticoids

Hydrocortisone, prednisolone and dexamethasone all have their advocates. Hydrocortisone needs to be given several times daily to adequately suppress androgens, and may be appropriate in very compliant patients. Missed doses of hydrocortisone will cause spikes in ACTH and androgens. Longer acting agents such as prednisolone and dexamethasone are thus easier to remember and may be better at suppressing androgens, but may have more cushingoid side-effects, regardless of dose. There is at present no evidence that slow-release, delayed-release or dual-release hydrocortisone or prednisone has any advantages over the three generic agents in common use.

Dexamethasone (0.25–0.75 mg) is given at bedtime in older adolescents and adults. Once-daily dosing improves compliance. The aim is to suppress the early morning peak of ACTH and thus androgen secretion, although the reverse circadian nature of this regimen needs to be considered. Alternatively, some endocrinologists give prednisolone either once or twice daily, and there are studies that suggest that once-daily morning prednisolone has better outcomes than thrice-daily hydrocortisone. As with other forms of adrenal insufficiency, glucocorticoid doses should be doubled during illness.

Mineralocorticoids

The usual adult dose of fludrocortisone is 100–200 µg per day, but some patients require more.

Simple virilising form

Adult women with the simple virilising form may require glucocorticoids. To enable regular menstrual periods (and thus fertility), relatively high glucocorticoid doses may be needed, often leading to weight gain. Men require glucocorticoids if they have testicular masses ('adrenal rests') or oligospermia. Testicular masses usually regress with glucocorticoid therapy.

Females with ambiguous genitalia

In children with ambiguous genitalia, karyotyping and gender assignment should be done as soon as possible. The gender assignment in a patient with a 46XX karyotyping and elevated 17-hydroxyprogesterone is female even if the external genitalia are male-like in appearance. Careful evaluation by an experienced multidisciplinary team of paediatric endocrinologists, geneticists and paediatric surgeons, as well as sophisticated psychosocial support, is essential. Parents should be offered counselling as soon as the diagnosis is established. Females with ambiguous genitalia may

be at risk of a salt-losing addisonian crisis shortly after birth, so treatment to prevent this must be considered in any child with ambiguous genitalia.

The surgical management of girls with ambiguous genitalia is complex and includes reconstructive surgery (usually clitoroplasty and vaginoplasty). Surgery should be done in a centre with substantial experience at age 2–6 months because it is technically easier than at a later age. Occasionally, revisional vaginoplasty may be required at adolescence or young adulthood.

Non-classic CAH

Female patients with non-classic CAH who are not pursuing fertility are treated with oral contraceptives or cyproterone acetate (an antiandrogen) for acne and hirsutism. Spironolactone should be avoided because of the potential risk of salt wasting and hyperreninemia. Oral contraceptives are also recommended for menstrual cycle abnormalities.

Women with non-classic CAH with anovulatory cycles who desire fertility should receive glucocorticoids (prednisolone 2–6 mg or dexamethasone 0.25–0.75 mg) as initial therapy for ovulation induction. Those who do not ovulate with glucocorticoid therapy alone should receive additional clomiphene citrate.

Males do not usually require treatment unless they have testicular masses (testicular adrenal rest tumours [TART]) or oligospermia (in a man desiring fertility). Glucocorticoid therapy may be recommended in these men. Treatment may be discontinued when an adult male no longer seeks fertility.

Men who desire future fertility

Men with both forms of classic CAH (salt-losing and simple virilising) who desire future fertility should be evaluated with serum testosterone, semen analysis and testicular ultrasound. Adrenal rests may develop into TARTs from ACTH stimulation, which have high prevalence in adult men with CAH. The presence of TARTs may indicate the need for sperm preservation before the onset of testicular failure.

CAH in pregnancy

For the management of patients with CAH during pregnancy, see Chapter 31.

Follow-up and monitoring

Adults with CAH are at considerable risk of cardiovascular disease through glucocorticoid-induced metabolic syndrome (estimated to be 20%) and hypertension, often with young age of onset. Mortality is also increased in people with CAH due to adrenal crises, cardiovascular disease, cancer and suicide. Education and support are vital for patients; vigilance and understanding are essential from clinicians. Using the lowest possible dose of glucocorticoids in the long term will reduce mortality.

The aims of treatment of CAH in adulthood are:

- to give sufficient glucocorticoids to ensure normal cortisol replacement and to reduce the excessive secretion of ACTH and hyperandrogenaemia
- to avoid glucocorticoid over-replacement, which is associated with an increased risk of osteopenia, obesity and other clinical manifestations of Cushing syndrome. The lowest dose that ameliorates symptoms should be used
- to give sufficient mineralocorticoid (in patients with the salt-losing form) to restore blood pressure, serum electrolyte concentrations, and extracellular fluid volume to normal.

Classic CAH in adults

Annual follow-up is usually adequate in adults.

Clinical assessment should look for evidence of hyperandrogenism, glucocorticoid overtreatment (cushingoid appearance), mineralocorticoid undertreatment (postural hypotension) and overtreatment (e.g. dependent oedema). Menstrual frequency is considered a good marker of treatment adequacy. Amenorrhoea in females suggests inadequate treatment.

Serum *17-hydroxyprogesterone* levels should be monitored in women and men receiving glucocorticoid therapy. The aim is to lower serum levels to slightly above the normal range. Normal or low 17-hydroxyprogesterone levels suggest that the patient is on supraphysiological doses of glucocorticoids, which may result in complications associated with glucocorticoid excess.

Serum *androgen* levels (DHEA sulfate, androstenedione and testosterone) should be monitored in women and men receiving glucocorticoid therapy. The goal is to lower DHEA sulfate, androstenedione, and testosterone levels in women, and DHEA sulfate and androstenedione levels in men, to slightly above

the upper normal limits. High levels suggest undertreatment. Testosterone levels are measured in men to assess testicular function. Subnormal values should prompt additional evaluation.

Plasma *renin* activity and serum electrolytes should be monitored in patients on mineralocorticoid therapy. The aim is a plasma renin activity in the mid- to upper-normal range. Plasma renin activity is markedly raised in those who are inadequately treated and is suppressed in those who are overtreated.

Non-classic CAH

Patients should be assessed for an improvement in symptoms (e.g. acne, hirsutism) and features of glucocorticoid excess (cushingoid appearance).

Serum concentrations of 17-hydroxyprogesterone and androgens (DHEA sulfate, androstenedione, testosterone) should be measured in women with the goal of normalising testosterone levels. In men, a reduction of serum 17-hydroxyprogesterone levels to slightly above normal is a good index of therapeutic efficacy. Periodic DXA scans should be performed to look for bone loss.

KEY POINTS

- The most common form of CAH is due to 21-hydroxylase deficiency ('classic CAH'), which results in reduced aldosterone and reduced cortisol production causing increased ACTH secretion, which in turn stimulates an increased production of adrenal androgens.
- In patients with 21-hydroxylase deficiency, three main clinical phenotypes have been described: classic salt losing, classic simple virilising, and non-classic (late onset).
- Patients with the salt-losing form of classic CAH present as infants with failure to thrive, dehydration, hyponatraemia, and hyperkalaemia due to aldosterone deficiency.
- Girls with both forms of classic CAH present with ambiguous genitalia caused by the effects of androgen excess on the development of external genitalia *in utero*.
- Non-classic or late-onset CAH may present as hirsutism, acne, and menstrual irregularity in young women, and early pubarche or sexual precocity in school-age children, or there may be no symptoms.
- Patients with 21-hydroxylase deficiency have elevated 17-hydroxyprogesterone levels.
- Infants with the salt-losing form are treated with glucocorticoids and mineralocorticoids.
- Female patients with non-classic CAH who are not pursuing fertility are treated with oral contraceptives.

10

Adrenal incidentalomas

An adrenal incidentaloma is an adrenal mass greater than 1 cm in diameter that is incidentally discovered during imaging done for other reasons (Figure 10.1).

Adrenal incidentalomas may be found in 0.4–4.2% of CT scans. Abdominal imaging may also reveal unilateral or bilateral enlarged or unusually shaped adrenals. Although the importance of these changes is not known, the possibility of adrenal disease should be considered.

Following the discovery of an adrenal incidentaloma, close examination of the radiological characteristics, clinical and biochemical assessments should be performed to answer two important questions.

- Is the adrenal incidentaloma *benign* or *malignant*? Malignant incidentalomas include metastases from other cancers (e.g. lung) or, less commonly, primary adrenal carcinomas.
- Is the adrenal incidentaloma *functioning* or *non-functioning*? Up to 15% are functioning (about 9% are cortisol secreting, 4–5% are phaeochromocytomas, 1–2% are aldosterone secreting).

Adrenal cysts, adrenal haemorrhage and myelolipoma are usually easily identified as they have distinctive imaging characteristics.

Radiological evaluation

The size and imaging characteristics ('imaging phenotype') of the incidentaloma are important determinants of whether the adrenal mass is benign or malignant. CT scanning is the primary modality of adrenal imaging. The imaging characteristics of adrenal carcinomas, metastases and phaeochromocytomas include:

- size greater than 4 cm in diameter (93% sensitivity but limited specificity; 76% may actually be benign)
- inhomogeneous density (central tumour necrosis resulting in low attenuation)
- irregular border
- attenuation greater than 20 Hounsfield units on unenhanced CT (unlike benign adenomas, which have low attenuation due to a high lipid content)
- less than 50% contrast wash-out at 10 minutes.

Clinical assessment

A majority of patients have an obviously benign lipid-rich adrenal lesion which does not need any follow-up, but where there is any doubt, patients should be assessed clinically for the possibility of adrenal hormonal hyperfunction and malignancy. A thorough history should be taken to look for features of malignancy and phaeochromocytoma (headache, sweating, palpitations). Physical examination may reveal signs of malignancy, hypertension or features of Cushing syndrome.

Biochemical assessment

Twenty-four-hour *urinary catecholamines* and *fractionated metanephrines* (i.e. metanephrine and normetanephrine measured separately) or plasma metanephrines should be quantified to exclude phaeochromocytoma (see Chapter 8). If the pretest probability of phaeochromocytoma is high (e.g. a vascular mass with high-attenuation precontrast/delayed contrast wash-out, pallor spells, or a known germline mutation), plasma free metanephrine and normetanephrine should be measured as this test has a sensitivity of 97–99%.

Autonomous cortisol secretion should be excluded by measuring a baseline serum dehydroepiandrosterone sulfate (DHEAS) and performing the 1 mg overnight dexamethasone suppression test. A low DHEAS is

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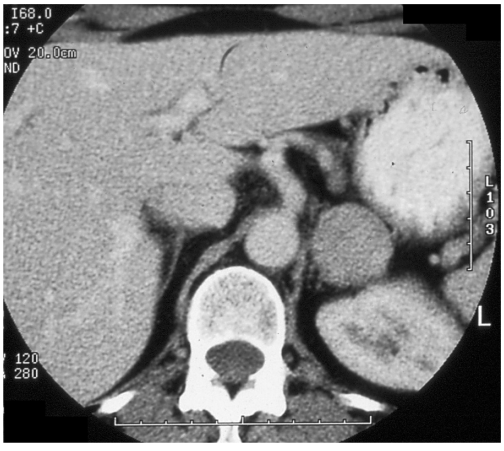


Figure 10.1 Computed tomography scan showing a left-sided adrenal mass.

suggestive of chronic suppression of ACTH secretion. The overnight dexamethasone suppression test should not be performed if a phaeochromocytoma is suspected on imaging due to a risk of catecholaminergic crisis. If the overnight dexamethasone suppression test is abnormal (i.e. an 8–9 a.m. serum cortisol >50 nmol/L after overnight dexamethasone), baseline serum ACTH is indicated to confirm the autonomy (see Chapter 16). If the cortisol is between 50 and 138 nmol/L after the overnight dexamethasone suppression test, then it is not clear whether adrenalectomy will be of benefit, and one should manage this mild autonomy with careful management of vascular risk factors.

If the patient is hypertensive, plasma potassium concentration and plasma *aldosterone-to-renin activity ratio* should be measured to screen for primary hyperaldosteronism. Note that patients with primary hyperaldosteronism *may not be* hypokalaemic. Patients need to be off spironolactone (for 6 weeks) and off angiotensin-converting enzyme inhibitors, angiotensin receptor blockers and beta-blockers (for 2 weeks) prior to this test (see Chapter 7).

Treatment

Indications for surgery

Surgery for an adrenal incidentaloma is recommended in patients with:

- adrenal masses greater than 4 cm in diameter or with a suspicious imaging phenotype
- phaeochromocytoma
- a unilateral aldosterone-secreting mass
- Cushing syndrome.

Surgery for subclinical Cushing syndrome (i.e. patients who demonstrate a lack of cortisol suppression after the low-dose dexamethasone suppression test but who do not have any discernible clinical signs) is controversial; a study aiming to address this definitively is currently under way. Adrenalectomy may be considered in younger patients and those with disorders potentially attributable to the autonomous cortisol secretion (e.g. recent onset of hypertension, diabetes, obesity, osteoporosis). All patients should receive perioperative hydrocortisone because of the risk of adrenal insufficiency.

If there is evidence that the mass is a secondary deposit, a diagnostic CT-guided fine needle aspiration biopsy may be indicated (only after excluding phaeochromocytomas with biochemical testing).

Adjuvant mitotane is recommended for all patients who have undergone surgical resection of an adrenocortical carcinoma as it may prolong recurrence-free survival. Prednisolone or hydrocortisone replacement is necessary because mitotane's adrenolytic activity will result in adrenal insufficiency. Mitotane can also cause aldosterone deficiency. Plasma concentrations of mitotane should be measured; for a response, the level needs to be >14 mg/L but levels >20 mg/L cause neurological toxicity (dysphasia, ataxia).

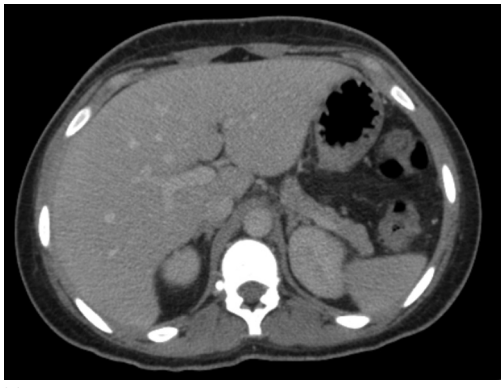
Laparoscopic adrenalectomy is preferred in most cases as it is an effective, safe and less expensive procedure than open adrenalectomy. However, open adrenalectomy should be performed when adrenocortical cancer is suspected.

Follow-up

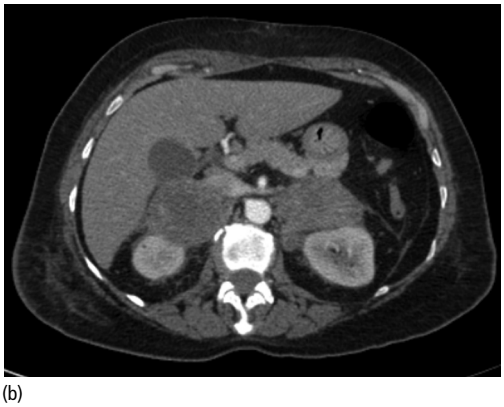
Those patients who have non-functioning tumours that are less than 4 cm in size and have a benign imaging phenotype can be reassured. If a scan a year later does not show significant growth, they can usually be reassured and discharged, and there is no evidence that lifetime follow-up achieves anything apart from a significant radiation burden for no benefit.

Bilateral adrenal masses

Incidentalomas may be bilateral in 10–15% of cases (Figure 10.2). In some patients with bilateral masses, one of the adrenal masses may be a non-functioning adenoma and the other may be hormone secreting. Box 10.1 summarises the causes of bilateral adrenal masses.



(a)



(b)

Figure 10.2 (a) Computed tomography scan showing normal adrenals for comparison. (b) CT scan showing bilateral adrenal metastases.

Box 10.1 Causes of bilateral adrenal masses

Cortical adenomas
Congenital adrenal hyperplasia
Bilateral macronodular hyperplasia
Adrenocorticotrophic hormone-dependent Cushing disease
Malignancy: phaeochromocytoma, metastases, lymphoma
Infection, e.g. tuberculosis, fungal
Infiltration: amyloidosis
Haemorrhage

KEY POINTS

- An adrenal incidentaloma is an adrenal mass greater than 1 cm in diameter that is incidentally discovered when an abdominal CT or MRI is done for other reasons.
- Close examination of the imaging characteristics and clinical and biochemical assessments should be performed to determine whether the incidentaloma is benign or malignant, and whether it is functioning (cortisol secreting, phaeochromocytoma, or aldosterone secreting).
- The imaging phenotype (characteristics) of adrenal carcinoma, metastases, and phaeochromocytomas includes size greater than 4 cm in diameter, inhomogeneous density, irregular border, and high attenuation on unenhanced CT scanning.
- Patients with non-functioning tumours that are less than 4 cm in size and have a benign imaging phenotype should be reassured and discharged. There is no indication for annual scans.

11

Pituitary anatomy and physiology

The pituitary gland (also called the hypophysis) sits in the pituitary fossa (sella turcica) in the sphenoid bone and is anatomically close to some critically important structures (Figure 11.1). It is connected to the hypothalamus via the pituitary stalk. The size and volume of pituitary gland may vary, nearly doubling in pregnancy but decreasing in size with older age. It weighs between 400–900 mg and measures approximately 13 mm in the sagittal plane and <10 mm in other dimensions.

Branches of the superior hypophyseal artery form a capillary plexus in the median eminence and upper part of the pituitary stalk (Figure 11.2). This capillary plexus gives rise to the hypophyseal *portal vessels*, which transmit hypothalamic releasing and inhibitory hormones to the anterior pituitary gland. The posterior pituitary gland is supplied directly by the inferior hypophyseal artery.

Venous blood from the pituitary gland drains by a number of veins into the adjacent cavernous sinuses. The pituitary gland is divided into anterior pituitary and posterior pituitary.

- The *anterior pituitary* (adenohypophysis) is derived from an upward growth of the ectoderm of the roof of the oropharynx (Rathke's pouch), which becomes pinched off (Figure 11.3).
- The *posterior pituitary* (neurohypophysis) is derived from a downgrowth of neuroectoderm of the floor of the third ventricle (diencephalon).

Anterior pituitary hormones

The anterior pituitary secretes at least six different peptide hormones (Table 11.1). Each hormone is secreted by a specific group of cells.

- *Growth hormone* (GH) is secreted by somatotrophs (50% of cells).
- *Prolactin* is secreted by lactotrophs (10–30% of cells).
- *Adrenocorticotrophic hormone* (ACTH) is secreted by corticotrophs (20% of cells).
- *Thyroid-stimulating hormone* (TSH) is secreted by thyrotrophs (5% of cells).
- *Luteinising hormone* (LH) and *follicle-stimulating hormone* (FSH) are secreted by gonadotrophs (15% of cells).

Folliculostellate cells within the anterior pituitary gland do not secrete hormones but play a crucial role integrating autocrine and paracrine feedback loops.

Growth hormone

Effects

Binding of GH to its plasma membrane receptor (mostly in the liver) leads to receptor dimerization. GH stimulates the hepatic synthesis and secretion of insulin-like growth factor-1 (IGF-1), a potent growth, and differentiation factor. GH stimulates epiphyseal prechondrocyte differentiation and linear bone growth in children, stimulates lipolysis, increases protein synthesis, antagonises insulin action, and stimulates phosphate, water, and sodium retention.

Regulation of secretion

Growth hormone secretion is stimulated by hypothalamic gonadotrophin-releasing hormone (GnRH), which acts via a G-protein-coupled receptor and increases cyclic AMP levels. Other factors that may stimulate GH release include stress, exercise, sleep, prolonged fasting, and ghrelin

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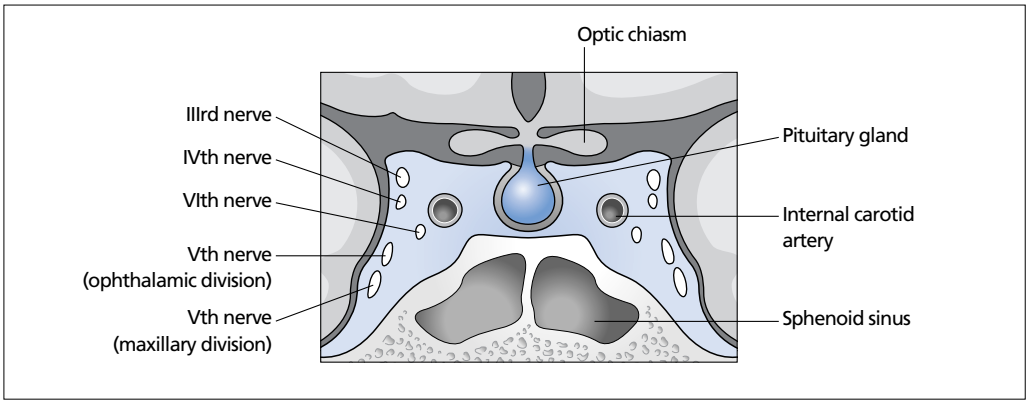

Figure 11.1 The pituitary gland and its anatomical relation to the cavernous sinus and optic chiasm.

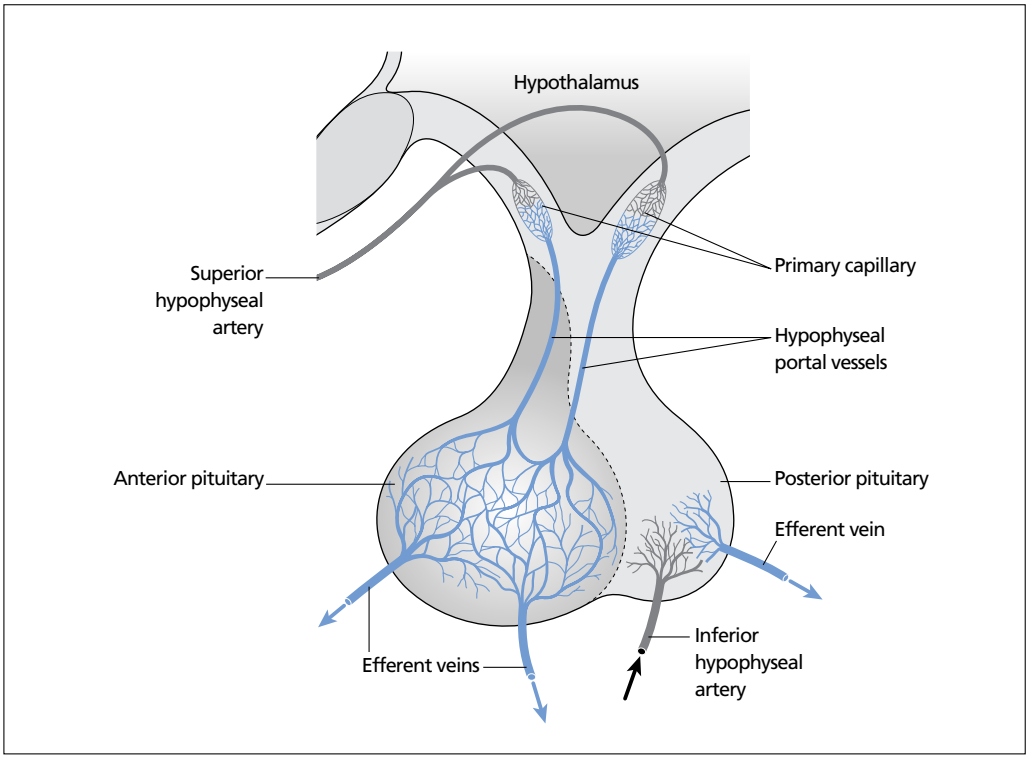

Figure 11.2 The blood supply of the pituitary gland and its vascular connections with the hypothalamus.

(a gastric-derived peptide). GH secretion is inhibited by IGF-1 (negative feedback) and hypothalamic somatostatin. GH secretion is pulsatile (6–10 pulses separated by long periods during which GH may be undetectable) so undetectable levels do not confirm GH deficiency. Undetectable levels also exclude GH hypersecretion.

Prolactin

Effects

Prolactin stimulates the proliferation of the breast lobulo-alveolar epithelium and lactation. It also decreases reproductive function by suppressing

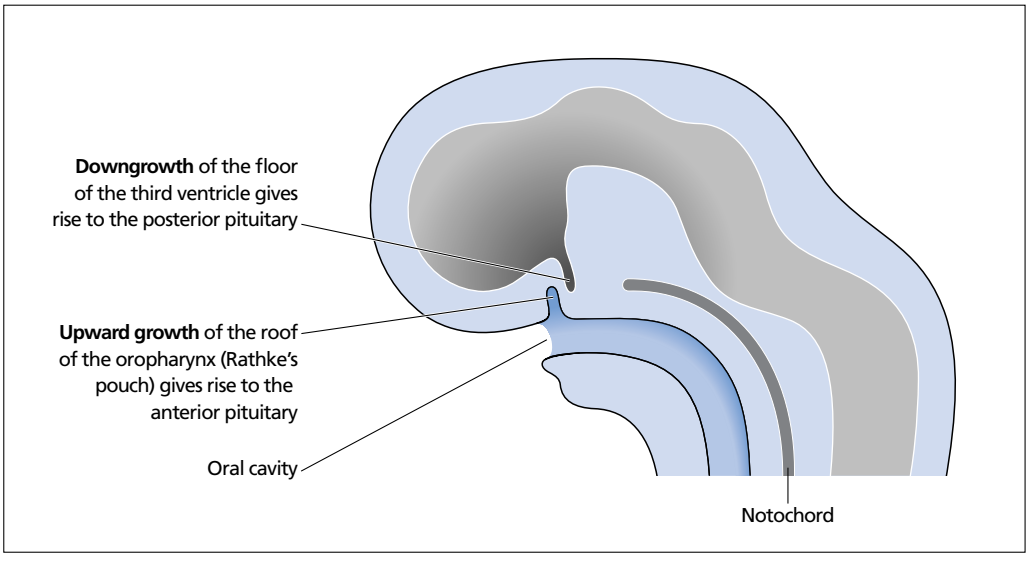

Figure 11.3 The embryological origin of the two parts of the pituitary gland.

Table 11.1 Properties of anterior pituitary hormones

Hormone	Cell type	Percentage of cells in anterior pituitary	Type	Number of amino acids	Structure	Molecular weight (kDa)	Notes
Growth hormone	Somatotrphs	40–50	Protein	191	2 disulfide bonds	22	Most abundant anterior pituitary hormone
Prolactin	Lactotrophs	15–20	Protein	198	3 disulfide bonds	22	
ACTH	Corticotrophs	15–20	Peptide	39		4.5	ACTH, melanocyte-stimulating hormone and endorphins are products of the same gene: POMC (pro-opiomelanocortin)
TSH	Thyrotrophs	5–10	Glycoprotein	n/a	2 non-covalently bound chains (alpha and beta subunits)	30	Alpha subunit the same as LH, FSH, and human chorionic gonadotrophin. Beta subunit is unique to TSH
FSH and LH	Gonadotrophs	10–15	Glycoprotein	n/a	2 non-covalently bound chains (alpha and beta subunits)	30	

ACTH, adrenocorticotrophic hormone; FSH, follicle-stimulating hormone; LH, luteinising hormone; TSH, thyroid-stimulating hormone.

GnRH and pituitary gonadotrophin secretion, and by impairing gonadal steroidogenesis in both males and females.

Regulation of secretion

Prolactin secretion is inhibited by hypothalamic dopamine binding to D_2 receptors. Prolactin secretion is stimulated by hypothalamic thyrotrophin-releasing hormone (TRH) and other factors including oestrogen, opiates, serotonin, and acetylcholine. Prolactin levels may be higher in stress, during sleep and following a suckling stimulus, exercise, meals, sexual intercourse, and an epileptic fit.

Prolactin secretion is pulsatile, with the highest secretory peaks occurring during rapid eye movement sleep. Peak serum levels occur between 4 and 6 a.m.

ACTH

Effects

ACTH stimulates the conversion of cholesterol to pregnenolone and activates enzymes on the steroid synthetic pathway towards cortisol in the zona fasciculata and reticularis, and therefore stimulates the production of cortisol and adrenal androgens.

Regulation of secretion

ACTH is stimulated by hypothalamic corticotrophin-releasing hormone (CRH) as well as other factors, including stress (e.g. acute inflammatory insults), and is inhibited by cortisol (negative feedback). ACTH secretion is pulsatile and exhibits a characteristic circadian rhythm with a peak at about 8 a.m. and a nadir about midnight.

TSH

Effects

TSH stimulates every step in thyroid hormone synthesis and secretion. It also stimulates the expression of many genes in thyroid tissue and causes thyroid hyperplasia and hypertrophy.

Regulation of secretion

TSH secretion is stimulated by hypothalamic TRH. TSH synthesis and release is inhibited by thyroxine (T_4) and triiodothyronine (T_3) directly (via inhibition of transcription of the TSH subunit genes), and indirectly (via inhibition of TRH release). Other factors that may reduce TSH secretion include dopamine, somatostatin, acute non-thyroidal illness, and increased human chorionic gonadotrophin (e.g. in early pregnancy).

Gonadotrophins in males

Effects

LH stimulates the production of testosterone by Leydig cells in the testes. FSH stimulates spermatogenesis (along with testosterone).

Regulation of secretion

LH and FSH secretion are stimulated by a pulsatile release of hypothalamic GnRH. Testosterone inhibits hypothalamic GnRH and pituitary LH production (negative feedback). Inhibin B (a glycoprotein consisting of two subunits produced by germ cells) inhibits FSH production. In addition, several other hormones, hypothalamic kisspeptin, neurotransmitters, and cytokines modulate GnRH secretion.

Gonadotrophins in females

Effects

LH stimulates the early steps in steroidogenesis and the production of androgens in ovarian theca cells. The 'LH surge' induces ovulation and thereafter maintains the secretory functions of the corpus luteum. FSH stimulates the recruitment and growth of ovarian follicles and their secretion of oestradiol (by stimulating the aromatase enzyme that locally converts androgens to oestrogens within the ovary, mainly in the granulosa cells).

Regulation of secretion

Gonadotrophin (LH and FSH) secretion is stimulated by pulsatile GnRH secretion from the hypothalamus. The secretion of FSH and LH is fundamentally under negative feedback control by ovarian steroids (particularly oestradiol) and by inhibin (which suppresses FSH). The negative feedback effect of oestradiol on LH secretion changes to a positive feedback effect as oestradiol levels peak before the ovulation (i.e. the oestrogen peak causes the LH surge).

A L G r a w a n y

Posterior pituitary hormones

The posterior pituitary stores and secretes *oxytocin* and *vasopressin*, also known as antidiuretic hormone (ADH). Vasopressin and oxytocin precursors are synthesised and packaged in granules in the cell bodies of specific magnocellular neurones in the supraoptic and paraventricular nuclei of the hypothalamus. The hormone precursors are transported down the axons in the pituitary stalk to the posterior pituitary. During this transport, they are enzymatically cleaved in the granules to give rise to oxytocin or vasopressin and neurophysin. Neurophysins act as carrier proteins for oxytocin and vasopressin during axonal migration.

Vasopressin

Vasopressin (a nonapeptide also known as ADH) binds to VR_2 membrane receptors on the distal renal tubular cells (in the collecting duct) and causes the activation of adenylate cyclase, generation of cyclic AMP and activation of intracellular protein kinases. This results in the insertion of water channel proteins (aquaporin-2) into the tubular membrane, allowing a flow of solute-free water from the hypotonic luminal fluid into the hypertonic renal interstitium. This results in the concentration of urine. At higher concentrations, vasopressin binds to VR_1 receptors on vascular smooth muscle and causes vasoconstriction.

Vasopressin is also secreted into the portal circulation and, together with CRH, stimulates ACTH release from the anterior pituitary.

Vasopressin secretion is stimulated by an increase in serum osmolality (mediated by hypothalamic osmoreceptors), decreased extracellular volume and blood pressure (mediated by baroreceptors in the carotids, atria, and aorta), and stress. Vasopressin secretion is inhibited by alcoho and cold.

Oxytocin

Oxytocin release is stimulated by vaginal stimulation caused by the fetus during parturition (the Fergusson reflex), sexual intercourse in both sexes and by nipple stimulation by suckling during lactation. Oxytocin release is inhibited by stress.

Oxytocin stimulates contractions of the uterine muscle, which helps delivery of the fetus and the placenta. It may also help sperm transport in the uterus during sex. Another function of oxytocin is to stimulate the contraction of the myoepithelial cells that surround the alveoli in the breast to aid milk ejection.

KEY POINTS

- The pituitary gland sits in the sella turcica in the sphenoid bone and has close anatomical relations with the optic chiasm and the cavernous sinus.
- Hypophyseal portal vessels transmit hypothalamic releasing and inhibitory hormones to the anterior pituitary gland.
- The anterior pituitary secretes at least six peptide hormones: GH, prolactin, ACTH, TSH, LH and FSH.
- GH is secreted by somatotrophs (stimulated by GH-RH), prolactin is secreted by lactotrophs (inhibited by dopamine), ACTH is secreted by corticotrophs (stimulated by CRH), TSH is secreted by thyrotrophs (stimulated by TRH), and LH and FSH are secreted by gonadotrophs (stimulated by pulsatile GnRH).
- The posterior pituitary secretes oxytocin and vasopressin (also known as ADH).
- Vasopressin secretion is stimulated by an increase in serum osmolality and decreased extracellular volume and blood pressure.

12

Pituitary tumours and other sellar disorders

Pituitary tumours

Pituitary tumours (adenomas) account for about 10–15% of all intracranial tumours. Pituitary tumours are almost always benign and 90% of pituitary tumours are adenomas.

Pituitary adenomas may be classified according to their size:

- *macroadenomas*: ≥1 cm
- *microadenomas*: <1 cm.

'Functioning' pituitary tumours are associated with excess anterior pituitary hormone secretion. Clinical syndromes caused by the hypersecretion of adrenocorticotrophic hormone (ACTH; Cushing disease), growth hormone (GH; acromegaly), prolactin and thyroid-stimulating hormone (TSH) are described in later chapters.

'Non-functioning' pituitary tumours (adenomas) are not associated with excess anterior pituitary hormone secretion and make up 15–37% of pituitary adenomas. Non-functioning microadenomas of less than 6 mm are extremely common and present in over 20% of the population. With increasing sensitivity of magnetic resonance imaging (MRI) scanning, an increased number of small microadenomas of no consequence are being discovered.

Pituitary adenomas can arise from any type of cell in the anterior pituitary gland (Box 12.1).

Epidemiology

The incidence of pituitary tumours is 25 per million per year, peaking at around 30–60 years. Female patients usually present earlier than males. The prevalence of pituitary disease has increased over the last 10 years because of increased imaging, better understanding and awareness of the associated diseases. Up to 0.2% are malignant and spread locally.

Lactotroph adenomas (prolactinomas) account for approximately 30–40% of all clinically recognised pituitary adenomas. Non-functioning pituitary adenomas account for 25–30% and are the most common pituitary macroadenoma. Non-functioning pituitary adenomas affect males and females equally and usually present in patients over the age of 50 years.

Aetiology

The mechanism of pituitary tumorigenesis is largely unexplained. Pituitary adenomas are monoclonal in origin and are true neoplasms. Mutations in the following genes may play a role in the development of pituitary adenomas:

- Activating mutations of the alpha subunit of the stimulatory G protein (which links the somatotroph cell membrane GH-releasing hormone receptor to adenylate cyclase) are seen in up to 40% of somatotroph adenomas.
- *PTTG* (the pituitary tumour-transforming gene) is overexpressed in most pituitary adenomas.
- A truncated form of the receptor for fibroblast growth factor-4 has been identified in some pituitary adenomas.
- Familial pituitary adenomas (Table 12.1).

Physiological and pathological hyperplasia of the pituitary gland should be distinguished from pituitary adenoma. Examples include lactotroph hyperplasia

Endocrinology and Diabetes: Lecture Notes, Second Edition. Amir H. Sam, Karim Meeran and Neil Hill.
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Box 12.1 Pituitary adenomas

Lactotroph adenoma (prolactin secreting): 26%
Corticotroph adenoma (adrenocorticotrophin-secreting or non-functioning): 15%
Somatotroph adenoma (growth hormone-secreting): 14%
Gonadotroph adenoma (usually non-functioning): 8%
Thyrotroph adenoma (TSH-secreting): 1%
Null cell adenomas (non-functioning): 23%
Plurihormonal cell adenoma (particularly prolactin and growth hormone co-secreting): 13%

in pregnancy and lactation, thyrotroph hyperplasia in primary hypothyroidism, gonadotroph hyperplasia in primary hypogonadism, and somatotroph and corticotroph hyperplasia due to ectopic GH-releasing hormone and corticotrophin-releasing hormone hypersecretion, respectively.

Clinical presentations

The onset of symptoms and signs of pituitary tumours is often insidious, particularly with non-functioning adenomas. Patients with pituitary tumours may present with features of:

- *hypersecretion* of pituitary hormone(s) in functioning adenomas
- *hypopituitarism*
- *compression* of the surrounding structures such as the optic chiasm
- with no symptoms, but found incidentally on MRI scan done for another reason.

Hypersecretion of pituitary hormones

- *Prolactin*-secreting adenomas may present with galactorrhoea, oligo/amenorrhoea, infertility and impotence.
- *ACTH*-secreting adenomas cause Cushing disease (see Chapter 16). ACTH-expressing tumours may also be non-functioning.
- *GH*-secreting adenomas cause acromegaly (see Chapter 15).
- *Luteinising hormone* (LH) and *follicle-stimulating hormone* (FSH) secretion in LH and/or FSH synthesising tumours is uncommon and they are usually non-functioning, but they may rarely present with hypogonadism (due to biologically inactive gonadotrophins). Males may also have testicular hypertrophy, and premenopausal females may develop oligomenorrhoea and/or ovarian hyperstimulation.
- *TSH*-secreting adenomas (TSHomas) present with secondary hyperthyroidism with or without a goitre.

Hypopituitarism

A pituitary tumour (usually non-functioning) in the anterior pituitary may go undetected for long periods. Decreased secretion of anterior pituitary hormones due to compression or destruction of the surrounding normal pituitary cells may occur. Involvement of the posterior pituitary resulting in vasopressin insufficiency (diabetes insipidus) is less common. The order in which hormone deficiencies develop is highly variable. Signs and symptoms resulting from various pituitary hormone deficiencies are summarised below.

GH deficiency

Growth hormone deficiency in children may present with failure to grow and short stature compared to their peers. Symptoms are non-specific in adults and may include impaired psychological well-being, reduced muscle strength and exercise capacity, and increased abdominal adiposity (fat mass).

LH and FSH deficiency

- LH and FSH deficiency in *males* may present with reduced libido, impotence, infertility, loss of body hair, and flushes.
- LH and FSH deficiency in *females* may present with oligomenorrhoea, amenorrhoea, infertility, dyspareunia, breast atrophy, and flushes.

TSH deficiency

Deficiency, leading to hypothyroidism, may present with fatigue, apathy, muscle weakness, cold intolerance, constipation, weight gain, and dry skin. This is very difficult to diagnose and is often missed because the TSH may be in the normal range.

ACTH deficiency

Adrenocorticotrophic hormone deficiency, resulting in hypocortisolaemia, may present with fatigue, weakness, nausea, vomiting, weight loss, hypoglycaemia, and loss of pubic and axillary hair in females.

Table 12.1 Familial pituitary tumours

Condition	Multiple endocrine neoplasia type-1 (MEN-1)	Multiple endocrine neoplasia type-4 (MEN-4)	Carney complex	Pituitary adenomas associated with phaeochromocytomas or paragangliomas (3Ps)	Familial isolated pituitary adenomas (FIPA)	
Affected gene	MEN1	Unknown, possibly CDKN1B/p27	PRKAR1A in 70%	Genes encoding succinate dehydrogenase subunits A, B, C, D, (SDHA, SDHB, SDHC, SDHD) and tricarboxylic acid cycle (SDHx)	Aryl-hydrocarbon receptor-interacting protein (AIP) in 20%	AIP mutation negative in 80%
Phenotype	Tumours in parathyroid, pancreas, pituitary (60% are prolactinomas)	As per MEN-1	Pigmented skin/ mucosal lesions, cardiac atrial myxomas, multiple endocrine neoplasias	Pituitary adenoma and a phaeochromocytoma or paraganglioma	Somatotroph or lactotroph macroadenomas, may co-secrete growth hormone and prolactin	Variable
Clinical notes	Pituitary tumours occur in 1/3 and typically present at younger age, are more aggressive and less responsive to treatment	Very rare	30% are sporadic, the rest autosomal dominant. Acromegaly occurs in up to 12% affected patients	Described in more than 70 patients	Autosomal dominant inheritance, typically present at younger age, are more aggressive and less responsive to treatment than sporadic or AIP-negative FIPA cases	Present at older age than AIP-positive cases, more aggressive than sporadic cases

Antidiuretic hormone (vasopressin) deficiency

Antidiuretic hormone (ADH, vasopressin) insufficiency may present with polyuria, nocturia and polydipsia.

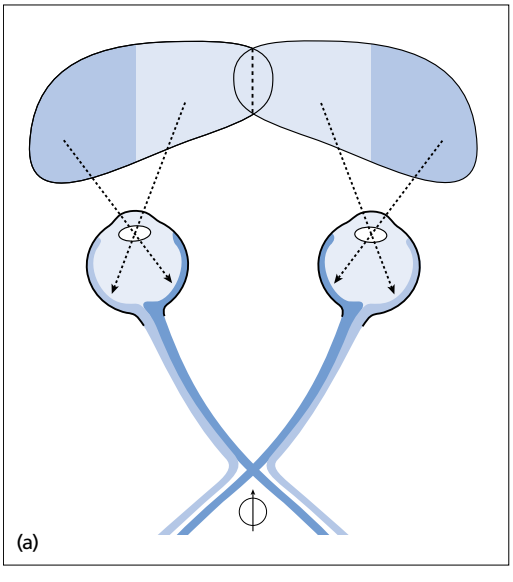
Headache

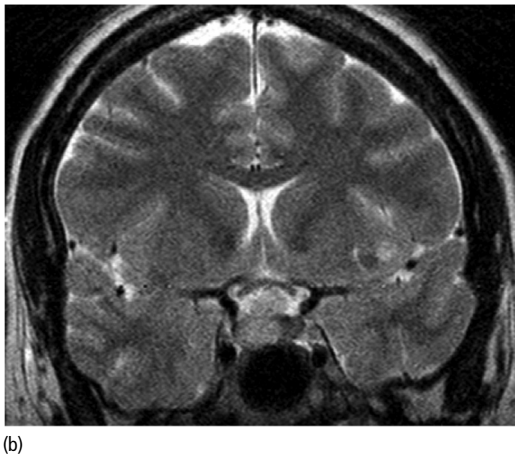
Headaches are caused by stretching or invasion of the dura. Large tumours with suprasellar extension may occasionally cause obstructive hydrocephalus.

Compression of surrounding structures

Suprasellar extension of the tumour may result in involvement of the optic chiasm, causing bitemporal visual field loss. Superior quadrants are initially affected, and this gradually progresses to a *bitemporal hemianopia* that is characteristically asymmetrical (Figure 12.1). Other rarer presentations include hemifield slide and postfixational blindness.

Stalk compression causes hyperprolactinaemia, which may in turn cause hypogonadism by suppressing hypothalamic pulsatile secretion of GnRH. Other less common complications include third ventricle obstruction





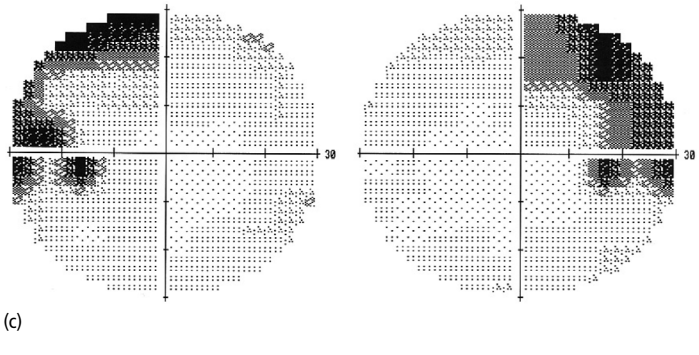


Figure 12.1 (a) Compression of the optic chiasm by a pituitary tumour affects those nerve fibres that carry the visual impulse from the nasal retina (dark blue), resulting in an inability to view the temporal fields (dark blue areas). (b) Pituitary MRI showing a non-functioning adenoma compressing the optic chiasm. (c) Humphrey visual field revealing bilateral (mostly superior) temporal field defects.

(causing hydrocephalus, vomiting, papilloedema, reduced consciousness level) and hypothalamic damage associated with diabetes insipidus and changes in food intake, temperature regulation, or behaviour.

Lateral extension and *cavernous sinus invasion* may cause cranial nerve (IIIrd, IVth, VIth) palsies and diplopia. *Inferior extension* may result in cerebrospinal fluid (CSF) rhinorrhoea due to erosion of the sphenoid sinus.

Pituitary incidentalomas

Pituitary incidentalomas are mass lesions (usually adenomas) that are detected following radiological imaging of the skull base or brain for another clinical reason.

Management depends on pituitary function and whether the optic chiasm is involved. Microadenomas that are intrasellar and non-functioning may be followed up with one MRI scan a year later and if there is no growth, no further MRI scans are warranted. Macroadenomas that are non-functioning, have not caused hypopituitarism and do not involve the optic chiasm may also be followed up clinically with regular visual field monitoring.

Investigations

Investigations in patients with suspected pituitary tumours include basal and dynamic *pituitary function tests*, *pituitary MRI* and formal *visual field assessment*. In addition, patients with suspected syndromes of pituitary hormone hypersecretion such as Cushing disease and acromegaly should undergo specific investigations for these disorders. These are described in detail in separate chapters.

Basal pituitary function tests

Basal anterior pituitary function tests are summarised in Box 12.2.

Prolactin

Prolactin levels can be elevated in non-functioning adenomas due to compression of the pituitary stalk, resulting in a reduction of the inhibitory effect of dopamine on prolactin secretion ('disconnection' hyperprolactinaemia). However, prolactin levels of more than 4000 mU/L are usually due to prolactin hypersecretion from a lactotroph adenoma (prolactinoma).

When measuring prolactin levels, it is important to be aware of two laboratory pitfalls.

Box 12.2 Basal anterior pituitary function tests

Prolactin
Insulin-like growth factor-1
Luteinising hormone, FSH, testosterone in men, oestradiol in women
Thyroid-stimulating hormone and free thyroxine
9 a.m. cortisol

- The '*hook effect*' occurs when the assay uses antibodies that recognise two different sites on the prolactin molecule. The prolactin molecule is 'sandwiched' between these two antibodies, one capturing it and the other labelling it (Figure 12.2a). Very high prolactin levels may be artefactually reported as normal or only modestly elevated. This is because the very high serum prolactin saturates both the capture and labelling antibodies and prevents the binding of the two in a 'sandwich' (Figure 12.2b). This can be avoided by repeating the assay using a dilution of serum (e.g. 1:100).
- Hyperprolactinaemia may be due to decreased clearance of a complex of prolactin with immunoglobulin G ('macroprolactin'). This condition is referred to as *macroprolactinaemia*. Macroprolactin is not biologically active but does get measured in routine assays, thereby causing falsely elevated results. The percentage of macroprolactin should be identified and, if significant, the prolactin result should be amended accordingly. Misdiagnosis can be avoided by pretreating the serum with polyethylene glycol to precipitate the macroprolactin before the immunoassay for prolactin.

Insulin-like growth factor-1

Insulin-like growth factor-1 (IGF-1) is a peptide that is synthesised and secreted by the liver under the control of GH. IGF-1 adjusted for sex and age is low in patients with GH deficiency. GH levels are affected by a number of factors including stress, and therefore GH deficiency can only be proven by failure to respond to stimulation in dynamic tests (see below). IGF-1 levels are high in patients with GH-secreting pituitary tumours, causing acromegaly.

LH, FSH, testosterone in men and oestradiol in women

- *Women* with secondary hypogonadism have reduced oestradiol with reduced or inappropriately normal LH and FSH.

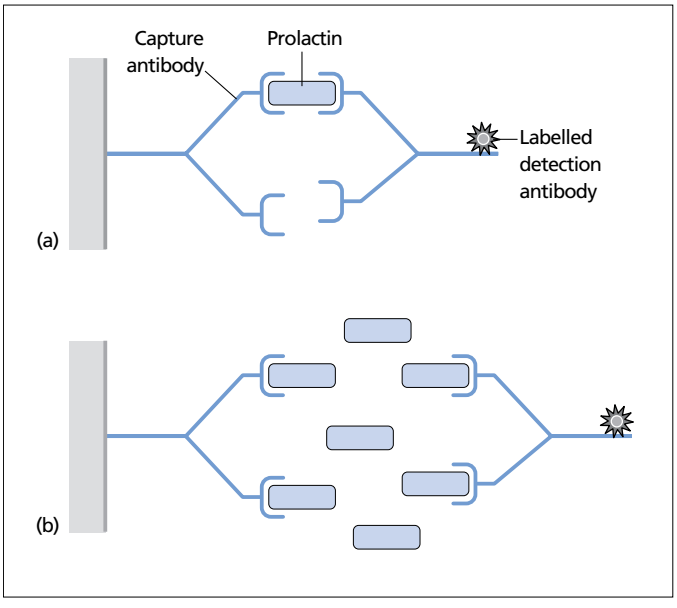


Figure 12.2 (a) A two-site immunometric assay for the measurement of serum prolactin uses two antibodies that are specific for different epitopes of prolactin. Prolactin is sandwiched between a 'capture' antibody attached to a solid-phase matrix and a labelled detection antibody. (b) The hook effect: very high serum prolactin levels simultaneously saturate both the capture and detection antibodies, preventing sandwich formation and the detection of prolactin.

- *Men* with secondary hypogonadism have reduced testosterone with reduced or inappropriately normal LH and FSH (see Chapter 19).

TSH and free thyroxine

In secondary hypothyroidism, free thyroxine is low and TSH is either low or inappropriately normal.

8–9 a.m. cortisol and ACTH

In secondary adrenal insufficiency, 8–9 a.m. cortisol levels are low, and ACTH levels are either reduced or inappropriately normal. However, cortisol levels, like GH, are affected by stress, and deficiencies can be proved only by a failure to respond to stimulation in dynamic tests (see below).

ADH (vasopressin) deficiency

Tests of posterior pituitary function include measurement of serum and urine osmolality and sodium concentrations, and the water deprivation test (see Chapter 17).

Dynamic pituitary function tests

Insulin tolerance test

Insulin-induced hypoglycaemia (plasma glucose <2.2 mmol/L) stimulates GH (to >20 mU/L or 6 µg/L) and cortisol (to >450 nmol/L) in normal individuals. Patients with a basal cortisol below 80 nmol/L are very unlikely to have a normal response and may therefore not need the test.

The *insulin tolerance test* (ITT) is contraindicated in patients with a history of epilepsy or ischaemic heart disease. All patients should have a normal ECG before the test. Untreated hypothyroidism impairs the GH and cortisol response.

Insulin is injected intravenously at a dose of 0.10 U/kg (0.2–0.3 U/kg in acromegaly and Cushing disease). Blood samples are taken for GH, cortisol and glucose, and blood glucose is also checked with a glucometer before insulin injection and after 30, 60, 90, and 120 minutes. A further insulin dose may be given if the patient does not become hypoglycaemic by 30 minutes. Once blood glucose is less than 2.2 mmol/L and blood specimens have been taken, patients do not need to remain hypoglycaemic.

Glucagon test

The glucagon test may be done when an ITT is contraindicated. This test is slightly less reliable than an ITT. In adults, 1 mg of intramuscular glucagon is given. Blood samples are taken for glucose, cortisol and GH prior to glucagon injection and at 90, 120, 150 and 180 minutes. The criteria for adequate cortisol and GH response are the same as those for ITT. The false-positive rate is about 8%. The false-negative rate for cortisol response is 30% so that patients who would have a normal cortisol response if given insulin

will apparently be cortisol deficient, resulting in a dangerous overtreatment of normal people with steroid replacement.

Metyrapone test

Some endocrinologists prefer to test the ACTH reserve using the metyrapone test. Metyrapone blocks the conversion of 11-deoxycortisol to cortisol. Thus in normal individuals, a single dose of metyrapone (30 mg per kg, or 3 g in a 90 kg patient) given at midnight causes a fall in serum cortisol (8 a.m. cortisol < 200 nmol/L) and stimulates ACTH secretion. The increase in ACTH leads to an increase in adrenal steroid synthesis up to and including 11-deoxycortisol (8 a.m. 11-deoxycortisol ≥ 200 nmol/L). In patients with ACTH deficiency, 8 a.m. 11-deoxycortisol after 24 hours of metyrapone is <200 nmol/L.

The metyrapone-induced cortisol deficiency should be reversed by 3 mg of oral prednisolone after the 8 a.m. blood sample is taken. The main disadvantage of this test is that the patient must be in hospital for one night.

Pituitary imaging

MRI is the preferred imaging modality for the pituitary gland. It can effectively characterise soft tissues, and demonstrates the size of the adenoma and whether it extends outside the sella turcica.

On T1-weighted MRI images (Figure 12.3), the anterior pituitary is isointense with white matter. The posterior pituitary exhibits a higher signal intensity (due to an accumulation of neurosecretory granules consisting of an ADH–neurophysin complex packaged within phospholipid membranes). Following gadolinium administration, the pituitary gland and stalk enhance brightly.

In patients with suspected microadenomas, both coronal and sagittal sections are required. Pituitary microadenomas are usually hypointense relative to the surrounding normal pituitary tissue. This can be further clarified following enhancement with gadolinium as microadenomas take longer to enhance.

In patients with macroadenomas, pituitary MRI can detect involvement of the surrounding structures (i.e. optic chiasm, cavernous sinus, carotid arteries, sphenoid sinus, orbit, temporal lobe) and the presence of haemorrhage.

A computed tomography (CT) scan may be done when an MRI is contraindicated (some cardiac pacemakers, metallic clips on aneurysms – except for newer titanium clips – and any metallic foreign body in the eye, spinal canal or close to a major blood vessel) or when patients refuse to have an MRI because they feel claustrophobic. The quality of MRI is improving, and every effort should be made to get an MRI, with sedation if an image will change management. MRI scanners at cardiac centres can be used when a patient with a pacemaker or defibrillator needs an MRI, where the cardiac technicians can ensure that the cardiac support continues while the MRI is carried out. Artefacts from the skull base and metallic dental materials can obscure and compromise the characterisation of soft tissues.

Treatment

The aims of treatment for patients with pituitary tumours should be discussed and planned at a multidisciplinary meeting with pituitary surgeons, radiologists, radiotherapists, endocrinologists, pathologists and someone who knows the patient. Treatment options include:

- the treatment of pituitary hormone hypersecretion: see the specific chapters on Cushing disease, acromegaly and prolactinomas
- the treatment of hypopituitarism (see Chapter 13)
- the treatment of space-occupying (local compression) effects of the tumour.

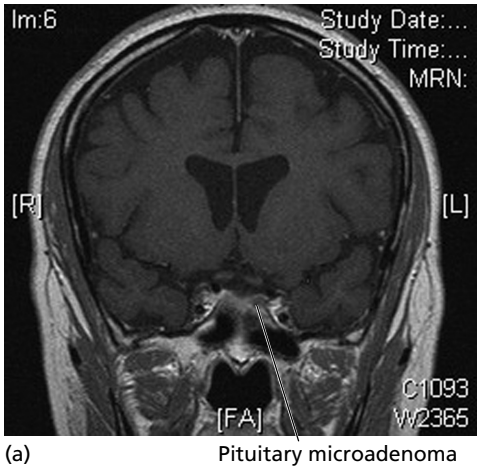
The space-occupying effects of pituitary tumours are treated with *pituitary surgery*. In some cases, pituitary surgery may be followed with *radiotherapy*.

Pituitary surgery

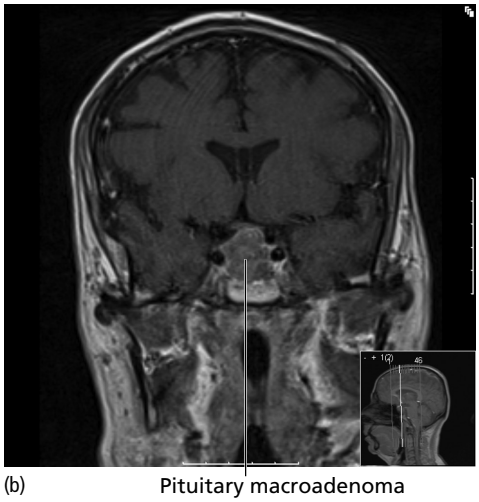
The indications for pituitary surgery include:

- reducing local compression effects such as worsening visual fields (Figure 12.4). Surgery may also be indicated to prevent future compressive effects if the pituitary is shown to be growing over time on serial scans and likely to cause problems before the patient dies of natural causes
- reducing excess hormone secretion (e.g. Cushing disease, acromegaly, TSHomas and prolactinomas not responding to medical treatment).

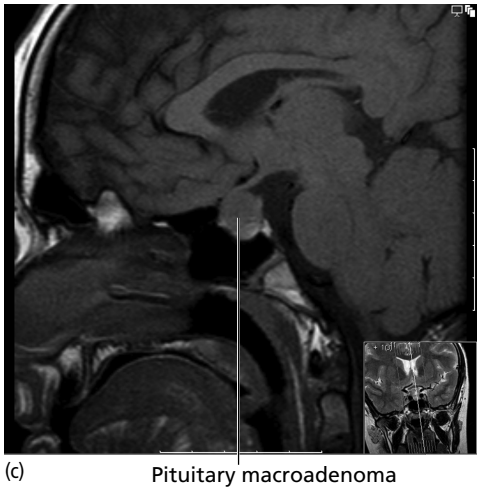
When surgery is indicated, the *trans-sphenoidal* approach is the first-line choice for almost every case. Patients must be informed of the possible complications of trans-sphenoidal pituitary surgery (Box 12.3). Patients should be aware of the need for lifelong follow-up.



(a) Pituitary microadenoma



(b) Pituitary macroadenoma



(c) Pituitary macroadenoma

Figure 12.3 (a) Coronal magnetic resonance imaging scan showing a pituitary microadenoma (note that the microadenoma is hypointense relative to the surrounding normal pituitary tissue). Coronal (b) and sagittal (c) MRI scans showing a pituitary macroadenoma.

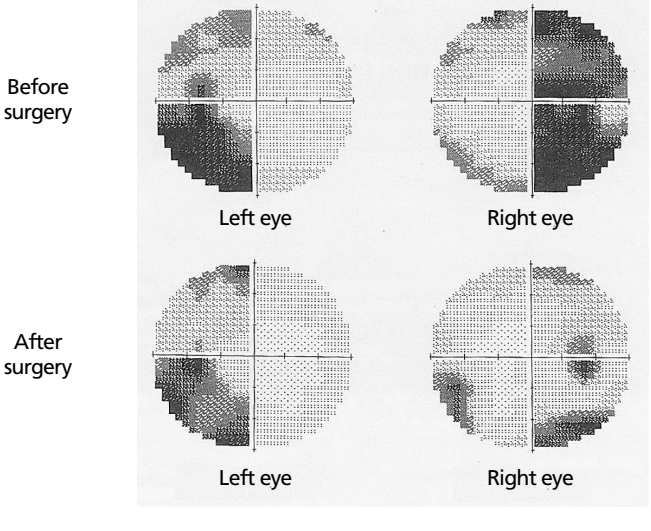


Figure 12.4 Improvement in temporal visual field defects before and after trans-sphenoidal surgery.

Box 12.3 Complications of trans-sphenoidal surgery

Anterior pituitary hormone deficiencies (about 10% for macroadenomas, uncommon with microadenomas)
Bleeding, carotid artery injury (rare)
Cerebrospinal fluid leakage/rhinorrhoea, meningitis
Diabetes insipidus (transient 5%, permanent 0.1%)
Eyes: visual deterioration, cranial (e.g. IIIrd) nerve damage
Failure of the surgery
General anaesthetic complications
Hyponatraemia

Secondary adrenal insufficiency should be treated with prednisolone once daily or hydrocortisone (see Chapter 13). Treatment of secondary hypothyroidism should be commenced only after excluding or treating adrenal insufficiency. Secondary hypothyroidism is treated with thyroxine.

For the management of patients with prolactinomas, acromegaly and Cushing disease, see the specific chapters. In patients with Cushing disease, metyrapone or ketoconazole may be given for at least 6 weeks prior to surgery. These inhibit adrenal steroid hormone synthesis, correcting the hypercortisolaemia, which allows for an improvement in healing and in the general state of the patient.

Craniotomy may be required for craniopharyngiomas, parasellar tumours (e.g. meningiomas), and very large tumours with extensive suprasellar extension and lateral invasion where trans-sphenoidal surgery is unlikely to achieve removal of a significant portion of the tumour.

Perioperative measures

Perioperative *hydrocortisone* must be given to patients with Cushing disease and those with a deficient or unknown steroid reserve. Hydrocortisone 50 mg intramuscularly is started with premedication on the day of surgery and is continued 6-hourly throughout the next day. On the second postoperative day, this may be converted to prednisolone (10 mg once a day) or oral hydrocortisone (20 mg, 10 mg, 10 mg) if the patient starts eating and drinking. On the third postoperative day, the patient is given prednisolone (5 mg once a day) or oral hydrocortisone (10 mg, 5 mg, 5 mg). On the fourth postoperative day, oral glucocorticoid replacement may be delayed until an early morning cortisol has been taken. No doses need be omitted because absorbed hydrocortisone from the evening before or prednisolone from the previous morning is not detectable as it has been completely metabolised.

In those without Cushing disease on postoperative day 4 (or 5):

- If 9 a.m. cortisol >350 nmol/L, the patient can stay off steroid replacement.
- If 9 a.m. cortisol <300 nmol/L, the patient is sent home on regular oral prednisolone (4 mg od) or hydrocortisone (10 mg, 5 mg, 5 mg) until further assessment. Patients must be provided with advice regarding sick day rules (doubling the dose during illness), intramuscular preparation of hydrocortisone for emergencies, a steroid warning card and a MedicAlert bracelet.
- If 9 a.m. cortisol is 300–350 nmol/L, the patient should be supplied with oral prednisolone or hydrocortisone (and an intramuscular preparation of hydrocortisone) and written advice about starting glucocorticoids if he or she becomes unwell.

In those with Cushing disease, a day 5 postoperative 9 a.m. cortisol below 50 nmol/L is suggestive of remission, and regular glucocorticoid replacement should be started. This is because prolonged elevation of circulating cortisol levels has suppressed the hypothalamic–pituitary axis and, following cure, patients may become steroid deficient. Some endocrinologists recommend hydrocortisone replacement (for approximately 4-6 weeks) until further assessment for all patients with Cushing disease regardless of the immediate postoperative cortisol levels due to the risk of delayed remission. Generous hydrocortisone or prednisolone (possibly 6 mg) replacement sometimes helps patients recover, as they may be used to very high levels of cortisol, but the aim will be to reduce the dose over a few weeks, first to normal replacement (4 mg) and then if there is pituitary recovery, gradual withdrawal of the prednisolone.

Visual fields should be formally assessed 3–5 days postoperatively.

Fluid balance must be very closely monitored postoperatively to watch for the possible development of *vasopressin insufficiency* (formerly diabetes insipidus), which may occur due to manipulation of the pituitary and its stalk during surgery. Vasopressin insufficiency presents with polyuria. Postoperatively, the patient's urine must be checked regularly for specific gravity (SG) on the ward. This is much more practical and quicker than sending urine to the laboratory for measurement of osmolality.

The SG of dilute urine is less than 1.005. If the patient becomes polyuric (i.e. passes 200–300 mL per

A L G r a w a n y

hour for three or more consecutive hours), it is important to distinguish polydipsia caused by the patient drinking water because of a sense of thirst (caused by a dry mouth after prolonged mouth breathing as the nose is packed) from true vasopressin insufficiency. Both result in dilute urine but in true vasopressin insufficiency, the plasma osmolality is high. Both sodium and plasma osmolality should be measure as the accuracy of measurement of sodium is better than osmolality. If the serum sodium or osmolality is low, the patient may be overdrinking. A low urine SG (<1.005) or osmolality is appropriate in this case.

Vasopressin insufficiency is confirmed if the plasma osmolality is high (>295 mosm/L) or plasma sodium is over 145 mmol/L in the presence of an inappropriately low urine osmolality/SG (SG < 1.005). Patients must be encouraged to drink more. However, if they cannot keep up with the diuresis and plasma osmolality rises to more than 299 mosm/L or sodium increases to over 147 mmol/L, desmopressin is given (1 µg subcutaneously). If polyuria recurs up to 4 days postoperatively, regular desmopressin should be considered.

Serum sodium must be checked 7–10 days postoperatively as there is a risk of late *hyponatraemia*. Hyponatraemia occurring 5–10 days postoperatively may be due to the syndrome of inappropriate antidiuretic hormone (SIADH) or, rarely, cerebral salt wasting (CSW). SIADH is probably due to excess ADH released from degenerating ADH-producing neurones whose axons were damaged during the surgery. CSW is associated with large amounts of urinary salt loss and hypovolaemia. This should be differentiated from SIADH by assessing fluid status and central venous pressure which shows hypovolaemia in CSW and euvolaemia in SIADH. CSW is treated using saline administration, whereas SIADH is treated with fluid restriction.

Some centres advocate prophylactic perioperative antibiotics, which may reduce the risk of meningitis.

Pituitary radiotherapy

Conventional radiotherapy delivers repeated small doses (fractions) of radiation (e.g. over 35 days). *Stereotactic radiosurgery* delivers a single, relatively large dose of radiation to a precisely defined target. A 'gamma knife' delivers convergent radiation beams from an array of ^{60}cobalt sources (Figure 12.5). A linear accelerator delivers the radiation beam via a gantry that rotates around the patient.

The indications for radiotherapy following pituitary surgery are to shrink residual or recurrent tumour, to reduce the likelihood of regrowth and to treat persistent hormone hypersecretion.

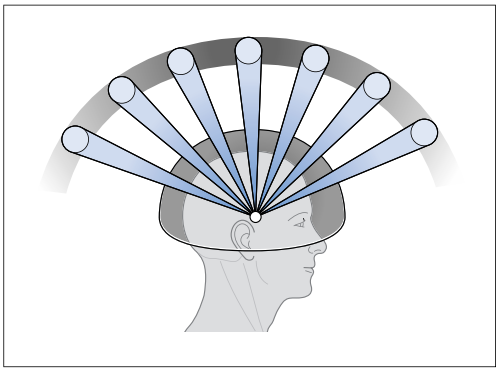


Figure 12.5 The gamma knife delivers convergent radiation beams from an array of ^{60}cobalt sources.

Short-term complications include nausea, headache and hair loss. Long-term complications include hypopituitarism (due to the effect of radiotherapy on the hypothalamus) and visual impairment (which may occur within 3 years of radiotherapy and is possibly due to damage to the vascular supply of the optic chiasm).

Radiotherapy is also associated with a small increased risk of second intracranial tumours, for example astrocytoma, meningioma and meningeal sarcoma (a 1.9% cumulative risk over 20 years), and stroke.

Follow-up and monitoring

Patients should be evaluated 4–6 weeks after the surgery with a formal assessment of *visual acuity and fields*, and *pituitary function testing*, including 8–9 a.m. serum cortisol before taking their morning dose of prednisolone/hydrocortisone, free thyroxine, TSH, LH, FSH, testosterone in men or oestradiol in premenopausal women. Prednisolone or hydrocortisone can be taken after the morning sample has been taken until the results are known.

Patients should be assessed with an ITT at 6 weeks unless contraindicated or a morning cortisol >400 nM. Patients on hydrocortisone or prednisolone replacement should be offered an ITT 1–2 years after surgery as there is a chance of recovery of normal corticotroph function.

If the patient has polyuria, a 24-hour urine collection should be made, and a water deprivation test should be done if the urine output is above 3 L per day.

Pituitary MRI is best repeated 3 months after the surgery so that the immediate inflammatory postoperative changes will not influence the results.

Long-term monitoring should include clinical assessment of replacement therapy, visual field assessment and sometimes a repeat MRI.

Visual fields should be assessed annually, and a pituitary MRI should be done if any deterioration is noted.

Following postoperative radiotherapy, loss of any pituitary hormone can occur from a few months to at least 10 years after radiation. Therefore, pituitary function should be monitored 6 months after radiotherapy and then annually.

Other pituitary and sellar disorders

Pituitary apoplexy

Pituitary apoplexy is acute haemorrhagic infarction of a pituitary tumour (usually large) resulting in gland destruction and compression of surrounding structures by the oedematous enlarged pituitary tumour. Hypertension may be an important predisposing factor. It presents with acute headache, meningism, visual impairment and field defects, ophthalmoplegia and sometimes altered consciousness. Patients may also have hyponatraemia due to acute cortisol deficiency causing failure of free water clearance. Silent bleeds into a pituitary adenoma are much more common. Apoplexy may be the first presentation of a previously undiagnosed adenoma.

Investigations include pituitary MRI and pituitary function tests. In the first 3–5 days, haemorrhage within the sella is isointense on T1-weighted images and hypointense on T2-weighted sequences.

Initial treatment should include cortisol replacement with prednisolone or hydrocortisone. It has been suggested that surgery within 8 days provides the optimal chance of neurological recovery although there is no evidence that surgery improves outcome. Patients with no significant visual or other neurological loss may be managed conservatively.

Sheehan syndrome

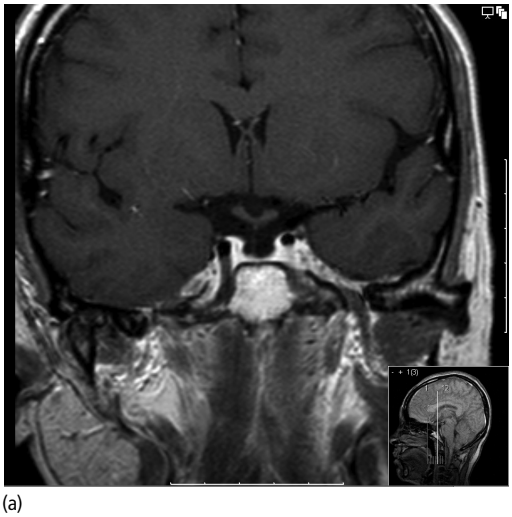
Sheehan syndrome refers to pituitary gland necrosis caused by hypotension due to postpartum haemorrhage. Patients may present after delivery with failure of lactation, failure to resume menses as well as signs of other pituitary hormone deficiencies, for example fatigue, anorexia and weight loss.

Empty sella syndrome

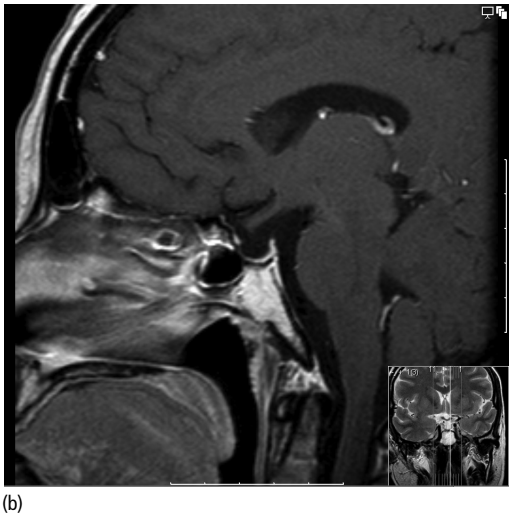
Empty sella syndrome (Figure 12.6) is characterised by an enlarged sella filled with CSF.

'Primary' empty sella syndrome may be due to a defective and enlarged diaphragma sella opening. It may be caused by a developmental anomaly or increased intracranial pressure, and can result in compression and posterior displacement of the anterior pituitary. It is more common in middle-aged women and is usually incidental with no clinical significance. Hyperprolactinaemia (due to the stalk effect) and intrasellar prolapse of the optic chiasm may occasionally occur. The latter is usually asymptomatic.

'Secondary' empty sella syndrome may be due to infarction, surgery or radiotherapy of a pituitary



(a)



(b)

Figure 12.6 Coronal (a) and sagittal (b) magnetic resonance imaging scans showing an empty sella.

adenoma/sella mass. Visual impairment may occur due to fibrosis and ischaemia of the prolapsed optic chiasm.

Other sellar and parasellar disorders

In addition to pituitary adenomas, a number of other disorders can also occur in or near the sella turcica and suprasellar cistern (Box 12.4). These lesions can have similar presentations to pituitary adenomas, with headaches, visual impairment, hypopituitarism and hydrocephalus depending on their size, location and the extent of their impingement on the local tissues. Vasopressin insufficiency is more common in patients with non-pituitary lesions than those with pituitary adenomas.

The diagnosis is dependent on careful clinical and radiological assessment of these lesions.

Craniopharyngiomas are benign tumours that arise from squamous epithelial remnants of Rathke's pouch. Around 50% present during childhood and adolescence. Most are suprasellar, are often large, and only 20% originate in the sella. Craniopharyngiomas can be cystic and/or solid. Histology may be either 'adamantinous', with cyst formation and calcification, or 'papillary' (with generally a better prognosis).

Craniopharyngiomas commonly cause vasopressin insufficiency. The major presenting symptoms are growth retardation in children and visual abnormalities in adults.

Total excision of craniopharyngiomas may be associated with considerable morbidity, operative mortality, recurrence and long-term neurological and endocrine complications. Therefore, many centres recommend less aggressive surgery followed by external beam irradiation.

Box 12.4 Sellar and parasellar disorders

Pituitary adenoma
Pituitary carcinoma (very rare)
Cysts: Rathke's cleft, arachnoid, dermoid
Craniopharyngioma
Meningiomas
Malignant tumours: germ cell tumour, sarcoma, chordoma, lymphoma, metastases (lung, breast)
Infection: abscesses (bacterial, tuberculosis, fungal, parasitic)
Inflammation/infiltration: lymphocytic hypophysitis, sarcoidosis, haemochromatosis, Langerhans cell histiocytosis
Vascular: aneurysms
Trauma

Craniopharyngioma is a locally aggressive tumour which may affect the hypothalamus as well as the pituitary and has a high recurrence rate. Further surgical removal may be indicated when symptoms are caused by increased tumour size.

Meningiomas are usually benign tumors arising from the meninges. Some arise near the sella, causing visual impairment and hormonal deficiencies. On MRI, they are isointense with grey matter, and following gadolinium contrast they become hyperintense.

Germ cell tumours are usually associated with simultaneous lesions in the pineal gland, and patients may have a paralysis of upward conjugate gaze (Parinaud syndrome). Human chorionic gonadotrophin-beta is detected in the serum or CSF. These tumours are very radiosensitive. Fifty percent are malignant and metastasise.

Abscesses in the pituitary may result from local spread, for example from sphenoid sinusitis, or may be secondary to septicaemia. Tuberculosis may present with hypopituitarism and basilar meningitis. Some but not all patients have fever, leucocytosis and meningism. Imaging studies may be unable to distinguish between pituitary abscess and pituitary adenoma, and most patients are diagnosed at the time of surgical exploration.

Lymphocytic hypophysitis is characterised by lymphocytic infiltration of the anterior pituitary followed by fibrosis. It is associated with other autoimmune endocrine conditions and possibly has an autoimmune origin. It almost always affects women, most commonly during pregnancy or the postpartum period. It is characterised by headaches of an intensity out of proportion to the size of the lesion and hypopituitarism, in which adrenal insufficiency is unusually prominent.

Sarcoidosis is an inflammatory granulomatous multisystem disorder that may affect multiple organs such as the eyes (anterior uveitis), skin (erythema nodosum, papules), lungs (e.g. hilar lymphadenopathy, pulmonary fibrosis), joints, and central nervous system (with a predilection for the base of the brain). It may affect the pituitary stalk or hypothalamus.

Hereditary haemochromatosis is an inherited disorder characterised by increased intestinal iron absorption and iron deposition in various organs (e.g. liver, heart, pituitary gland) due to mutations in the *HFE* gene. Gonadotrophin deficiency is the most common endocrine abnormality. Iron studies should be performed if there is an appropriate family history or if the patient has other suggestive manifestations such as bronzed skin, diabetes mellitus, or otherwise unexplained heart or liver disease. Repeated phlebotomy to remove iron may reverse the gonadotrophin deficiency.

Langerhans cell histiocytosis may present with diabetes insipidus. The lesions are eosinophilic granulomata and affect multiple organs such as bones (e.g. radiolucent lesions in the skull, marrow involvement), skin (histiocytomas), central nervous system (particularly the hypothalamic–pituitary axis), ear (otitis externa, discharge), lungs (obstructive and restrictive defects), lymph nodes, liver, and spleen (enlargement).

Cysts: Rathke's cleft, arachnoid and dermoid cysts can produce sellar enlargement and may cause visual impairment, hypopituitarism and hydrocephalus. Rathke's cleft cysts (like craniopharyngiomas) are derived from the remnants of Rathke's pouch. They are lined by ciliated cuboidal/columnar epithelium (compared with squamous epithelium in craniopharyngiomas). Symptomatic patients are treated by decompression. Recurrence after treatment is rare.

Aneurysms are best diagnosed with magnetic resonance angiography.

Traumatic brain injury may result in hypopituitarism. In the acute phase, patients may show evidence of deficiency of gonadotrophins (80%), GH (18%), ACTH (16%) and ADH abnormalities (40%) causing diabetes insipidus or SIADH. Some of the early abnormalities are transient. However, new endocrine dysfunctions may become apparent in the postacute phase. About 25% of long-term survivors have one or more pituitary hormone deficiencies. This is a higher frequency than previously thought and suggests that most cases of post-traumatic hypopituitarism remain undiagnosed.

*Immunoglobulin-G4-related disease (*IgG4-RD*)* is a fibroinflammatory condition that can affect multiple organs. It has been associated with autoimmune pancreatitis with raised serum IgG4 levels, along with infiltration of IgG4 in other organs, including the lung, liver, kidney, lymph nodes and salivary glands. The pituitary gland may also be affected. Immunosuppression with steroids has been the mainstay of treatment although rituximab has also been used with some success.

KEY POINTS

- Pituitary tumours are classified according to size (microadenoma < 1 cm, macroadenoma ≥ 1 cm) and whether they are functioning (secreting one or more anterior pituitary hormones) or non-functioning.
- Tumours may present with hormone hypersecretion syndromes, hypopituitarism or mass effects due to tumour impingement on surrounding structures.
- Work-up includes basal and dynamic pituitary function testing, visual field assessment and pituitary MRI.
- Pituitary surgery is indicated for certain hypersecretion syndromes, to relieve pressure effects or where medical therapy has failed.
- The trans-sphenoidal approach is favoured where possible. Patients should be cared for by a multidisciplinary team including a specialist pituitary neurosurgeon and endocrinologists.
- Postoperative complications include hypopituitarism, cerebral infection and diabetes insipidus.
- Radiotherapy may be considered for large postoperative tumour remnants, to reduce the risk of tumour regrowth or for persistent hormone hypersecretion. Subsequent hypopituitarism may ensue, often after a long latency, so long-term endocrine follow-up is mandatory.
- Pituitary apoplexy is acute haemorrhagic infarction of a pituitary tumour presenting with acute headache, meningism, visual impairment, ophthalmoplegia, and sometimes altered consciousness. Initial life-saving treatment is with intravenous hydrocortisone. All cases, particularly those with neurological complications, should be discussed with a neurosurgeon.
- Other sellar and parasellar pathologies that may present with hypopituitarism or mass effects include cysts, tumours of surrounding structures, infiltrative disorders, infection, and vascular abnormalities. These are more likely to cause posterior pituitary dysfunction compared with pituitary adenomas.

13

Hypopituitarism

Hypopituitarism refers to the reduced secretion of pituitary hormones, which can result from diseases of either the pituitary gland or the hypothalamus (causing a decreased secretion of hypothalamic releasing hormones that stimulate anterior pituitary hormone release).

A total of 76% of cases of hypopituitarism are due to pituitary tumours or their treatment. Another 13% may be due to extrapituitary tumours (e.g. craniopharyngioma). The cause of hypopituitarism in up to 8% of patients may remain unknown.

Box 13.1 summarises major causes of hypopituitarism. Pituitary adenomas and other sellar and parasellar disorders were discussed in Chapter 12.

Genetic causes of hypopituitarism may be due to mutations in the genes encoding the transcription factors necessary for the differentiation of anterior pituitary cells. Mutations in the *PROP1* gene are the most common cause of both familial and sporadic congenital combined pituitary hormone deficiency. Mutations in *PROP1* result in deficiencies in growth hormone (GH), prolactin, thyroid-stimulating hormone (TSH), luteinising hormone (LH), and follicle-stimulating hormone (FSH).

Mutations in *HESX1*, *LHX3* and *LHX4* also cause deficiencies of GH, prolactin, TSH, LH and FSH. Mutations of the gene that encodes *PIT1* (which acts temporally just after *PROP1*) lead to congenital deficiencies of GH, prolactin, and sometimes TSH. Mutations in *TPIT* cause adrenocorticotrophic hormone (ACTH) deficiency, and result in neonatal death if not detected early.

Clinical presentations

Signs and symptoms resulting from various pituitary hormone deficiencies are summarised below.

GH deficiency

GH deficiency can result in fatigue, impaired psychological well-being, reduced energy, muscle strength and exercise capacity, and increased abdominal adiposity (fat mass). In children with GH deficiency, short stature and poor development of the midfacial bones may occur.

LH and FSH deficiency

- LH/FSH deficiency in *men* results in secondary hypogonadism: reduced libido, oligospermia and infertility, loss of body hair, fine perioral wrinkles, flushes and osteoporosis (see Chapter 19).
- LH/FSH deficiency in *women* results in secondary hypogonadism: oligomenorrhoea/amenorrhoea, infertility, dyspareunia, breast atrophy, hot flushes, and osteoporosis (see Chapter 21).

ACTH deficiency

ACTH deficiency results in secondary adrenal insufficiency with hypocortisolaemia which may lead to adrenal failure with symptoms of fatigue, weakness, nausea, vomiting, weight loss, and hypoglycaemia. Preservation of adrenal mineralocorticoid secretion may prevent the acute shock sometimes seen in primary adrenal insufficiency. Hyponatraemia may occur because cortisol is required for normal free water clearance, so that patients with ACTH deficiency have a pattern of water handling similar to syndrome of inappropriate antidiuretic hormone secretion (SIADH).

TSH deficiency

TSH deficiency results in secondary hypothyroidism: fatigue, apathy, muscle weakness, cold intolerance, constipation, weight gain, and dry skin (see Chapter 2). This

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Box 13.1 Causes of hypopituitarism

Pituitary adenomas

Other tumours/cysts

Craniopharyngiomas, meningiomas, malignant tumours (germ cell tumours, chordoma, sarcoma), pituitary metastases (e.g. lung, breast), cysts (e.g. Rathke's cleft)

Pituitary/hypothalamic surgery

Trauma (basal skull fracture)

Pituitary/hypothalamic radiation

Infarction

Apoplexy, Sheehan syndrome

Inflammation/infiltration/infection

Lymphocytic hypophysitis, sarcoidosis, haemochromatosis, Langerhans cell histiocytosis, tuberculous meningitis

Genetic

e.g. *PROP1* or *PIT1* mutations

diagnosis may be missed because the TSH may be in the low-normal reference range, and screening tests may only measure the TSH and not the free thyroxine level.

Antidiuretic hormone deficiency

Antidiuretic hormone (ADH) deficiency results in vasopressin insufficiency (formerly diabetes insipidus): polyuria, nocturia and polydipsia (see Chapter 17).

Prolactin deficiency

The only known presentation of prolactin deficiency is the inability to lactate after delivery.

Investigations

Pituitary function tests and pituitary imaging are discussed in Chapter 12.

Treatment and Monitoring

ACTH deficiency

Glucocorticoid replacement is discussed in Chapter 6. Hydrocortisone or prednisolone may be used. It is essential that patients are provided with:

- information regarding doubling of glucocorticoid dose at times of intercurrent illness
- an emergency intramuscular hydrocortisone supply (to be given at times of vomiting on their way to hospital)
- a steroid card and MedicAlert bracelet.

Glucocorticoid replacement may unmask underlying central vasopressin insufficiency (diabetes insipidus), leading to marked polyuria.

These patients usually do not require mineralocorticoid replacement therapy (unlike patients with primary adrenal failure) because aldosterone release is under the control of the renin–angiotensin system and is not ACTH driven.

Follow-up and monitoring

Under-replacement results in persistence (or recurrence) of the symptoms of cortisol deficiency, whereas over-replacement may result in symptoms and signs of cortisol excess and bone loss. The adequacy of treatment is monitored by:

- asking about symptoms
- measurement of lying and standing blood pressure (to exclude postural hypotension)
- hydrocortisone and prednisolone day curves.

Many endocrinologists use day curves to adjust the dose and timing of glucocorticoid replacement therapy. All oestrogen therapy should be discontinued 6 weeks prior to the test as this increases cortisol-binding globulin levels and results in misleadingly high measured total cortisol levels. Blood is taken in the morning, before and 1 hour after the lunchtime and evening doses. Aim for adequate cortisol levels throughout the day (peak <900 nmol/L, trough >50–100 nmol/L). Once adequate levels have been achieved, this process rarely needs to be repeated.

TSH deficiency

Levothyroxine is started at a dose of 100 µg per day in young patients without cardiac disease. In the elderly or those with cardiac disease, levothyroxine is started at a dose of 25–50 µg per day. Levothyroxine must only be started *after* hydrocortisone replacement as it may increase the clearance of the little cortisol that is produced, and may precipitate an addisonian crisis.

Follow-up and monitoring

Serum TSH cannot be used to monitor treatment in central (secondary) hypothyroidism. The treatment aim should be a serum thyroxine in the middle of the

normal range. We find it helpful to include a sentence in our clinical correspondence to support other colleagues, with wording to the effect of 'TSH should not be used to guide levothyroxine dose adjustment as it will always be low due to previous pituitary pathology; instead free hormone levels alone should guide changes in levothyroxine dose'. Long-term over-replacement increases the risk of osteoporosis and atrial fibrillation.

LH and FSH deficiency in women

- Women who *do not desire fertility* should receive oestrogen–progestin replacement therapy for the prevention of osteoporosis, for symptomatic control (vasomotor symptoms, vaginal dryness) and possibly for the prevention of coronary heart disease (see Chapter 21).
- Those who *do wish to become fertile* may be treated with pulsatile gonadotrophin-releasing hormone (GnRH) or gonadotrophins (daily FSH to stimulate follicle development followed by human chorionic gonadotrophin [hCG] to induce ovulation when the ovarian follicles are mature). This should typically be managed by fertility specialists.

Gonadotrophin replacement

FSH is given according to a step-up or step-down protocol. The step-down protocol mimics the physiology of normal cycles more closely. FSH is started at a dose of 150 IU per day shortly after progesterone-induced bleeding and is continued until a dominant follicle (>10 mm) is seen on transvaginal ultrasonography. The dose is then reduced to 112.5 IU per day followed by a further reduction to 75 IU per day after 3 days, which is continued until hCG is administered. The ovarian response to FSH therapy is monitored using transvaginal ultrasonography and serum oestradiol.

Human chorionic gonadotrophin is given on the day that at least one follicle appears to be mature (a follicle diameter of 18 mm and a serum oestradiol of 734 pmol/L per dominant follicle). If three or more follicles bigger than 15 mm are present, stimulation should be stopped to prevent multiple pregnancies and ovarian hyperstimulation.

Pulsatile GnRH is more likely than gonadotrophins to result in the development and ovulation of a single follicle, thereby reducing the risk of ovarian hyperstimulation and multiple gestations. However, in more than 50% of women with organic pituitary disease, residual gonadotrophin function may be insufficient to allow pulsatile GnRH therapy.

LH and FSH deficiency in men

- Men with secondary hypogonadism who *do not desire fertility* should receive testosterone replacement therapy if there are no contraindications. For the treatment and monitoring of patients on testosterone replacement therapy, see Chapter 19.
- Men with secondary hypogonadism who *do desire fertility* can be treated with gonadotrophin replacement therapy or pulsatile GnRH. Both regimens may take up to 2 years to achieve adequate spermatogenesis.

Gonadotrophin replacement

Initially, hCG injections are administered (1000–2000 IU intramuscularly or subcutaneously, three times a week). hCG has the biological activity of LH but a longer half-life in the circulation. It stimulates the Leydig cells to secrete testosterone. Serum testosterone is measured every 1–2 months and is used to adjust the hCG dose. The response to therapy is measured on semen analysis (every 4 weeks).

Most patients who eventually reach a normal sperm count (>20 million/mL or 40 million/ejaculate) do so within 6 months. If adequate spermatogenesis is not achieved within 6–12 months, human menopausal gonadotrophin or recombinant FSH is added (37.5–75 IU three times a week). Human menopausal gonadotrophin is purified from the urine of postmenopausal women and contains FSH. It may take 12 months or more for a response to be seen.

Pulsatile GnRH may be given subcutaneously via a catheter attached to a mini-pump. This regimen is suitable in men with a hypothalamic defect with normal pituitary gonadotrophin function.

GH deficiency

Adult-onset GH deficiency is associated with unfavourable serum lipid profiles, increased body fat, decreased muscle mass and bone mineral density, and a lower sense of well-being and overall quality of life.

In the USA, many endocrinologists replace GH in patients with adult-onset GH deficiency if they meet at least two criteria for GH therapy: a poor GH response to at least two standard stimuli, and hypopituitarism due to pituitary or hypothalamic damage.

In the UK, GH replacement in adults is considered only in GH-deficient patients with a severely impaired quality of life, reflected by a score of at least 11 (range 0–25) in the Quality of Life Assessment of GH Deficiency in Adults (QoL-AGHDA) questionnaire. GH therapy should be discontinued after 9 months if

the QoL-AGHDA score improves by fewer than seven points. The 9-month period allows a dose titration interval of 3 months followed by a 6-month therapeutic trial period.

ACTH deficiency should be excluded before starting GH therapy. GH may be started at a low dose (0.15–0.3 mg per day) given once daily subcutaneously. The dose may be increased every 4–6 weeks based on the clinical response and insulin-like growth factor-1 (IGF-1) levels until a steady replacement dose is reached (maximum 1 mg daily).

In adults with severe GH deficiency, GH treatment results in:

- decreased fat mass and increased muscle mass (following 12 months' therapy)
- increased bone mineral density (over 24 months of GH replacement)
- an improved sense of well-being and overall quality of life in some patients
- reduced serum total cholesterol, low-density lipoprotein and triglyceride levels.

However, a complicating factor is the apparent increase in lipoprotein (a) (a lipoprotein associated with increased risk of coronary heart disease) seen in some studies.

Follow-up and monitoring

Monitoring includes:

- assessment of quality of life
- measurement of weight, waist-to-hip ratio, and blood pressure
- measurement of lipid profile, glycated haemoglobin, and IGF-1.

ADH deficiency

For details of ADH replacement therapy, see Chapter 17.

Prolactin deficiency

The only known presentation of prolactin deficiency is the inability to lactate after delivery. There is currently no treatment available for this.

KEY POINTS

- Hypopituitarism refers to a reduced secretion of pituitary hormones.
- Hypopituitarism may be caused by sellar/parasellar tumours, surgery, trauma, radiation, infarction, inflammation/infiltration, or mutations in the genes involved in the differentiation of anterior pituitary cells.
- Patients with hypopituitarism may present with features of GH deficiency, hypogonadism, secondary adrenal insufficiency, hypothyroidism, and occasionally diabetes insipidus. Depending on the specific pituitary hormone deficiency, patients may require replacement therapy with hydrocortisone, levothyroxine, sex steroids, and GH. Pulsatile GnRH or gonadotrophins may be given if the patient desires fertility.

14

Hyperprolactinaemia

Hyperprolactinaemia is the presence of abnormally high circulating prolactin levels secreted by the lactotroph cells in the anterior pituitary. The causes of hyperprolactinaemia are summarised in Box 14.1.

Prolactin gene expression and synthesis are upregulated by *oestrogen*. This explains the higher prolactin levels in premenopausal women than in men, and the higher prolactin levels (up to 10-fold) seen during pregnancy and lactation.

Prolactin secretion is inhibited by dopamine (via activation of D_2 receptors). Therefore hyperprolactinaemia may be caused by:

- reduced dopamine secretion
- reduced dopamine delivery to the anterior pituitary via the portal vessels (due to pituitary stalk compression by a sellar/parasellar lesion or stalk section caused by trauma), so-called 'disconnection' hyperprolactinaemia
- dopamine (D_2) receptor antagonists (e.g. antipsychotics and some antiemetics).

Prolactin levels are also higher following exercise, meals and sexual intercourse, during physical or psychological stress, and following an epileptic fit.

In some patients, the underlying cause of the hyperprolactinaemia is not found ('idiopathic hyperprolactinaemia'). Many of these patients may have microadenomas not visible on magnetic resonance imaging (MRI).

Epidemiology

Prolactinomas are the most common functioning pituitary tumour. Lactotroph adenomas (prolactinomas) account for approximately 30–40% of all clinically recognised pituitary adenomas. Microprolactinomas (<1 cm) are more common than macroprolactinomas (>1 cm). Women with microprolactinomas present earlier (with menstrual irregularities) than men.

Clinical presentations

The main action of prolactin is to stimulate lactation. Excess prolactin can result in an inhibition of gonadotrophin-releasing hormone (GnRH) and pituitary gonadotrophin release, and an impairment of gonadal steroidogenesis. Therefore patients with hyperprolactinaemia may present with *galactorrhoea* and symptoms of *hypogonadism*.

Women present with galactorrhoea (30–80%) and menstrual irregularities (oligomenorrhoea or amenorrhoea) or delayed menarche.

Men present with reduced libido, impotence or infertility. They rarely present with galactorrhoea.

In addition to the symptoms of hyperprolactinaemia, patients with pituitary tumours may present with local mass affects, i.e. *headache* and *visual field defects*, and cranial nerve palsies (due to cavernous sinus invasion) or symptoms of *hypopituitarism* (e.g. adrenal insufficiency, hypothyroidism). Long-standing hyperprolactinaemia may result in low bone mineral density and osteoporosis. Most prolactinomas in females are small at the time of diagnosis. This is because the interruption of a regular cycle is more likely to prompt investigation, compared to the gradual onset of subtle symptoms that occurs in men.

Evaluation

It must be remembered that stress, sleep, exercise, intercourse and meals can cause a transient rise in serum prolactin levels. Thus, borderline results should be repeated. Serial measurements using a cannula may be obtained if the stress of venipuncture may be contributing to borderline results ('cannulated prolactin'). Pregnancy should also be considered.

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Box 14.1 Causes of hyperprolactinaemia

Physiological
Pregnancy
Lactation
Stress
Sexual intercourse
Nipple stimulation

Drugs
Antipsychotics: phenothiazines, butyrophenones, flupenthixol, risperidone
Antidepressants: tricyclic antidepressants, selective serotonin reuptake inhibitors, monoamine oxidase inhibitors
Metoclopramide, domperidone
Oestrogens (contraceptive pill)
Opiates
Others: omeprazole, H_2 antagonists, verapamil, methyldopa, bezafibrate, protease inhibitors

Pituitary tumours and other sellar/parasellar lesions
Prolactinomas
Mixed growth hormone/prolactin-secreting tumours
Sellar and parasellar lesions causing stalk compression ('disconnection' hyperprolactinaemia)

Primary hypothyroidism (thyrotrophin-releasing hormone stimulates prolactin release)

Chronic renal failure (reduced clearance of prolactin)

Severe liver disease (disordered hypothalamic regulation)

Polycystic ovary syndrome

As mentioned above, prolactin levels can be elevated in patients with non-functioning adenomas due to pituitary stalk compression resulting in a reduction of the inhibitory effect of dopamine on prolactin secretion ('disconnection' hyperprolactinaemia). In non-functioning adenomas, elevated prolactin levels due to pituitary stalk compression rarely exceed 2000 mU/: and are almost never more than 4000 mU/L. Prolactin levels of more than 4000 mU/L are usually due to prolactin hypersecretion from a lactotroph adenoma (prolactinoma).

When measuring prolactin levels, it is important to be aware of the following two laboratory pitfalls (Figure 14.1).

Macroprolactinaemia

Hyperprolactinaemia may be due to a decreased clearance of '*macroprolactin*', which is a complex of the normal 22 kDa prolactin with immunoglobulin G (Figure 14.1b). In macroprolactinaemia, the free prolactin concentration may be normal. The method most commonly used to detect macroprolactin is to pretreat the serum with polyethylene glycol to precipitate the macroprolactin before the immunoassay for prolactin. Most laboratories now perform an automatic screen for macroprolactin on samples with an elevated result. The laboratory will report either the percentage of macroprolactin or the corrected monomeric prolactin estimation. Macroprolactin is present in 1.5% of the normal population and is biologically inactive.

The hook effect

The 'hook effect' occurs when the assay uses antibodies that recognise two ends of the molecule (one capturing it and the other labelling it). Very high prolactin levels may be artefactually reported as normal or modestly elevated. This is because the very high serum prolactin saturates both the capture and labelling antibodies and prevents the binding of the two in a 'sandwich' (Figure 14.1c). This can be avoided by repeating the assay using a 1:100 dilution of serum. This has clinical significance in the case of large prolactinomas, which may be misdiagnosed as non-functioning tumours if the hook effect is not taken into account, resulting in the patient undergoing unnecessary surgery. It is worth checking with your laboratory as some assays are affected by the hook effect more than others.

The cause of hyperprolactinaemia (Box 14.1) can usually be identified by taking a history (with particular attention to drug history), examining the patient, performing a pregnancy test and measuring thyroid, renal and liver function. Familial pituitary adenoma should be considered in young patients (<30 years old) and those with a family history of pituitary adenoma or multiple endocrine neoplasia.

Once physiological causes, drugs and metabolic causes (primary hypothyroidism, chronic renal failure, severe liver disease) have been excluded, a *pituitary MRI with contrast* should be performed. Prolactinomas can be divided into *macroadenomas*

A L G r a w a n y

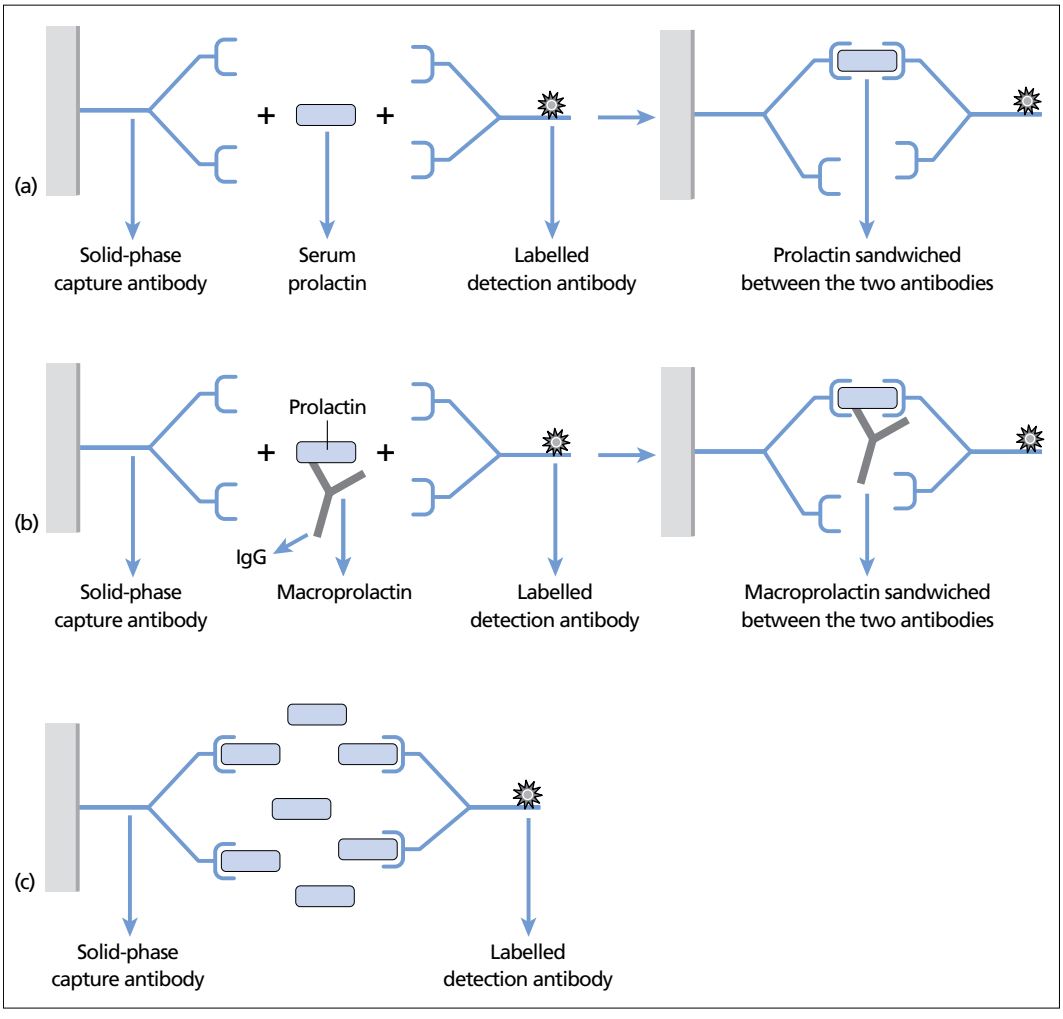

Figure 14.1 (a) A two-site immunometric assay for the measurement of serum prolactin uses two antibodies that are specific for different epitopes of prolactin. Prolactin is sandwiched between a capture antibody attached to a solid-phase matrix and a labelled detection antibody. (b) Circulating macroprolactin (complexes of immunoglobulin G [IgG] and prolactin) is detected but it is not bioactive. Thus, the result is a false positive and clinically misleading. (c) The hook effect: very high serum prolactin levels simultaneously saturate both the capture and detection antibodies, preventing 'sandwich formation' and the detection of prolactin. This will result in a falsely low measurement.

(>1 cm) and *microadenomas* (<1 cm) based on MRI measurement of the tumour size.

Patients with macroadenomas should have formal *visual field testing* and *pituitary function tests* to look for hypopituitarism.

Dual-energy X-ray absorptiometry scans should be done to assess the bone mineral density in patients with long-standing hyperprolactinaemia.

Treatment

The goals of treatment in people with hyperprolactinaemia are to normalise prolactin level, restore normal gonadal function, and maintain fertility. Indications for treatment of hyperprolactinaemia include:

- existing or impending neurological symptoms due to local compression by a macroprolactinoma
- a desire for fertility
- the presence of symptoms: oligomenorrhoea/amenorrhoea, galactorrhoea, loss of libido
- bone density maintenance.

Dopamine agonists

Dopamine agonists reduce prolactin secretion and the size of prolactinomas. Prolactinomas (micro- and macroadenomas) are treated first line with dopamine (D_2) receptor agonists (cabergoline or bromocriptine) regardless of the size of the adenoma and the severity of the neurological sequelae. It is important to note that 15% of patients can develop behavioural changes when taking dopamine agonists, so it is important to counsel patients that this might occur. The patient may report irritability or an increase in risk-taking behaviour, although they sometimes do not have insight into this. It is therefore important to warn patients to ask a close friend or family member to let them know if such changes occur, and in such situations, one should discontinue the dopamine agonist and discuss the case at a pituitary multidisciplinary meeting to consider pituitary surgery as an alternative strategy.

Cabergoline

Cabergoline is a long-acting D_2 receptor agonist and is the initial choice of dopamine agonist. It is preferred to bromocriptine because it is:

- better tolerated (fewer and milder side-effects) for a similar drop in prolactin
- more effective in reducing prolactin levels (90% vs 59%)
- more effective in restoring ovulatory cycles (85% vs 52%).

Cabergoline can reduce the size of macroadenomas in 90% of patients. The initial dose in adults is 250 µg twice weekly. The dose may be increased by 250 µg twice weekly at four weekly intervals to a maximum of 4.5 mg weekly (usually 1.5 mg three times a week). However, prolactin levels are usually normalised with a dose of 250 µg twice weekly.

It was previously reported that patients with Parkinson disease treated with doses of cabergoline much higher than that used in the treatment of hyperprolactinaemia (e.g. >20 mg per week) have an increased risk of valvular heart disease, probably reflecting the cumulative dose exposure. Several studies have reported no increased risk of valvular dysfunction with the (much smaller) doses of cabergoline used to treat prolactinomas. Nevertheless, it has been recommended to use the lowest possible dose of cabergoline necessary to normalise prolactin levels. Those on very high doses of cabergoline for prolactinomas and with risk factors for valvular cardiac disease may benefit from serial echocardiography.

If the prolactin level and pituitary size have been normal for 2 or more years, a withdrawal trial should be attempted and prolactin should be monitored. If prolactin levels have normalised on dopamine agonist therapy but a small tumour remains on imaging, many endocrinologists still attempt weaning off drug treatment after a few years with monitoring of prolactin levels, since many patients will remain in remission.

In women, the menopause is often associated with a spontaneous resolution of prolactinomas. Moreover, at this stage in life, hypogonadism does not usually need to be treated. Most endocrinologists advocate treating until the age of 50 and then withdrawing cabergoline and monitoring prolactin levels. Reinitiation of treatment is reserved for the patients who undergo tumour expansion.

If a patient does not tolerate one dopamine agonist or fails to respond to it – in terms of prolactin levels and adenoma size – an alternative dopamine agonist should be tried.

Bromocriptine

Bromocriptine may be started at a dose of 1.25 mg once daily (usually taken at night to minimise the side-effects, such as nausea, postural hypotension, and depression). The bromocriptine dose can be increased by 1.25 mg per week (i.e. 1.25 mg twice a day after the first week). A dose of 5–7.5 mg of bromocriptine is usually needed to normalise prolactin levels and restore normal menstrual cycles.

Pregnancy and conception

For a woman who wishes to conceive, cabergoline (used since 1994) has not been shown to be unsafe in early pregnancy and is widely used. For the management of prolactinomas in pregnancy, see Chapter 31.

Treatment in those who cannot tolerate or do not respond to dopamine agonists

- Premenopausal women with microadenomas who wish to conceive should be referred to fertility specialists.
- In premenopausal women with microadenomas who do not wish to conceive, oestrogen and

progesterone replacement therapy may be given to prevent osteoporosis.

- Trans-sphenoidal surgery should be discussed at a multidisciplinary meeting as small prolactinomas can be completely removed without the side-effects seen with dopamine agonists. Surgery should also be considered in patients in whom dopamine agonists have failed to lower the serum prolactin level or if the size of the macroadenoma is large, and in whom symptoms or signs due to hyperprolactinaemia or adenoma size (e.g. visual field defect) persist during medical treatment. Radiotherapy may be considered in patients with large macroadenomas following trans-sphenoidal surgery to prevent regrowth of the residual tumour.

Treatment of other causes of hyperprolactinaemia

Hyperprolactinaemia due to causes other than prolactinoma should be treated if it results in hypogonadism. In patients with hyperprolactinaemia and hypogonadism secondary to antipsychotic drugs, withdrawal of the antipsychotic drug may not be possible. These patients should receive gonadal steroid replacement (oestrogen–progesterone in women, testosterone in men). Antipsychotics such as quetiapine, which are relatively 'prolactin sparing', may be considered. As a rule, patients stable on antipsychotics should not have these altered to manage hyperprolactinaemia, which is a trivial side-effect, where possible.

Prognosis

In a prospective study of 200 patients treated with cabergoline for hyperprolactinaemia (105 with microadenomas, 70 with macroadenomas, 25 with idiopathic hyperprolactinaemia), dopamine agonist withdrawal was attempted when serum prolactin levels normalised, and MRI showed no adenoma or a greater than 50% reduction with no cavernous sinus invasion and more than 5 mm distance from the optic chiasm. After 2–5 years of observation, hyperprolactinemia recurred in 24%, 31%, and 36% of patients with idiopathic hyperprolactinaemia, microadenomas, and macroadenomas, respectively. Adenoma regrowth was not seen in any patient. Hyperprolactinaemia was more likely to recur if an adenoma remnant was seen on MRI when treatment was stopped (78 vs 33% for macroadenomas, 42 vs 26% for microadenomas).

Giant adenomas (>3 cm) may behave more aggressively, as shown by case reports of rapid, significant regrowth within weeks of withdrawal of treatment.

KEY POINTS

- Causes of hyperprolactinaemia include physiological (pregnancy, lactation), drugs (e.g. antipsychotics), pituitary tumours (prolactinomas or due to stalk compression), primary hypothyroidism, chronic renal failure, and severe liver disease.
- Prolactinomas are the most common functioning pituitary tumour.
- Women present with galactorrhoea and oligomenorrhoea/amenorrhoea. Men present with reduced libido, impotence, and infertility. Patients with macroadenomas may present with local mass affects (headache and visual field defects).
- Once physiological causes, drugs, and metabolic causes have been excluded, a gadolinium-enhanced pituitary MRI should be performed.
- Prolactinomas are treated medically with dopamine agonists (cabergoline or bromocriptine).
- Indications for treatment include existing or impending neurological symptoms due to local compression by the prolactinoma, other symptoms (oligomenorrhoea/amenorrhoea, galactorrhoea, loss of libido), a desire for fertility, and bone density maintenance.

15

Acromegaly

Acromegaly is a clinical condition caused by chronic excessive circulating levels of *growth hormone* (GH) in adults. Excessive GH secretion before epiphyseal fusion results in gigantism.

Epidemiology

The incidence of acromegaly is 3–5 per million per year, and the prevalence is 50–60 per million. Males and females are equally affected. Patients with acromegaly are mostly diagnosed at age 40–60 years. Pituitary gigantism is less common than acromegaly.

Aetiology

Around 99% of cases are caused by a GH-secreting pituitary adenoma. Macroadenomas (i.e. >1 cm) are more common than microadenomas, partly because of a delay in the diagnosis. Prolactin is co-secreted by 30% of tumours; rarely thyroid-stimulating hormone is co-secreted.

An ectopic secretion of GH-releasing hormone from a carcinoid tumour (e.g. lung, pancreas) or hypothalamus is a much rarer cause. Ectopic secretion of GH (from a pancreatic islet cell tumour) is extremely rare. An activating mutation of the gene encoding the alpha subunit of the stimulatory G protein, resulting in a constitutive activation of adenylyl cyclase, is seen in about 40% of GH-secreting pituitary adenomas.

Familial cases may be seen as part of multiple endocrine neoplasia type 1 (see Chapter 32) and Carney complex (see Chapter 16).

Clinical presentations

Acromegaly is an insidious disease, and the average time from the onset of symptoms to diagnosis may be 5–10 years or longer. Acromegaly in older patients usually presents with a smaller tumour and lower GH levels. Patients may present with:

- symptoms and signs of acromegaly due to *excess GH* or *insulin-like growth factor-1* (IGF-1) secretion (summarised in Box 15.1)
- *local compression* of the optic apparatus resulting in visual field defects (often initially bitemporal superior quadrantanopia progressing to bitemporal hemianopia)
- *hypopituitarism* (symptoms of other anterior pituitary hormone deficiencies).

Pituitary gigantism is suspected when increased growth velocity is seen without manifestations of premature puberty. An arm span larger than standing height suggests an onset of disease before fusion of the epiphyses.

Investigations

Measurement of random GH has little value in the diagnosis of acromegaly. This is because GH secretion is pulsatile and the pulses are separated by long periods during which GH may be undetectable. In addition, GH secretion may be stimulated by a variety of factors such as short-term fasting, exercise, stress, and sleep.

IGF-1 levels do not fluctuate widely throughout the day and are almost always raised in patients with acromegaly,

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Box 15.1 Clinical presentations of acromegaly due to excess growth hormone/insulin-like growth factor-1

General
Increased sweating (>80%), headache, fatigue/lethargy

Face
Coarse features, frontal bossing, enlarged nose, deep nasolabial furrows, prognathism, increased interdental separation, macroglossia

Hands/feet
Enlarged (change in ring/shoe size; Figure 15.1), carpal tunnel syndrome (40%)

Cutaneous
Oily skin, skin tags

Cardiovascular
Coronary artery disease probably related to an increased incidence of hypertension, impaired glucose tolerance (40%) and type 2 diabetes (20%), cardiac failure

Respiratory
Obstructive sleep apnoea

Gastrointestinal
Colonic polyps (9–39%)

Musculoskeletal
Osteoarthritis, arthralgia

Other
Goitre, deep voice, oligomenorrhoea/amenorrhoea, hypercalcaemia, hypercalciuria (growth hormone stimulates the renal 1-alpha-hydroxylation of vitamin D), type 2 diabetes

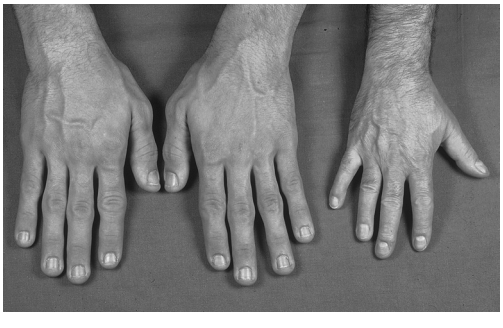

Figure 15.1 Acromegalic hands and a normal hand for comparison.

except in severe intercurrent illness. A patient with a normal serum IGF-1 is unlikely to have acromegaly. However, IGF-1 levels may be decreased by malnutrition, liver disease (as the liver is the source of 75% of plasma IGF-1), uncontrolled type 2 diabetes and exogenous oestrogen. IGF-1 levels are increased during adolescence and pregnancy, and also in hyperthyroidism.

Like IGF-1, serum insulin-like growth factor-binding protein-3 (IGFBP-3) secretion is GH dependent, and IGFBP-3 levels are elevated in acromegaly. However, there is considerable overlap of IGBP-3 values between those with acromegaly and normal persons, so its clinical utility is limited.

If serum IGF-1 concentration is high (or equivocal), serum GH should be measured after a 75 g *oral glucose tolerance test* (OGTT). In normal individuals, GH levels fall following oral glucose. Acromegaly is diagnosed when there is a failure of GH suppression to less than 1 µg/L. False-positive results may be seen in anorexia nervosa or malnutrition, adolescence, chronic liver and renal failure, diabetes mellitus, and opiate addiction.

When acromegaly is biochemically confirmed, *pituitary magnetic resonance imaging* (MRI) should be performed to determine the presence of a pituitary adenoma and whether there is suprasellar extension or invasion of the cavernous sinus by the tumour.

If the pituitary MRI is normal, a chest and abdominal computed tomography scan and serum GH-releasing hormone measurements may be performed to look for an extrapituitary cause. However, these are extremely rare.

Once the diagnosis is established, patients should have:

- anterior pituitary function tests: prolactin, 9 a.m. cortisol, thyroid-stimulating hormone and free thyroxine, luteinising hormone, follicle-stimulating hormone, testosterone (in men), oestradiol (in women)
- formal visual field perimetry
- tests to look for any complications: ECG, chest X-ray, echocardiography, sleep study (if obstructive sleep apnoea is suspected), fasting glucose, glycated haemoglobin, serum calcium, large-joint X-rays (if osteoarthritis is suspected).

Treatment

Overview

Patients with acromegaly should be referred to a centre with endocrinologists, dedicated pituitary neurosurgeons and radiotherapists experienced in treating this condition. Goals of treatment are to normalise GH/IGF-1 levels

whilst maintaining normal pituitary function, minimise the mass effect of the pituitary adenoma, and manage complications of previously high GH levels to achieve optimal health-related quality of life:

- *Trans-sphenoidal surgery* by an experienced neurosurgeon is the first-line treatment for all microadenomas and macroadenomas that are fully resectable or are causing visual impairment.
- *Somatostatin analogues* (SSA) may be given as primary therapy in those with macroadenomas that are not fully resectable and in patients who are unfit for general anaesthesia or are unwilling to have surgery. SSAs are also used to treat patients whose disease remains active after surgery (see below).
- If SSAs alone are ineffective, other treatments such as *cabergoline* or *pegvisomant* (see below) may be used either alone or in combination.
- If, despite medical therapy, the pituitary adenoma continues to increase in size, *radiotherapy* or repeat surgery should be considered.

Somatostatin analogues

Somatostatin analogues (Table 15.1) such as *octreotide* and *lanreotide* mimic the action of the hypothalamic peptide somatostatin, which inhibits GH secretion, by binding to somatostatin receptor-2 and somatostatin receptor-5 (SSTR2 and SSTR5) on somatotrophs. They may lead to normal IGF-1 levels in up to 60% of patients. Variation in response to treatment by SSAs may be determined by differing somatostatin receptor expression profiles in adenomas, with SSTR5 predominating in just over 50% of tumours.

Interestingly, SSTR2 expression positively correlates with biochemical response to octreotide LAR (long-acting repeatable). The long-term response may be predicted before starting treatment by measuring hourly GH levels for 6 hours after a subcutaneous injection of 100 µg of octreotide.

Short-acting octreotide is useful in patients with 'acromegaly headache'. Side-effects include nausea, diarrhoea and gallstones.

Cabergoline

Cabergoline is an orally administered dopamine agonist which binds to D_2 receptors on somatotrophs, inhibiting GH release. It may be particularly helpful in patients with adenomas that co-secrete prolactin. Significant tumour shrinkage may occasionally be seen in these cases. Side-effects include nausea, constipation and mood changes, particularly irritability. Care should be taken when prescribing cabergoline to people with low mood or depression as these may be worsened. Cabergoline alone may lead to normal IGF-1 in 20–40% of patients. Cabergoline can be given with SSAs, increasing the response to 50%. People who respond best to cabergoline usually have milder disease (IGF-1 less than twice the upper limit of normal).

Cabergoline is started at a dose of 250 µg twice a week and may be increased as required to maximum 1.5 mg three times weekly.

Table 15.1 Somatostatin analogues

	Route	Initial dose and dose adjustment
Short-acting octreotide	Subcutaneous	50 µg three times a day Adjust the dose every 2 wks based on levels of insulin-like growth factor-1 Maximum: 500 µg three times a day
Long-acting octreotide LAR	Intramuscular	20 mg every 4 wks Adjust at 3 mos Maximum: 40 mg every 4 wks
Lanreotide LA	Intramuscular	30 mg every 2 wks Increase frequency according to response Maximum: 30 mg every 7 d
Lanreotide Autogel®	Deep subcutaneous	60 mg every 4 wks Adjust at 3 mos Maximum: 120 mg every 4 wks

Pegvisomant

Pegvisomant binds to GH receptors and blocks receptor dimerisation and activation. Given by injection, pegvisomant is usually reserved for people in whom SSAs and/or cabergoline have not worked or not been tolerated, those who cannot have surgery, or following surgery that fails to normalise GH/IGF-1 levels. It may result in normalisation of IGF-1 in about 97% of patients, but in more than 75% there is no effect on tumour size. Serum GH increases with pegvisomant, and only IGF-1 is used to monitor the response. Serious side-effects include hepatitis in about 1% of patients. Pegvisomant can be given in combination with cabergoline and SSAs.

Pasireotide

Pasireotide is a newer injectable SSA that binds to receptors 1–5 on somatotrophs and normalises IGF-1 in ~60% patients. Side-effects include diarrhoea, gallstones, headache and frequently hyperglycaemia. The positioning of pasireotide in the management of acromegaly has yet to be clarified.

Radiotherapy

The number of patients treated with radiotherapy has declined as medical treatment is now mostly used for patients who are not cured by surgery. However, radiotherapy is an important treatment option for large and invasive tumours.

Two techniques are available: external beam radiation (usually given in several fractions over several weeks) or a single dose of highly focused stereotactic radiotherapy. Both techniques result in hypopituitarism. It may take about 4–6 years to achieve 'safe' GH levels following radiotherapy. Those who have had radiotherapy and are on medical treatment with SSAs should have a withdrawal period every year to assess disease activity.

Temozolomide

Temozolomide, an oral alkylating chemotherapeutic agent, may offer an additional option for the management of pituitary carcinomas and aggressive adenomas. Oncology experience using temozolomide for the management of glioblastomas suggests that patients' O6-methylguanine-DNA methyltransferase (MGMT; a DNA repair protein) status determines response to treatment (with low levels of MGMT conferring benefit). However, clinical experience in treatment of pituitary tumours remains very limited at present. There are a small number of case reports in difficult cases where temozolomide has been helpful in shrinking the tumour, although recurrence occurred in some of them.

'Safe' GH levels

It is difficult ever to say that a patient with acromegaly is 'cured'. The aim of treatment is to reduce the GH level to one that will no longer present the risks of acromegaly in terms of morbidity or mortality (a 'safe' GH level). The actual 'safe' level of GH is, however, controversial.

A normal serum IGF-1 concentration (for age and gender), a serum GH concentration less than 1 µg/L after an OGTT and a mean GH of less than 1.9 µg/L during a GH day curve (involving GH measurement at five points during the day) have been used as markers of remission.

Follow-up and monitoring

- Pituitary function tests and an OGTT are repeated about 4–6 weeks after pituitary surgery (see Chapter 12).
- Patients are monitored during treatment with clinical examination, serum IGF-1 levels and OGTTs. Some endocrinologists use GH day curves (see above). Medical treatment may then be titrated up or down accordingly.
- Pituitary function tests should be performed annually.
- Formal visual field assessment should be performed annually.
- The MRI should be repeated yearly for the first few years after initial treatment, and less often thereafter.
- *Colonoscopy* should be done every 3 years in patients over 50 years old and in those with more than three skin tags for the early detection and treatment of premalignant colonic polyps. Patients with polyps should have annual colonoscopy.

Prognosis

Life expectancy in untreated individuals is reduced by approximately 10 years. Mortality in untreated patients is twice that of the normal population. Cardiovascular disease is the major cause of mortality in these patients.

The early remission rate following surgery is 80–90% for microadenomas and 40–50% for macroadenomas. Bony abnormalities generally do not regress, and joint symptoms persist after treatment.

KEY POINTS

- Acromegaly is caused by chronic excessive circulating levels of GH in adults.
- Patients may present with symptoms and signs due to excess GH/IGF-1, local compression (e.g. visual field defects), or hypopituitarism.
- A patient with normal serum IGF-1 is unlikely to have acromegaly.
- If the serum IGF-1 concentration is high or equivocal, an OGTT should be performed. Acromegaly is diagnosed when there is failure of suppression of GH following a glucose load.
- Patients who have a biochemical diagnosis of acromegaly should have formal visual field perimetry, anterior pituitary function tests, and a pituitary MRI.
- Trans-sphenoidal surgery by an experienced neurosurgeon is the first-line treatment for all microadenomas and macroadenomas that are fully resectable or are causing visual impairment.
- SSAs may be given in those who are unfit for or unwilling to have surgery.
- Follow-up should include measurement of serum IGF-1, an OGTT or GH day curve, pituitary function tests, visual field assessment, pituitary MRI, and colonoscopy (for the early detection of premalignant colonic polyps).

16

Cushing syndrome

Cushing syndrome comprises a collection of signs and symptoms caused by a chronic inappropriate elevation of free circulating cortisol.

Aetiology

The most common cause of Cushing syndrome is iatrogenic from excess exogenous glucocorticoids (oral, inhaled, topical, rectal, injected).

The aetiology of endogenous Cushing syndrome can be divided as follows:

- Adrenocorticotrophic hormone (ACTH) dependent (80%):
  - excess ACTH secreted from a pituitary adenoma, which is referred to as *Cushing disease* (80%) and is caused by somatic mutations in the USP8 deubiquitinase gene in 40–50% of cases
  - ACTH secreted from an ectopic source, mostly tumours arising from neuroendocrine cells, for example small cell lung carcinomas, pulmonary, pancreas and thymic carcinoid tumours (20%)
  - ectopic secretion of corticotrophin-releasing hormone (CRH) from neuroendocrine tumours, phaeochromocytomas and medullary thyroid cancer is very rare.
- ACTH independent (20%):
  - excess cortisol secreted from a benign adrenal adenoma (60%)
  - excess cortisol (and androgens) secreted from an adrenal carcinoma (40%).

Adrenal Cushing syndrome is caused by somatic mutations in the protein kinase A in 40–50% of cases. Rarer causes of Cushing syndrome include a CRH-secreting tumour and excess cortisol secretion by ACTH-independent macronodular or micronodular adrenal hyperplasia (Box 16.1).

Several disorders other than Cushing syndrome (Box 16.2) can be associated with hypercortisolism and some of the clinical features of Cushing syndrome ('pseudo-Cushing syndrome'). The abnormal cortisol secretion presumably results from hypothalamic–pituitary–adrenal axis hyperactivity. In these conditions, hypercortisolism disappears after reversal of the underlying cause (e.g. abstinence with chronic alcoholism).

Epidemiology

The incidence of Cushing syndrome is 0.2–5.0 per million per year. However, Cushing syndrome may be more common than previously thought. An unexpectedly high incidence of unrecognised Cushing syndrome has been demonstrated in high-risk populations, for example 0.5–1% of hypertensive patients, 2–3% of patients with poorly controlled diabetes mellitus and 3–5% of obese, hypertensive patients with type 2 diabetes. Endogenous Cushing syndrome is more common in females.

Clinical presentations

Many features of Cushing syndrome, such as weight gain, fatigue, depression, hirsutism, acne, and menstrual abnormalities, are also common in the general population, and the spectrum of clinical presentation is broad. Therefore, suspicion and subsequent confirmation of the diagnosis may be delayed until 1–2 years after the onset of the symptoms. A review of old photographs of the patient may be useful as those with Cushing syndrome usually have progressive clinical features.

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Box 16.1 Causes of Cushing syndrome

Excess exogenous glucocorticoids
ACTH - secreting pituitary adenoma
Ectopic ACTH - secreting tumours
Adrenal adenoma
Adrenal carcinoma

Rare causes

ACTH – independent micronodular adrenal hyperplasia
ACTH – independent macronodular adrenal hyperplasia
Ectopic corticotrophin - releasing hormone

Box 16.2 Physiological causes of Hypercortisolism

Stress: physical or psychological
Depression or other psychiatric disorders
Chronic alcoholism
Severe obesity
Poorly controlled diabetes mellitus
Pregnancy

Some features of Cushing syndrome that are common in the general population are more likely to be due to Cushing syndrome if the onset is at a younger age. These include:

- type 2 diabetes mellitus
- hypertension
- osteoporosis
- thin skin.

Signs that are more discriminatory (although not unique to Cushing syndrome) include:

- easy bruising
- proximal muscle weakness
- thin skin
- facial plethora
- reddish-purple striae on the abdomen, breast or thighs more than 1 cm wide (Figure 16.1)
- weight gain with decreasing growth velocity in children.

Patients with pseudo-Cushing syndrome seldom have easy bruising, thin skin or proximal muscle weakness.

Other features seen in Cushing syndrome that may have other causes include:

- reduced concentration, impaired memory, psychosis
- reduced libido
- unusual infections

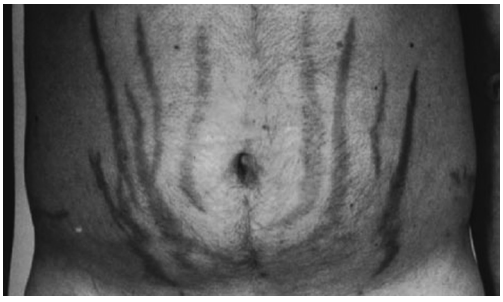

Figure 16.1 Abdominal striae in a patient with Cushing syndrome.

- poor wound healing
- interscapular fat pad
- pigmentation (in ACTH-dependent cases)
- hypokalaemia (usually in ACTH-dependent ectopic cases)
- increased risk of venous thromboembolic disease.

Investigations

A thorough history should be taken to exclude exogenous glucocorticoid use causing iatrogenic Cushing syndrome before performing any biochemical tests. Confirmation of biochemical hypercortisolaemia should take place before attempting to identify the source.

Endogenous Cushing syndrome is rare, and conditions such as obesity, depression, diabetes and hypertension are common. Diagnosis is challenging; the risk of false-positive results following biochemical tests is high. The rate of false-positive cases may be reduced if tests are performed only in patients with a *high pretest probability* of having Cushing syndrome, i.e. those with:

- unusual features for their age (see above)
- multiple and progressive signs and symptoms, especially those which best discriminate Cushing syndrome (see above)
- adrenal incidentalomas (2–20% prevalence of Cushing syndrome)
- increasing weight and reducing height percentile (in children).

Initial high-sensitivity tests

The following tests have a sensitivity of more than 90%, and any one of them may be used as the initial test depending on their suitability (some tests are preferred over others in certain situations; see the sections on pitfalls on the next page).

24-Hour urinary free cortisol

Two or three 24-hour urinary free cortisol (UFC) measurements should be made. Urinary creatinine and volume should also be measured to ensure adequate urine collection over 24 hours.

Pitfalls

UFC measurement is not recommended in patients with renal failure as levels may be falsely low due to reduced glomerular filtration. A high fluid intake (≥5 L per day) may result in false-positive results.

Overnight dexamethasone and low-dose dexamethasone suppression tests

In the *overnight test*, 1 mg dexamethasone is taken at midnight. If the serum cortisol measured next morning between 8 and 9 a.m. is over 50 nmol/L (failure of suppression in response to exogenous steroids), the test is considered abnormal.

In the *low-dose dexamethasone suppression test* (LDDST), 0.5 mg is taken at intervals of exactly 6 hours for 48 hours (i.e. at 9 a.m., 3 p.m., 9 p.m. and 3 a.m.). If serum cortisol measured at 9 a.m. on day 3 (48 hours after the first dose of dexamethasone) is over 50 nmol/L (a failure of suppression), the test is considered abnormal.

Pitfalls

Assays used for serum cortisol in dexamethasone suppression tests measure total cortisol (free and bound to cortisol-binding protein). Oestrogens increase cortisol-binding protein levels and therefore increase total cortisol levels (but not free cortisol levels). They should be stopped for 6 weeks prior to the test as they may result in false-positive results.

Dexamethasone metabolism and clearance may be affected by some drugs (Table 16.1). Dexamethasone clearance is decreased in patients with renal or liver failure. Thus, simultaneous measurement of cortisol and dexamethasone (if available) in these circumstances is helpful.

Late-night salivary cortisol measurements (if available)

In normal individuals, cortisol falls to very low levels at midnight. In Cushing syndrome, there is a loss of normal circadian rhythm. Saliva is collected either into a plastic tube by passive drooling or by placing a cotton pledget (Salivette®) in the mouth and chewing for 1–2 minutes. The sample should be collected at home (in a stress-free environment).

Table 16.1 Medications that affect dexamethasone metabolism via effects on hepatic CYP 3A4 enzyme complex

Induce CYP 3A4; increase dexamethasone metabolism causing false-negative or normal results	Inhibit CYP 3A4; reduce dexamethasone metabolism causing false-positive results
Carbamezapine	Fluoxetine
Phenytoin	Diltiazem
Rifampicin	Itraconazole
Pioglitazone	Ritonavir
Phenobarbital	Aprepitant/ fosaprepitant
Primidone	Cimetidine
Rifapentine	
Ethosuximide	

Pitfalls

Circadian rhythm may be blunted in shift workers. Cigarette smoking should be avoided prior to the collection of salivary cortisol as tobacco contains an inhibitor of 11-beta-hydroxysteroid dehydrogenase type 2, an enzyme that metabolises cortisol.

In patients with normal test results, Cushing syndrome is unlikely. However, if signs or symptoms progress, tests may be repeated in 6 months' time. If any one of the above tests is abnormal, another one or two of the above high-sensitivity tests should be performed.

As mentioned above, some conditions, such as depression, anxiety, obesity, alcoholism and poorly controlled diabetes, may be associated with hypercortisolism. These conditions may cause abnormal results on UFC measurement or the overnight dexamethasone suppression test. In these cases, the results should be treated with caution.

Hypokalaemia occurs more commonly in patients with ectopic ACTH secretion, but it may also be seen in up to 10% of patients with Cushing disease. This is because these patients have higher levels of cortisol, which saturate the cortisol metabolising enzyme 11-beta-hydroxysteroid dehydrogenase type 2. This results in excess cortisol acting as a mineralocorticoid in the kidney, causing potassium loss.

Determining the cause

Patients with positive results on the initial screening tests should have further tests to determine the cause of Cushing syndrome.

Plasma ACTH

Samples should be cold-centrifuged immediately after venesection and flash-frozen before storage, as ACTH is degraded quickly and falsely low results may be measured.

- ACTH levels of less than 5 pg/mL are seen in patients with adrenal causes of Cushing syndrome.
- ACTH levels of more than 20 pg/mL can be attributed to ACTH-dependent causes of Cushing syndrome.
- Plasma levels of between 5 and 20 pg/mL should be repeated and interpreted with caution.

Imaging

Pituitary magnetic resonance imaging (MRI) scans with contrast should be performed if the biochemical tests have indicated the presence of an ACTH-secreting corticotroph adenoma (Cushing disease). Initial biochemical confirmation is important as pituitary incidentalomas may be seen in up to 10% of normal people, and 40% of corticotroph adenomas may be missed on MRI. Corticotroph adenomas may be seen as hypointense lesions on pituitary MRIs that do not enhance with gadolinium.

A low plasma ACTH concentration (<5 pg/mL or <1.1 pmol/L) should be followed by thin section computed tomography (CT) or MRI of the adrenal glands.

Those with a suspected ectopic source of ACTH should have further imaging (a radiolabelled octreotide scan and MR/CT imaging) to look for ectopic ACTH-secreting tumours. High-resolution chest CT may identify the most common sites of ectopic ACTH secretion, i.e. small cell lung cancer and bronchial carcinoid tumours. Radiolabelled octreotide scans are also used to detect carcinoid tumours as they express somatostatin receptors.

Inferior petrosal sinus sampling

This is the most reliable test for differentiating pituitary and non-pituitary sources of ACTH.

The inferior petrosal sinuses receive venous drainage from the cavernous sinus (which in turn receives blood from the pituitary gland) and drain into the sigmoid sinuses. Femoral catheters can be advanced bilaterally up to the internal jugular vein, sigmoid sinuses and finally into the inferior petrosal sinuses to collect 'central' blood. Skilled radiologists are required to undertake this procedure. Blood is also collected from a peripheral vein.

Patients with Cushing disease show a basal central-to-peripheral ACTH ratio of more than 2:1 or a central-to-peripheral ACTH gradient of over 3:1 after CRH administration. This test has approximately 95% sensitivity and specificity. False positives may occur in rare cases of cyclical ectopic ACTH secretion or CRH-secreting tumours.

High-dose dexamethasone suppression test

The high-dose dexamethasone suppression test (HDDST) has now been largely abandoned in centres where inferior petrosal sinus sampling is available (see above).

The HDDST test was previously used to differentiate excess ACTH secretion from a pituitary adenoma and from an ectopic source. The HDDST is based on the observation that hypercortisolaemia caused by pituitary ACTH-secreting tumours is more sensitive to suppression by dexamethasone than hypercortisolaemia caused by ectopic ACTH-secreting tumours.

The HDDST involves giving 2 mg of dexamethasone at 6-hourly intervals. Serum cortisol is measured before the first dexamethasone dose and 48 hours after the first dose. Cortisol is suppressed to less than 50% of the basal value in about 80% of patients with Cushing disease (i.e. a sensitivity of around 80%). The test has a specificity of about 80% (i.e. cortisol suppression is also seen in some patients with ectopic ACTH secretion). The pretest probability that a female patient has Cushing disease is 90%, so the HDDST does not add additional diagnostic value.

Treatment

The treatment of Cushing syndrome due to exogenous glucocorticoid therapy is to reduce the glucocorticoid dose and discontinue it if possible. This should be done gradually as most patients will have developed hypothalamic–pituitary–adrenal suppression and insufficiency following chronic glucocorticoid treatment. Management of Cushing syndrome should be undertaken by a multidisciplinary team.

ACTH-secreting pituitary adenomas (Cushing disease)

The treatment of choice for Cushing disease is *trans-sphenoidal surgery* by an experienced neurosurgeon.

- If a clearly circumscribed microadenoma is identified by the neurosurgeon, trans-sphenoidal microadenectomy is the treatment of choice.
- If no clearly circumscribed microadenoma is identified and future fertility is not an issue, subtotal (85–90%) anterior pituitary resection may be performed.
- If no clearly circumscribed microadenoma is identified by the neurosurgeon and future fertility is an important concern, radiotherapy may be used.

Patients with post trans-sphenoidal surgery cortisol levels of less than 50 nmol/L are more likely to have prolonged remission. Patients with evidence of remission (cortisol <50 nmol/L) following surgery should have hydrocortisone replacement. This is because prolonged exposure to high cortisol levels in these patients has resulted in suppression of the hypothalamic–pituitary–adrenal axis. Patients with high postoperative cortisol levels (>200 nmol/L) may need further surgery although this increases the risk of intraoperative complications and subsequent hypopituitarism and diabetes insipidus.

Medical treatment has traditionally been with *adrenal enzyme inhibitors* (ketoconazole, metyrapone), which may be given before surgery to control hypercortisolism and stabilise the patient. The dose is titrated to achieve a mean serum cortisol of 150–300 nmol/L. Other agents are available, although there is generally less clinical experience of their use (Table 16.2).

Metyrapone inhibits 11-beta-hydroxylase and blocks the final step in cortisol biosynthesis. It can exacerbate hirsutism due to increased adrenal androgen production. Hypertension can also occur as a result of increased production of deoxycorticosterone (see the steroid synthesis pathway in Chapter 5). Metyrapone may be started at a dose of 250 mg twice a day and may be increased every 3 days up to 1 g four times a day.

Ketoconazole inhibits the first step in cortisol biosynthesis (side chain cleavage) and to a lesser extent the conversion of 11-deoxycortisol to cortisol. It also inhibits ACTH secretion by impairing corticotroph adenylate cyclase activation. Ketoconazole may be started at a dose of 200 mg twice a day and is increased at 2–3-weekly intervals. Doses higher than 400 mg three times a day are seldom effective. Ketoconazole requires stomach acid in order to be absorbed, so may be ineffective in people treated with proton pump inhibitors or H_2-receptor antagonists.

Liver function tests should be monitored weekly initially as ketoconazole can cause hepatitis. Other side-effects of ketoconazole include headache, sedation, nausea, vomiting, gynaecomastia, impotence, and decreased libido (due to inhibition of testosterone production).

Hypertension and diabetes mellitus should be treated as normal. Patients with marked bone loss should receive oral bisphosphonate therapy, calcium and vitamin D supplementation.

Radiotherapy may be used in those who are not cured and have persistent hypercortisolaemia after trans-sphenoidal resection of the tumour. Pituitary irradiation is as likely to cure children as is surgery and may therefore be considered as the initial therapy. Stereotactic radiotherapy provides less irradiation to the surrounding tissues (see Chapter 12).

Pituitary irradiation using a linear accelerator corrects hypercortisolism in about 45% of adults and 85% of children. Maximal benefits do not occur for at least 9–12 months and occasionally as long as 2 years in adults. Children usually respond within 3 months. During this time, adrenal enzyme inhibitors should be used to control the hypercortisolism.

The major side-effect of radiotherapy is *progressive hypopituitarism*. Nearly all patients will have growth hormone deficiency 10 years after radiotherapy, and luteinising hormone/follicle-stimulating hormone deficiency is seen in up to 15%.

In refractory cases where surgery and radiotherapy fail to normalise cortisol secretion, surgical bilateral total adrenalectomy or medical adrenalectomy with mitotane with lifelong glucocorticoid and mineralocorticoid replacement is the final definitive cure. Monitoring of mitotane levels and dose adjustment are frequently advocated.

In patients who cannot be treated with adrenalectomy, adrenal enzyme inhibitors may be used long term to ameliorate the hypercortisolism.

Bilateral adrenalectomy may rarely be complicated by development of *Nelson syndrome*. This was originally characterised by a locally aggressive pituitary tumour causing skin pigmentation due to excessive ACTH secretion. With the advent of pituitary imaging with CT/MR, corticotroph tumour progression can be detected very early and therefore Nelson syndrome is rarely seen. The corticotroph adenoma may require surgery and radiotherapy. Pituitary radiotherapy at the time of adrenalectomy is effective in preventing Nelson syndrome.

Ectopic ACTH-secreting tumours

In patients with ACTH-secreting ectopic tumours, complete excision often results in remission.

Table 16.2 Medications that can be used to treat Cushing disease

Site of action	Drug	Mode of action	Side-effects	Risk	Notes
Pituitary	Pasireotide	Somatostatin analogue	GI symptoms, sinus bradycardia, gallstones	Can cause hyperglycaemia	Lowers ACTH in 25% people with Cushing syndrome
	Cabergoline	Dopamine receptor agonist	Dizziness, nausea, postural hypotension, increased risk-taking behaviour		Lowers cortisol in 35% patients
Adrenal cortex	Metyrapone Osilodrostat	Inhibits 11-beta-hydroxylase	GI symptoms, rash, dizziness, headache, hirsutism, acne, oedema, hypertension, hypokalaemia		Cortisol lowering in 50% patients
	Ketoconazole	Inhibits several steroidogenic enzymes	GI symptoms, increase in liver enxymes, rash, sedation	Severe hepatotoxicity, male hypogonadism	Antifungal; cortisol lowering in 50% patients
	Mitotane	Inhibits several steroidogenic enzymes	GI symptoms, dizziness, ataxia, vertigo, confusion, dyslipidaemia	Teratogenicity	Toxic to adrenal cortex; takes 4 weeks to become effective; used mainly in adrenocortical cancer
	Etomidate	Inhibits 11-beta-hydroxylase and cholesterol side chain cleavage		Respiratory suppression, sedation	Anaesthetic agent, only used on intensive care units
Glucocorticoid receptor	Mifepristone	Glucocorticoid receptor antagonist	GI symptoms, hypoadrenalism, hypokalaemia, hypertension, oligomenorrhoea, endometrial hyperplasia, rash		Unable to monitor efficacy as dose not lower cortisol

ACTH, adrenocorticotrophic hormone; GI, gastrointestinal.

However, in patients who are not cured after surgical resection of the tumour, adrenal enzyme inhibitors may be used to control hypercortisolism.

Adrenal tumours

In patients with an isolated cortisol-secreting adenoma, unilateral laparoscopic adrenalectomy has a good prognosis. In patients with adrenocortical carcinoma, mitotane is used as adjuvant therapy following surgery. Adrenal enzyme inhibitors may be used when surgery is contraindicated or if the tumour is metastatic or occult.

Prognosis

In the past, Cushing disease had a 5-year survival rate of 50% when not treated. However, with modern treatments, the standard mortality ratio following normalisation of cortisol is similar to that of an age-matched population. In patients with persistent hypercortisolism after treatment, the standard mortality ratio may be increased to 4–5 times that of the general population. Most deaths are due to cardiovascular, thromboembolic or hypertensive complications, or bacterial/fungal infections.

The initial remission rate (normal ACTH and normal cortisol circadian rhythm) with an experienced neurosurgeon is about 70–80%. However, permanent cure rate is about 60–70% due to late recurrence.

The symptoms and signs of patients with Cushing syndrome gradually resolve in the year following surgery. Impaired glucose tolerance, hypertension and osteoporosis improve but may not disappear. Impaired health-related quality of life resolves partially but not completely after trans-sphenoidal surgery. It may remain below that of age- and gender-matched subjects for up to 15 years. Depression usually persists for many years following successful treatment.

In children, bone density and growth rate both increase after treatment, but neither returns to normal.

Patients with ectopic ACTH secretion may have a poor prognosis associated with the underlying tumour. The prognosis for adrenocortical carcinomas is poor. They almost invariably recur and usually do not respond to irradiation or chemotherapy.

Follow-up and monitoring

The follow-up of patients after pituitary surgery is discussed in Chapter 12.

Patients should be followed up clinically for recurrence of features of Cushing syndrome, and dexamethasone suppression tests should be performed when recurrence is clinically suspected. In patients in whom remission is achieved with surgery and who are taking hydrocortisone replacement, an insulin tolerance test should be done 1–2 years after surgery to look for the recovery of normal corticotroph function.

Rare causes of ACTH-independent Cushing syndrome

Micronodular adrenal hyperplasia

Micronodular adrenal hyperplasia, also known as primary pigmented nodular adrenocortical disease (PPNAD), is characterised by multiple small pigmented, autonomously functioning adrenocortical nodules. It may be sporadic or familial (isolated or as part of Carney complex).

Carney complex is an autosomal dominantly inherited syndrome characterised by spotty skin pigmentation (café-au-lait spots), endocrine tumours (most commonly PPNAD), and non-endocrine tumours (such as myxomas of the skin, heart, breast, and other sites). Three responsible genes have so far been identified: *PRKAR1A*, *PDE11A*, and *MYH8*.

Macronodular adrenal hyperplasia

Macronodular adrenal hyperplasia is characterised by adrenal glands that contain multiple non-pigmented nodules larger than 5 mm in diameter. An ectopic adrenal expression of some G-protein-coupled receptors (gastric inhibitory polypeptide, beta-adrenergic, luteinising hormone/human chorionic gonadotrophin, serotonin receptors), or an increased expression/activity of some eutopic receptors (e.g. V_1 vasopressin receptors) may mediate the increase in cortisol secretion.

These patients have increased serum and urinary cortisol, and undetectable plasma ACTH in the basal state and after administration of CRH. Cortisol production is suppressed minimally, if at all, by high-dose dexamethasone.

Cushing syndrome associated with McCune–Albright syndrome is a rare variant of ACTH-independent macronodular adrenal hyperplasia. McCune–Albright syndrome is a sporadic disease caused by activating mutations of the gene coding for the alpha subunit of stimulatory G protein, which results in constitutive activation of the cyclic AMP pathway in the nodules and excess cortisol secretion. McCune–Albright syndrome is characterised by café-au-lait spots, polyostotic fibrous dysplasia, precocious puberty, and other endocrine disorders.

Surgical bilateral adrenalectomy is used in patients with micronodular adrenal hyperplasia and most patients with macronodular adrenal hyperplasia.

KEY POINTS

- Cushing syndrome comprises a collection of signs and symptoms caused by a chronic inappropriate elevation of free circulating cortisol.
- Cushing syndrome may be caused by excess exogenous glucocorticoids, an ACTH-secreting pituitary adenoma, an ectopic ACTH-secreting tumour, an adrenal adenoma, or an adrenal carcinoma.
- Biochemical tests should only be performed in patients with a high pretest

probability of having Cushing syndrome (e.g. patients with unusual features for their age or multiple and progressive features that best discriminate Cushing syndrome).

- Initial high-sensitivity tests for Cushing syndrome include 24-hour UFC measurements, an overnight dexamethasone suppression test, LDDST and a late-night salivary cortisol measurement (if available).
- Investigations to determine the underlying cause of Cushing syndrome include plasma ACTH, pituitary or adrenal imaging (depending on the plasma ACTH result), and inferior petrosal sinus sampling.
- The treatment of choice for Cushing disease is trans-sphenoidal surgery by an experienced neurosurgeon.
- The treatment of Cushing syndrome due to an adrenal adenoma is unilateral adrenalectomy.

17

Diabetes insipidus

Diabetes insipidus (DI) is characterised by excessive production of dilute urine (hypotonic polyuria, i.e. urine output of more than 3 L per day with osmolality <300 mosmol/kg). DI can be life-threatening if treatment is withheld and/or sufficient water for drinking is not provided to cover urinary losses.

Diabetes insipidus is classified into:

- *central DI*: due to a relative or absolute deficiency of the posterior pituitary hormone antidiuretic hormone (ADH), which is also known as arginine vasopressin (AVP). Central DI occurs when ~80% AVP production has been lost
- *nephrogenic DI*: due to partial or total renal resistance to ADH
- *dipsogenic DI* (more commonly known as *primary polydipsia*): due to excessive drinking.

Confusion between diabetes mellitus and diabetes insipidus can lead to treatment errors. It has therefore been proposed to rename central and nephrogenic DI to arginine vasopressin deficiency (AVP-D), and arginine vasopressin resistance (AVP-R) respectively. The new terminology also reflects the underlying pathophysiology.

Epidemiology

Diabetes insipidus is a rare condition. Males and female are affected equally, and most cases present in adults. However, familial cases mostly present in childhood. The prevalence of central DI is about 4 per 100 000. The prevalence of nephrogenic DI and primary polydipsia is not clear. Familial and nephrogenic DI may present in childhood.

Aetiology

Central DI

Causes of central DI include:

- idiopathic: 33% of cases (possibly due to autoimmune injury to the ADH-secreting neurones)
- head trauma/neurosurgery
- pituitary tumours (primary or metastases)
- granulomatous diseases (e.g. sarcoidosis, histiocytosis X).

Less common causes include vascular, for example Sheehan syndrome (see Chapter 12), central nervous system infections, hypoxic encephalopathy (cardiopulmonary arrest or shock), familial DI resulting from mutations of genes involved in ADH production and DIDMOAD (Wolfram syndrome, characterised by DI, diabetes mellitus, optic atrophy, and deafness).

Wolfram syndrome is inherited as an autosomal recessive trait with incomplete penetrance. It is caused by at least two different genes: *WFS1* and *ZCD2*. Wolframin, the product of *WFS1*, is a transmembrane protein expressed in pancreatic beta cells and neurones.

Nephrogenic DI

Nephrogenic DI is due to resistance to the action of ADH and may be secondary to:

- X-linked mutations in the gene encoding the ADH receptor V_2, or autosomal dominant mutations in the gene encoding aquaporin-2 (ADH-sensitive water channel)
- persistent hypercalcaemia (>2.75 mmol/L)

Endocrinology and Diabetes: Lecture Notes, Second Edition. Amir H. Sam, Karim Meeran and Neil Hill.
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- severe hypokalaemia (<3.0 mmol/L)
- drugs: lithium (may cause irreversible DI), demeclocycline, antifungals, and antineoplastic agents
- long-standing polyuria may decrease the renal solute gradient, leading to inability to adequately concentrate urine.

Gestational DI is an unusual condition due to increased placental vasopressinase activity and degradation of vasopressin. Gestational DI resolves after delivery, but pregnancy may also reveal incipient central DI.

Box 17.1 Initial tests for polydipsia/polyuria

Blood tests
Renal profile (including sodium and potassium)
Glucose and HbA1c
Calcium
Plasma osmolality

Urine tests
Urine osmolality

Primary polydipsia

Primary polydipsia is due to excess fluid intake resulting in an inhibition of ADH release. These patients often have a history of a psychiatric condition. Thirst may be affected by the psychiatric condition or the drugs used in the treatment.

Diagnosis

Initial tests (Box 17.1)

A urine volume of over 3 L per day with a urinary osmolality of 300 mosmol/kg or less is suggestive of DI. DI can be diagnosed if the following three criteria are met:

- plasma osmolality >295 mosmol/kg
- plasma sodium >145 mmol/L
- urine osmolality <300 mosmol/kg.

Moreover, DI can be excluded in people with a normal plasma sodium and urine osmolality >600 mosmol/kg.

In equivocal cases, a water deprivation test should be done (see next column).

Serum *sodium* is usually normal or only slightly elevated in DI as long as water is available to drink. Serum sodium is usually low in primary polydipsia because of water overload.

In all patients presenting with polyuria, *glucose*-induced osmotic diuresis due to uncontrolled diabetes mellitus should be excluded first.

Serum *potassium* and *calcium* should be measured to exclude nephrogenic DI caused by hypercalcaemia or hypokalaemia. The history may provide important clues: for example, a gradual onset and a history of psychiatric illness favour primary polydipsia or associated systemic illness, and medication use may suggest the underlying diagnosis

Water deprivation test

Water deprivation tests may be used to differentiate between cranial DI, nephrogenic DI and primary polydipsia. In the first stage of the test, no fluid is allowed for 8 hours (e.g. between 8.30 a.m. and 4.30 p.m.) to assess renal concentrating capacity with controlled dehydration. Plasma and urine osmolality are checked at intervals. It is essential to weigh the patient hourly; the test must be terminated if there is more than 3% weight loss (the test then being considered positive).

In the second stage of the test (i.e. after 8 hours) in patients who have not concentrated their urine adequately (i.e. to more than 750 mosmol/kg), desmopressin is given (20 µg intranasally or 2 µg intramuscularly) and hourly urine volumes and osmolality are measured for 4 hours, to determine renal response to (synthetic) ADH. Patients may drink freely during the second stage.

Plasma samples should also be collected at baseline and after 8 hours (i.e. prior to the administration of desmopressin) for measurement of ADH if necessary (i.e. in cases where the history and water deprivation test provide equivocal results).

Interfering medication such as diuretics should be stopped before the test. Cortisol and thyroxine deficiencies should be corrected before the test as their deficiency impairs water excretion.

Interpretation

In normal individuals, water deprivation stimulates ADH release. Urine is therefore concentrated to greater than 750 mosmol/kg, and plasma osmolality remains below 300 mosmol/kg.

In patients with central/nephrogenic DI, reduced ADH release/action inhibits urine concentration (urine osmolality remains less than 300 mosmol/kg), and plasma osmolality may rise above 300 mosmol/kg.

After desmopressin administration, patients with cranial DI (a deficiency of ADH) can concentrate their urine (osmolality >750 mosmol/kg). However, those with nephrogenic DI (resistance to the action of ADH) cannot concentrate their urine.

In patients with primary polydipsia, urine is concentrated to a lesser degree than in healthy individuals (between 300 and 750 mosmol/kg). This is because chronic polyuria washes out the medullary interstitial solutes (and the osmotic gradient) and impairs the urine-concentrating ability. In addition, chronic overhydration in primary polydipsia causes a suppression of ADH release. In these patients, plasma osmolality may initially be low but rises to normal with water deprivation.

Limitations of the water deprivation test

There is a potential error with the water deprivation test. Patients with primary polydipsia may have a water deprivation test result similar to those with partial central DI. Patients with partial central DI are hyper-responsive to a submaximal rise in ADH following the water deprivation test (possibly due to receptor upregulation) and may concentrate their urine to some extent. The water deprivation test has a sensitivity of 86% and specificity of 70%.

A therapeutic trial of desmopressin with careful in-hospital monitoring of fluid balance and plasma sodium may occasionally be used to differentiate between primary polydipsia and partial central DI. In patients with partial central DI, an improvement in polydipsia and polyuria may be seen. In patients with primary polydipsia, polyuria is decreased but polydipsia persists. These patients may develop acute hyponatraemia (hence the need for close monitoring). In patients with nephrogenic DI, no effect is seen.

In patients with cranial DI diagnosed on water deprivation testing, the hypothalamic–pituitary anatomy should be assessed with a *magnetic resonance imaging* (MRI) scan.

Alternative ways of diagnosing DI

Copeptin is a 39 amino-acid glycosylated peptide secreted in equimolar concentrations to ADH (copeptin, ADH, and neurophysin are derived from pre-provasopressin in the hypothalamus). ADH is difficult to measure so interest in copeptin as a direct biomarker in both DI and the syndrome of inappropriate ADH secretion is gathering momentum. Direct measurement of copeptin before and during an osmotic challenge has been shown to reliably differentiate nephrogenic DI, cranial DI, and primary polydipsia. Hypertonic saline-stimulated copeptin measurement obviates the need for prior dehydration of patients, but does carry the risk of hypernatraemia so should be performed only under controlled clinical conditions.

Treatment

People with mild central DI may not require treatment; significant polyuria or polydipsia can be treated with DDAVP.

Central DI

Desmopressin is a synthetic modification of ADH or AVP with prolonged antidiuretic effects and no vasopressive activity.

- *Intranasal administration*. An initial dose of 5 µg is usually given at bedtime to control nocturia. The dose can be titrated up according to night-time and daytime symptoms to a maintenance dose of about 10–20 µg once or twice daily. Some endocrinologists recommend starting with the intranasal preparation to ensure that the patient understands what a good antidiuretic response is. The therapy can then be changed to tablets.
- *Oral administration*. Only about 5% is absorbed from the gut. The initial dose is 100 µg at bedtime and can then be titrated up to 100–400 µg three times a day according to symptoms. The absorption of desmopressin may be decreased by up to 50% when taken with meals.
- *Subcutaneous administration* is occasionally used. The usual dose is 1 µg twice a day.

Desmopressin is safe during pregnancy for both mother and fetus.

Plasma sodium and osmolality and clinical response should be monitored, and the desmopressin dose should be modified if necessary to ensure that patients are not becoming hyponatraemic (due to water intoxication). Physicians should be aware of interactions of desmopressin with other drugs (e.g. carbamazepine, indapamide) that may increase its action.

Nephrogenic DI

The underlying cause (e.g. hypokalaemia or hypercalcaemia) should be treated if possible and the causative drug stopped. Treatment includes a low-sodium diet, thiazides and non-steroidal anti-inflammatory drugs (NSAIDs). Thiazides act by inducing mild volume depletion, resulting in increased proximal tubular sodium and water reabsorption. This leads to decreased water delivery to the collecting tubules (where ADH normally acts) and reduces urine output.

NSAIDs inhibit renal prostaglandin synthesis and augment ADH action. In patients who cannot be treated with NSAIDs or who have persistent symptomatic polyuria after the addition of NSAIDs, a trial of desmopressin may be given.

Primary polydipsia

The underlying psychiatric disorder should be treated.

KEY POINTS

- DI is characterised by hypotonic polyuria (a urine output of >3 L per day with osmolality <300 mosmol/kg).
- DI may be central (due to deficiency of ADH produced in the posterior pituitary), nephrogenic (due to renal resistance to the action of ADH) or dipsogenic, also known as primary polydipsia (due to excessive drinking).
- In all patients presenting with polyuria, glucose-induced osmotic diuresis should be excluded first.
- A water deprivation test is used to differentiate between cranial DI, nephrogenic DI and primary polydipsia.
- In patients with central DI, the hypothalamic–pituitary anatomy should be assessed with an MRI scan.
- Patients with central DI are treated with desmopressin. Plasma sodium and osmolality and clinical response should be monitored.

A L G r a w a n y

18

Hyponatraemia and syndrome of inappropriate antidiuretic hormone secretion

Hyponatraemia is commonly defined as a serum sodium concentration of less than 135 mmol/L.

Epidemiology

Hyponatraemia is the most common electrolyte disorder in hospitalised patients. Mild hyponatraemia is seen in up to 20% of hospitalised patients.

Aetiology

Causes of hyponatraemia are summarised in Box 18.1.

Hyponatraemia may be associated with low, normal, or high plasma osmolality. The majority of causes of hyponatraemia are associated with low plasma osmolality and increased antidiuretic hormone (ADH) levels (see below). Assessing the volume status of the patient is essential in determining the aetiology of hyponatraemia. The possibility of artifactually low sodium concentration in blood taken proximal to an intravenous infusion should always be excluded.

Hyponatraemia with low plasma osmolality

Most cases of hyponatraemia are caused by an increase in extracellular water relative to extracellular sodium. This is usually due to an impairment of renal water excretion capacity and water retention caused by increased plasma ADH levels.

Increased plasma ADH levels in hypovolaemic patients

Increased secretion of ADH in patients with volume depletion (e.g. secondary to urinary, gastrointestinal, or third-space fluid losses) is mediated by the carotid sinus baroreceptors, which sense the reduced pressure.

Thiazide diuretics are the most common cause of hyponatraemia in adults. Patients with hyponatraemia caused by thiazides may be either hypovolaemic or euvolaemic, depending on the magnitude of the sodium loss and water retention. Hyponatraemia is less common with loop diuretics, as the inhibition of sodium chloride transport in the loop of Henle prevents the generation of the countercurrent gradient and limits the ability of ADH to cause water retention.

Cerebral salt wasting is a rare syndrome described in patients with cerebral disease, particularly subarachnoid haemorrhage. Salt wasting is the primary defect and is possibly due to the release of brain natriuretic peptide and/or reduced central sympathetic activity. The ensuing volume depletion causes a rise in ADH release.

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Box 18.1 Causes of hyponatraemia

Hyponatraemia with low plasma osmolality

Increased plasma ADH in hypovolaemic patients

Renal fluid and sodium loss: thiazide diuretics, salt-losing nephropathy, cerebral salt wasting

Extrarenal fluid and sodium loss: diarrhoea, vomiting, third-space losses (burns, pancreatitis, bowel obstruction)

Increased plasma ADH in euvolaemic patients

Adrenal insufficiency

Hypothyroidism

Syndrome of inappropriate ADH secretion

Pregnancy

Increased plasma ADH in hypervolaemic patients

Cardiac failure

Cirrhosis

Nephrotic syndrome

Excessive water intake

Primary polydipsia

Ecstasy

Marathon runners (excessive water intake combined with sodium loss due to sweating)

Decreased solute intake

Beer drinkers

Hyponatraemia with normal plasma osmolality

Pseudohyponatraemia

Hyperlipidaemia

Paraproteinaemia

Renal failure

Sodium-free isosmotic irrigant solutions (used in laparoscopy, hysteroscopy and transurethral resection of the prostate)

Hyponatraemia with high plasma osmolality

Hyperglycaemia

Rarer causes: mannitol or maltose (e.g. intravenous immunoglobulin in 10% maltose)

Increased plasma ADH levels in hypervolaemic patients

The increased secretion of ADH in patients with cardiac failure and cirrhosis is mediated by the carotid sinus baroreceptors, which sense the reduced pressure due to reduced cardiac output and peripheral vasodilation respectively in these conditions.

Increased plasma ADH levels in euvolaemic patients

- *Hypothyroidism*: increased plasma ADH levels may be caused by reduced cardiac output and activation of the carotid sinus baroreceptors.
- *Adrenal insufficiency*: increased plasma ADH levels may be caused by reduced systemic blood pressure and cardiac output (due to a lack of cortisol) or removal of the inhibitory effect of cortisol on corticotrophin-releasing hormone and ADH.
- *Syndrome of inappropriate ADH secretion (SIADH)*: this may be due to central nervous system pathology, pulmonary pathology, malignancy (ADH secreted by the tumour), drugs or a number of other causes (Box 18.2). Increased ADH results in reduced water excretion. The elevated level of fluid is detected by the renal juxtaglomerular cells and causes a reduction in renin and aldosterone levels. This results in increased sodium excretion,

Box 18.2 Causes of syndrome of inappropriate antidiuretic hormone secretion (SIADH)

Central nervous system pathology

Vascular (infarction, haemorrhage, cerebral venous thrombosis), infection (meningitis, encephalitis), inflammatory conditions (e.g. systemic lupus erythematosus, demyelination), trauma, tumours

Pulmonary pathology

Infection (pneumonias, abscess, tuberculosis, aspergillosis), bronchiectasis, carcinoma, mesothelioma, mechanical ventilation

Malignancy

Small cell lung carcinomas, mesothelioma, oropharynx, stomach, duodenum, pancreas, ovaries, bladder, prostate, endometrium, thymoma, lymphoma, sarcoma, olfactory neuroblastoma

Drugs

Selective serotonin reuptake inhibitors, tricyclic antidepressants, antipsychotics, clofibrate, carbamazepine, nicotine, opiates, vincristine, cyclophosphamide, desmopressin

Miscellaneous

Acute intermittent porphyria, postoperative state, pain, severe nausea, AIDS

Idiopathic

which prevents fluid overload but perpetuates hyponatraemia.

Cases of 'nephrogenic syndrome of inappropriate antidiuresis' due to activating mutations of the V_2 receptor in the renal collecting ducts have been reported.

Excessive water intake

Excessive water intake (more than 10 L per day) may occasionally be seen in psychiatric patients with polydipsia, following ecstasy (MDMA) or in marathon runners. If the excessive water intake exceeds the water excretion capacity of the kidneys, water retention and hyponatraemia ensue.

Decreased intake of solutes

A decreased intake of solutes in beer drinkers or other malnourished patients may also result in hyponatraemia. Beer contains little or no sodium, potassium, or protein. The fall in daily solute excretion results in a reduction in water excretory capacity.

Hyponatraemia with normal plasma osmolality

In patients with marked hyperlipidaemia (e.g. uncontrolled diabetes) or hyperproteinaemia (e.g. multiple myeloma), the aqueous fraction of the plasma volume is reduced. This results in a decrease in the sodium concentration if it is measured in the total plasma volume. However, this is a measurement artefact since the sodium concentration in the aqueous fraction of plasma is unchanged ('pseudohyponatraemia'). This artefact may be avoided with the use of ion-selective electrodes that directly measure the sodium concentration in the aqueous fraction of the plasma.

In *renal failure*, water retention can lead to hyponatraemia with normal plasma osmolality, as the decrease in osmolality due to low sodium is offset by the increased urea. (Remember that osmolality = $2 \times [Na^+ + K^+]$ + urea + glucose.) Although plasma osmolality is normal, plasma tonicity (the contribution to osmolality by effective osmoles) is low since urea is an ineffective osmole (i.e. it can freely cross cell membranes and does not induce water movement out of the cell).

Hyponatraemia with normal serum osmolality may occasionally be seen in patients who have received and absorbed large volumes of isosmotic, sodium-free irrigant solutions (containing glycine or sorbitol) during laparoscopic surgery or transurethral prostatectomy.

Hyponatraemia with high plasma osmolality

Hyponatraemia with high plasma osmolality may be seen in patients with *hyperglycaemia*. The rise in plasma glucose pulls water out of the cells and results in a reduction in plasma sodium concentration by dilution ('translocational' hyponatraemia). An increase of 2.3 mmol/L in blood glucose decreases serum sodium concentration by about 1.0 mmol/L.

Hyponatraemia with increased plasma osmolality may also occur with the administration and subsequent retention of hypertonic mannitol or with maltose (e.g. when intravenous immune globulin is given in a 10% maltose solution).

Clinical presentations

Most patients with a serum sodium concentration of more than 125 mmol/L are asymptomatic.

The clinical manifestations of hypotonic hyponatraemia (Box 18.3) are more prominent when the decrease in the serum sodium concentration is large or has occurred rapidly within a period of hours.

Hypotonic hyponatraemia causes entry of water into the brain, resulting in cerebral oedema and intracranial hypertension. A process of adaptation starts within a few hours as solutes leave the brain tissues, resulting in a reduction of brain swelling.

Hypovolaemic patients may have tachycardia, postural hypotension, dry mucous membranes, and reduced tissue turgor. Hypervolaemic patients may have a raised jugular venous pressure and peripheral oedema.

In addition, patients may have features of the underlying cause, for example clubbing and cachexia

Box 18.3 Clinical presentations of hyponatraemia

Headache
Anorexia, nausea, vomiting
Lethargy
Muscle cramps
Depressed reflexes
Confusion, restlessness, disorientation
Seizures
Coma, death

in malignancy (causing SIADH) or increased pigmentation in Addison disease. Patients must be thoroughly examined for features of malignancy (including breast examination).

The correction in sodium concentration must not exceed 10 mmol/L in the first 24 hours and 18 mmol/L in the first 48 hours. Rapid correction of hyponatraemia must be avoided as it can result in shrinkage of the brain, which triggers demyelination of the pontine and extrapontine neurones. This 'osmotic demyelination' is known as *cerebral pontine myelinolysis*. Patients can present one to several days after aggressive treatment of hyponatraemia with quadriplegia, pseudobulbar palsy, seizures, coma, and death. The risk of this complication is higher in patients with alcoholism, malnutrition, liver failure, and potassium depletion.

Investigations

Figure 18.1 shows an algorithm for the diagnosis of hyponatraemia.

Serum lipids and protein should be measured to rule out pseudohyponatraemia. Blood glucose must be measured as hyperglycaemia causes translocational hyponatraemia (see above).

Hypothyroidism and adrenal insufficiency must be excluded by measuring thyroid-stimulating hormone, free thyroxine and 9 a.m. cortisol. If 9 a.m. cortisol is less than 550 nmol/L, a short Synacthen test must be done.

Hypovolaemic patients with a renal cause of fluid and sodium loss (e.g. thiazide diuretics) have a high spot urinary sodium (>20 mmol/L), whereas those with an extrarenal cause of fluid and sodium loss (e.g. diarrhoea or vomiting) have a low spot urinary sodium (<20 mmol/L).

SIADH should be considered in euvolaemic patients (who have been off diuretics for 2 weeks) in whom hypothyroidism and adrenal insufficiency have been excluded. The key tests are *paired plasma osmolality and urine osmolality* and *sodium concentration*. Patients with SIADH have low plasma osmolality, and high urine osmolality (>100 mosmol/kg) and sodium levels (>20 mmol/L).

It is important to remember that SIADH is not a diagnosis. Once it has been confirmed, the underlying cause must be diagnosed. Patients should be investigated by brain imaging (computed tomography [CT] scan with contrast, or magnetic resonance imaging) and chest CT. Patients with normal brain and lung imaging should have further imaging to look for malignancy elsewhere (e.g. with CT of the abdomen/pelvis).

Treatment

The treatment of hyponatraemia should include correction of the underlying cause, such as stopping the causative drug or the administration of hydrocortisone and mineralocorticoids to patients with adrenal insufficiency and thyroxine to hypothyroid patients.

Hypovolaemic patients

Hypovolaemic patients must be rehydrated with isotonic (0.9%) saline. The administration of isotonic saline to patients with volume depletion removes the hypovolaemic stimulus to ADH release and allows excretion of the excess water.

Hypervolaemic patients

Hypervolaemic patients (e.g. those with cardiac failure or cirrhosis) are treated with fluid restriction. Their drugs should be reviewed.

Euvolaemic patients with SIADH

Mild-to-moderate hyponatraemia

Patients with chronic mild-to-moderate hyponatraemia (serum sodium concentration of 120–130 mmol/L) are usually asymptomatic. However, recent observations suggest that some of these 'asymptomatic' patients have subtle neurological manifestations (e.g. reduced mental functioning, unsteadiness, and falls in elderly patients) that may be improved by raising the serum sodium. They are often treated with fluid restriction (up to 1 L per day). It is important to note that the administration of normal saline may worsen hyponatraemia in SIADH. This is because the administered sodium is excreted in the urine, while some of the water is retained.

If hyponatraemia continues, an increased dietary intake of salt should be encouraged. Patients who do not tolerate fluid restriction may occasionally receive demeclocycline (300–600 mg twice a day). Demeclocycline reduces the responsiveness of the collecting tubule cells to ADH and therefore increases water excretion. It may take 1–2 weeks to see its effect. Renal function should be monitored, since nephrotoxicity can occur with this drug. Alternatively, a loop diuretic (furosemide)

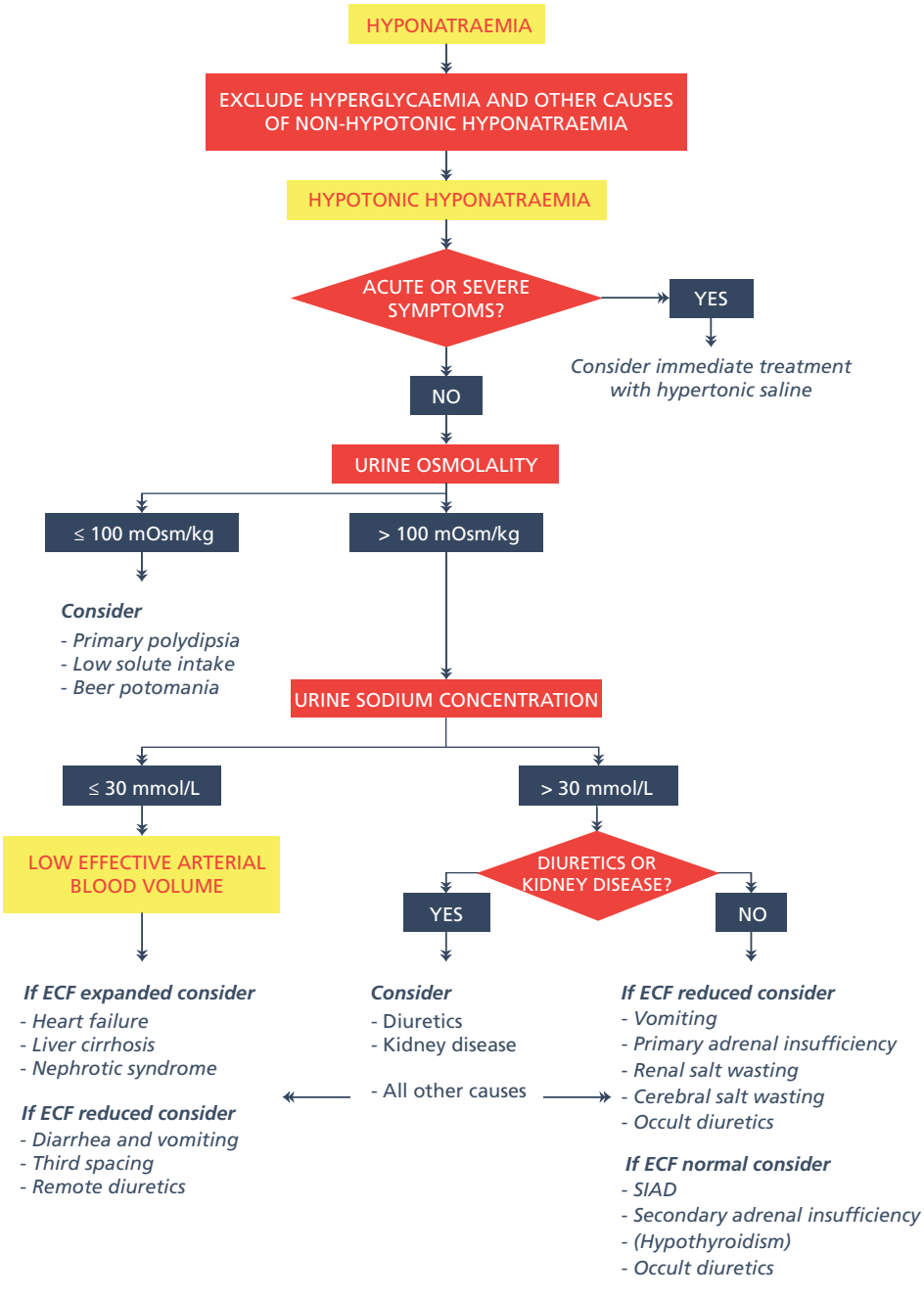

Figure 18.1 European Best Renal Practice algorithm for the diagnosis of hyponatraemia.

administered orally alongside slow sodium tablets may treat SIADH. Furosemide reduces sodium chloride reabsorption in the medullary aspect of the loop of Henle. The reduced concentration of solutes in the interstitium of the medulla impairs water reabsorption (and increases water excretion).

Severe hyponatraemia

Patients with severe hyponatraemia (<115 mmol/L) presenting with seizures and a reduced conscious level require hypertonic 3% saline (513 mmol/L) solution. The increase in plasma sodium concentration

following hypertonic saline is due to the water loss induced by excretion of the extra sodium. It is now recommended that, rather than calculating the rate of hypertonic saline infusion (which is unreliable due to the need to estimate total body water), a simplified regimen is administered. An IV infusion of 150 mL 3% hypertonic saline over 20 minutes should be given immediately, then the serum sodium concentration checked (after 20 minutes) while repeating an infusion of 150 mL 3% hypertonic saline for the next 20 minutes. These steps can be repeated twice or until a target of 5 mmol/L increase in serum sodium concentration is achieved.

Hypertonic saline must be given with extreme caution as rapid correction can result in central pontine myelinolysis (see above). The change in sodium concentration must not exceed 10 mmol/L in the first 24 hours, and 18 mmol/L in the first 48 hours. Serum sodium concentration should be increased by 1–2 mmol/L per hour in the first 3 hours. The rate of correction may then be slowed to 0.5 mmol/L per hour. Plasma sodium should be monitored regularly (initially every 2–4 hours).

A loop diuretic (e.g. furosemide 20 mg intravenously) may be beneficial as it inhibits sodium chloride reabsorption in the thick ascending limb of the loop of Henle and interferes with the countercurrent concentrating mechanism.

Effect of potassium

It is important to remember that giving potassium can raise the plasma sodium concentration in a hyponatraemic subject. This is because most of the given potassium goes into the cells, and to maintain electroneutrality sodium moves out of the cells. In addition, water moves into the cells secondary to a movement of chloride ions into the cells with potassium. This is clinically important in patients with severe diuretic- or vomiting-induced hyponatraemia who are also hypokalaemic.

The increase in sodium concentration caused by concurrent potassium administration should be taken into account to avoid an over-rapid correction of hyponatraemia.

Novel therapies

Vasopressin receptor antagonists cause a selective water diuresis without affecting sodium and potassium excretion. Tolvaptan (an oral selective V_2 receptor antagonist) has been used in clinical trials for the management of patients with euvolaemic hyponatraemia (mostly due to SIADH) and hypervolaemic hyponatraemia (e.g. heart failure, cirrhosis). Vasopressin receptor antagonists are likely to be useful in the management of moderate chronic hyponatraemia if water restriction is insufficient.

KEY POINTS

- Most cases of hyponatraemia are caused by an increase in the extracellular water due to increased plasma ADH levels.
- Assessing the volume status of the patient is essential in determining the aetiology of hyponatraemia.
- The clinical manifestations of hyponatraemia are more prominent when it has occurred acutely (i.e. within a period of hours).
- SIADH is not a diagnosis, and the underlying cause must be investigated.
- Correction of sodium concentration must not exceed 10 mmol/L in the first 24 hours.
- SIADH can be diagnosed in euvolaemic patients in whom hypothyroidism and adrenal insufficiency have been excluded and who have low plasma osmolality and high urine osmolality.
- Treatment of hyponatraemia generally includes correction of the underlying cause, volume replacement in hypovolaemic patients, and fluid restriction in euvolaemic and hypervolaemic patients.

19

Male reproductive physiology and hypogonadism

Testicular anatomy and physiology

Anatomy

The testes contain (Figure 19.1):

- seminiferous tubules composed of *Sertoli cells* and *germ cells*
- an interstitium containing *Leydig cells* that produce testosterone.

Physiology of the hypothalamic–pituitary–testicular axis

Pulsatile gonadotrophin-releasing hormone

Hypothalamic neurones (in the preoptic area) secrete gonadotrophin-releasing hormone (GnRH) in a *pulsatile* fashion into the hypophyseal portal system (see Chapter 11). Pulsatile GnRH in turn stimulates the pulsatile release of *luteinising hormone* (LH) and *follicle-stimulating hormone* (FSH) from the anterior pituitary (Figure 19.2).

GnRH binds to receptors on the plasma membrane of pituitary gonadotrophs and stimulates LH and FSH release by a calcium-dependent mechanism that may involve diacylglycerol.

LH and FSH

Luteinising hormone and FSH are composed of two glycoprotein chains. They interact with cell membrane receptors and stimulate adenylate cyclase. LH stimulates the production of testosterone by Leydig cells. It stimulates testosterone synthesis by acting on the steroidogenic acute regulatory protein, which delivers cholesterol to the inner mitochondrial membrane, where it is converted to pregnenolone (the rate-limiting reaction). Sperm are produced under stimulation from testosterone and FSH (Figure 19.2).

LH secretion is inhibited by testosterone, which acts on the hypothalamus (to slow the hypothalamic pulse generator) and directly on the anterior pituitary. Some of the effects of testosterone are mediated by oestradiol (produced from the aromatization of testosterone).

FSH secretion is inhibited by inhibin B (a glycoprotein consisting of two subunits, produced by Sertoli cells) as well as testosterone and oestradiol (produced from the aromatisation of testosterone).

In addition, several other hormones, neurotransmitters, and cytokines modulate GnRH secretion. Testosterone levels may be reduced in acute and chronic illnesses (due to increasing corticotrophin-releasing hormone and cytokines) and fasting (due to lower levels of leptin, which is required for normal pulse generator activity).

Free and total testosterone

Only ~2% of plasma testosterone is free (unbound). Of the rest, 44% of testosterone is bound to a hepatic

Endocrinology and Diabetes: Lecture Notes, Second Edition. Amir H. Sam, Karim Meeran and Neil Hill.
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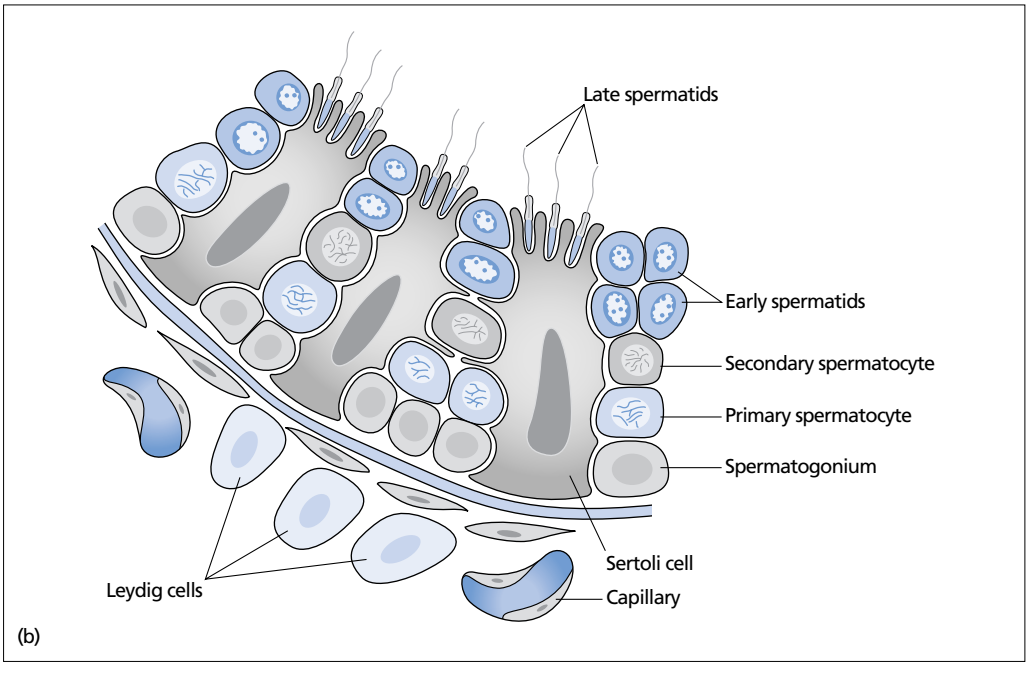

Figure 19.1 (a) A section of testis showing several seminiferous tubules containing Sertoli and spermatogenic cells. Leydig cells are in the interstitial space between the adjacent seminiferous tubules. (b) Part of a seminiferous tubule and interstitial space as indicated by the boxed area in (a). Spermatogonia differentiate into spermatocytes and spermatids as they move towards the lumen of the seminiferous tubules. Tight junctions between the Sertoli cells separate the tissue into two functional compartments.

glycoprotein called *sex hormone-binding globulin* (SHBG), and 54% of testosterone is loosely bound to albumin. Almost all of the albumin-bound testosterone is available for tissue uptake. Therefore, bioavailable testosterone in plasma is the sum of free (2%) plus albumin-bound hormone (54%).

The serum SHBG levels may be increased and decreased by a number of factors (Box 19.1). However, changes in the SHBG levels do not affect free androgen levels. This is because the hypothalamic–pituitary system responds to acute changes in the concentrations of bioavailable testosterone (caused by changes in SHBG levels) by altering testosterone synthesis.

Mechanism of action of testosterone

Testosterone is converted to active metabolites *5-alpha-dihydrotestosterone* (by 5-alpha-reductase)

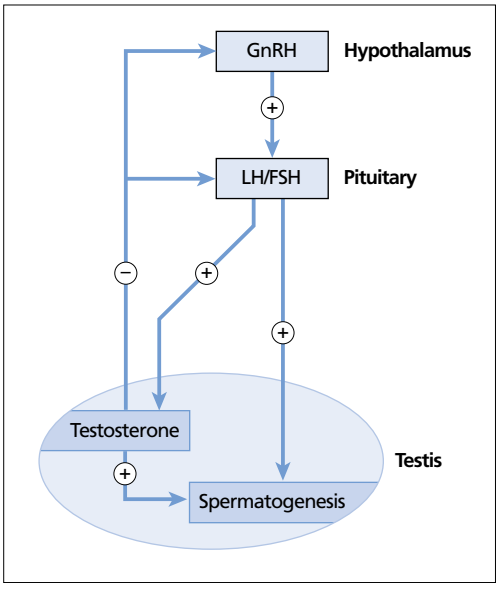

Figure 19.2 Pulsatile gonadotrophin-releasing hormone (GnRH) release from the hypothalamus stimulates luteinising hormone (LH) and follicle-stimulating hormone (FSH) release from the anterior pituitary. LH stimulates testosterone synthesis by the Leydig cells. Sperm are produced under stimulation by testosterone and FSH. LH secretion is inhibited by testosterone, which acts on the hypothalamus and directly on the anterior pituitary.

Box 19.1 Causes of altered sex hormone-binding globulin (SHBG)

Increased SHBG
Ageing
Antiepileptic agents
Liver disease
Oestrogens
Thyrotoxicosis
Growth hormone deficiency

Decreased SHBG
Diabetes mellitus
Obesity
Corticosteroids, anabolic steroids
Hypothyroidism
Acromegaly

and *17-beta-oestradiol* (by aromatase). Testosterone and its metabolites bind to intracellular receptors, which in turn bind to specific DNA sequences ('response elements') and regulate the transcription of certain genes.

Physiological actions of testosterone

The physiological actions of testosterone are the result of the combined effects of testosterone itself plus its active metabolites. The major functions of androgens in males include:

- the regulation of gonadotrophin secretion from the hypothalamic–pituitary system
- the initiation and maintenance of spermatogenesis
- the formation of the male genital tract during embryogenesis
- the development of male secondary sexual characteristics and sexual potency at puberty, and their maintenance thereafter.

Male hypogonadism

Male hypogonadism is a syndrome of decreased testosterone production, sperm production, or both.

Aetiology

Male hypogonadism may result from disease of the testes (*primary hypogonadism*) or disease of the pituitary or hypothalamus (*secondary hypogonadism*).

Known causes of hypogonadism are summarised in Box 19.2. However, many cases of hypogonadism remain unexplained (idiopathic).

Primary hypogonadism

In primary hypogonadism, reduced testosterone levels result in elevated gonadotrophin levels (due to a reduced negative feedback effect of testosterone on the hypothalamus and pituitary). Thus, primary hypogonadism is also known as hypergonadotrophic hypogonadism. Primary hypogonadism may be congenital or acquired.

Congenital causes

Congenital primary hypogonadism may be due to Klinefelter syndrome, other chromosomal abnormalities, or cryptorchidism.

Klinefelter syndrome is the most common congenital cause of primary hypogonadism and occurs in about 1 in 500–1000 live male births. The majority (~75%) are undiagnosed and most present in adulthood. It is caused by one or more extra X chromosomes in men, resulting in damaged seminiferous tubules and Leydig cells. The greater the number of extra X chromosomes, the greater the phenotypic

Box 19.2 Causes of male hypogonadism

Primary

Klinefelter' syndrome and other chromosomal abnormalities
Cryptorchidism
Infections (e.g. mumps orchitis)
Testicular trauma or torsion
Drugs, e.g. chemotherapy, ketoconazole, sulfasalazine, excess alcohol
Radiotherapy
Autoimmune damage
Chronic illnesses (e.g. renal failure, cirrhosis, diabetes, HIV)
Rare causes: mutations in genes encoding enzymes necessary for testosterone synthesis, mutations in the gene encoding the FSH receptor, myotonic dystrophy

Secondary

GnRH deficiency

Kallmann' syndrome (associated with anosmia), idiopathic

Pituitary or hypothalamic disease

Pituitary adenomas, cysts, craniopharyngiomas, other tumours, surgery, head trauma, infections, infarction, infiltrative disorders, e.g. haemochromatosis

Suppression of gonadotrophins

Chronic systemic illness, diabetes mellitus, hyperprolactinaemia, androgen excess (e.g. anabolic steroids), cortisol excess (exogenous or Cushing syndrome), oestrogen excess (e.g. produced by a testicular tumour), gonadotrophin-releasing hormone analogues, opiates

Rare causes: Laurence–Moon–Biedl syndrome, Prader–Willi syndrome, mutations in the genes encoding GPR54 (the kisspeptin receptor), gonadotrophin-releasing hormone receptor, LH, FSH, leptin, leptin receptor, DAX1 (associated with congenital adrenal hypoplasia), LHX3, LHX4, HESX1, and PROP1 (transcription factors necessary for early differentiation of the pituitary).

consequences. The most common genotype is 47XXY. The 47XXY genotype results from non-disjunction of the sex chromosomes of either parent during meiotic division. 46XY/47XXY mosaicism probably results from non-disjunction during mitotic division after conception.

In addition to features of hypogonadism, patients may have:

- a wide spectrum of cognitive effects which can encompass delayed speech and reading, difficulty with abstract concepts and problem solving, and an inability to apply consequences from past actions
- behavioural problems, including socially inappropriate interactions, a 'short fuse', and more mental ill health
- a predisposition to develop chronic bronchitis, bronchiectasis and emphysema, germ cell tumours (e.g. involving the mediastinum), breast cancer (a 20-fold increased risk), possibly non-Hodgkin lymphoma, varicose veins, leg ulcers, and diabetes mellitus.

A large number of *other chromosomal abnormalities* have been reported that result in testicular hypofunction. The 46XY/X0 karyotype results in a syndrome characterised by short stature and features typical of Turner syndrome (see Chapter 21). Gonadectomy should be performed in a patient who has both a streak gonad and a dysgenetic testis, as the risk of gonadoblastoma is about 20%. Up to 20% of men with azoospermia or severe oligospermia have microdeletions in specific regions of the long arm of the Y chromosome.

Cryptorchidism refers to unilateral or bilateral (10%) undescended testes (in the abdominal cavity or inguinal canal) that cannot be manipulated manually into the scrotum by the age of 1 year. The risk of testicular cancer is increased (3–14-fold).

Acquired causes

Acquired primary hypogonadism may be due to infections (e.g. mumps orchitis), testicular trauma or torsion, chemotherapy, radiotherapy, autoimmune damage, or chronic illnesses (e.g. chronic obstructive pulmonary disease, congestive cardiac failure, Crohn's disease, coeliac disease, chronic liver disease, chronic kidney disease, chronic anaemia, rheumatoid arthritis, AIDS).

Secondary hypogonadism

Secondary (or hypogonadotrophic) hypogonadism is due to impaired secretion of hypothalamic GnRH or pituitary gonadotrophins. Secondary hypogonadism may be congenital or acquired.

Congenital GnRH deficiency

Congenital secondary hypogonadism may be associated with anosmia in *Kallmann syndrome*. The incidence of Kallmann syndrome is 1 in 10000 males. Kallmann syndrome is usually X-linked (although autosomal dominant transmission can also occur). It may be due to sporadic or familial mutations of several genes (e.g. *KAL1* and *FGFR1* [*KAL2*], *PROK2*, *PROKR-2*)

encoding the cell surface adhesion molecules or their receptors required for the migration of GnRH-secreting neurones into the hypothalamus. Kallmann syndrome may also be associated with red–green colour blindness, midline facial abnormalities (e.g. cleft palate), urogenital tract abnormalities, synkinesis (mirror movements of the hands) and hearing loss.

Secondary hypogonadism may very rarely be caused by a number of mutations in the genes involved in the regulation of the hypothalamic–pituitary–gonadal axis (Box 19.2). Congenital secondary hypogonadism may be associated with learning difficulties and obesity in Prader–Willi syndrome (caused by deletion of part of paternally derived chromosome 15q) and Laurence–Moon–Biedl syndrome (also associated with polydactyly and retinitis pigmentosa).

Pituitary or hypothalamic disease

Secondary hypogonadism may be caused by any pituitary or hypothalamic disease such as pituitary adenoma, craniopharyngioma, pituitary surgery, infarction, infection and infiltrative disorders such as haemochromatosis, sarcoidosis, histiocytosis, tuberculosis, and fungal infections.

Suppression of gonadotrophins

Gonadotrophin secretion may be suppressed by chronic systemic illness, diabetes mellitus, hyperprolactinaemia, androgen excess (e.g. anabolic steroids, congenital adrenal hyperplasia, testicular/adrenal tumours), cortisol excess (exogenous or Cushing syndrome), oestrogen excess (e.g. produced by a testicular tumour), chronic opiate administration and GnRH analogues.

Clinical presentations

The clinical presentations depend on whether the onset of hypogonadism is before or after puberty.

Hypogonadism occurring before the onset of puberty results in delayed puberty (see Chapter 29). Hypogonadism occurring after the onset of puberty may present with:

- fatigue, reduced energy and lowered physical strength
- low mood, irritability and poor concentration
- reduced libido and/or sexual function, loss of spontaneous morning erections, infertility
- osteoporosis and fragility fractures.

The major action of testosterone on male sexuality is on libido. Testosterone deficiency accounts for fewer than 5% of cases of erectile dysfunction. Erectile responses to erotic stimuli are usually normal in hypogonadal men. Erectile dysfunction is usually caused by microvascular or macrovascular disease or psychosocial issues. However, spontaneous nocturnal or morning erections *are* testosterone dependent and are reduced in untreated hypogonadal men.

Patients should be asked about the features of the possible causes of hypogonadism (Box 19.2).

The clinical signs of hypogonadism are summarised in Box 19.3.

Primary hypogonadism is more likely to be associated with gynaecomastia, probably due to the stimulation of testicular aromatase activity by the increased serum FSH and LH, resulting in increased conversion of testosterone to oestradiol and also increased testicular secretion of oestradiol relative to testosterone.

Box 19.3 Clinical signs of hypogonadism

Hypogonadism occurring before onset of puberty

Testes <5 mL
Penis <5 cm long
Reduced pubic, axillary, and facial hair
Gynaecomastia
Eunuchoid proportions: arm span > height, lower segment > upper segment (due to delayed fusion of the epiphyses and continued growth of the long bones)
Features of the underlying cause, e.g. cryptorchidism, anosmia (Kallmann syndrome)

Hypogonadism occurring after puberty

Testes soft, <15 mL
Penis normal length (>5 cm) and width (>3 cm)
Reduced pubic, axillary and facial hair
Gynaecomastia
Normal skeletal proportions
Fine perioral wrinkles
Features of the underlying cause, e.g. visual field defects due to a pituitary tumour, signs of systemic/chronic illness

Investigations

The diagnosis of hypogonadism can be confirmed by finding low serum testosterone and/or decreased sperm in the semen.

Serum testosterone levels

Measurement of the serum total (free plus protein-bound) testosterone concentration is usually an

accurate reflection of testosterone secretion. Testosterone exhibits a diurnal variation (particularly in young men), with maximum levels at about 8 a.m. and lower levels in the evening. Thus testosterone levels should be measured at 8 a.m. If a single testosterone value is low or borderline low, it should be repeated once or twice, as up to 40% of abnormal values are normal on repeat testing. Testosterone levels also fall with age, although age-specific reference ranges are not used in routine clinical practice.

Measurement of the serum free testosterone concentration by equilibrium dialysis is usually not necessary (unless it is suspected that an abnormality in testosterone binding to SHBG co-exists with hypogonadism, e.g. in obesity). However, free and bioavailable testosterone levels (free testosterone plus testosterone bound weakly to albumin) can be calculated from the total testosterone, SHBG, and albumin levels.

LH and FSH levels

In a hypogonadal patient (with low serum testosterone and/or a subnormal sperm count):

- high LH and FSH concentrations indicate testicular damage (primary hypogonadism)
- low or inappropriately normal LH and FSH levels suggest pituitary or hypothalamic disease (secondary hypogonadism).

Semen Analysis

Semen analysis for sperm number and motility should be performed in men presenting with infertility. (Healthy men produce >40 million sperm per ejaculate; >50% are motile and >50% have normal morphology.) Four or more abnormal analyses over several months are necessary to indicate an abnormality that is likely to be of clinical importance.

Follow-up of initial tests

Men with primary hypogonadism should have a peripheral leucocyte *karyotype* to determine whether Klinefelter syndrome is present.

Men with secondary hypogonadism should have basal pituitary function tests: 8–9 a.m. cortisol, free thyroxine and thyroid-stimulating hormone, and prolactin. Transferrin saturation and ferritin levels should be measured if hereditary haemochromatosis is suspected.

Magnetic resonance imaging (MRI) of the hypothalamic–pituitary area should be performed if the patient has other pituitary hormonal abnormalities, headache, or visual field defects. If there is no other evidence of pituitary/hypothalamic disease, MRI is warranted in young men (<40 years old) if the confirmed testosterone value is less than 9 nmol/L. However, in elderly men (>60 years), a total testosterone value of below 7 nmol/L is necessary to warrant an MRI as the serum testosterone level decreases with increasing age.

Treatment

Treatment should be directed at any underlying disorders. The aim of therapy is to relieve the symptoms and preserve bone density.

Boys who have not gone through puberty are started on low doses of testosterone, which are gradually increased (see Chapter 29).

Primary hypogonadism

In symptomatic men with a total testosterone of consistently less than 8 nmol/L, testosterone replacement therapy may be started if there are no contraindications (Box 19.4). Those with testosterone levels of 8–10 nmol/L require careful individual evaluation. The borderline low levels of testosterone commonly seen in ageing men are generally compatible with adequate sexual function.

Box 19.4 Testosterone replacement therapy: side-effects and contraindications

Side-effects

Acne on the upper trunk, particularly in younger patients
Prostate: enlargement (obstructive symptoms), stimulation of growth in previously undiagnosed tumours
Polycythaemia
Gynaecomastia (develops during commencement of therapy, resolves with continued use)
Fluid retention (mild)
Sleep apnoea
Other: mood fluctuations and sexually aggressive behaviour with supraphysiological levels
Side-effects of the particular route of administration

Contraindications

Prostate cancer or severe symptomatic benign prostatic hypertrophy
Polycythaemia (haematocrit >0.54)
Breast carcinoma
Sleep apnoea
Conditions in which fluid retention may be harmful, e.g. congestive cardiac failure

Testosterone preparations

A number of different preparations are available for testosterone replacement therapy. The choice of preparation depends on local availability and patient preference.

Testosterone gel is applied on the skin of the shoulder and upper arm. When applied to the skin in doses of 50–100 mg once a day, the serum testosterone levels reach the normal male range within a month and remain steady throughout 24 hours. The gel has several advantages, including self-administration, avoidance of painful injections and stable pharmacokinetics. It dries quickly but could be transferred to the partner through skin contact. Patients should not shower for 6 hours.

Intramuscular testosterone (e.g. Sustanon®: mixed testosterone esters) may be given at a dose of 250 mg every 2–3 weeks. Disadvantages include pain at the injection site, fluctuating plasma testosterone levels that may lead to mood swings, hypersexuality, aggressiveness and polycythaemia caused by repetitive supraphysiological testosterone levels occurring after each injection. Nebido®, a depot preparation (1 g testosterone undecanoate in 4 mL castor oil), maintains stable physiological testosterone levels for about 12 weeks. The second dose is administered after 6 weeks to achieve rapid steady-state levels, and thereafter injections are given every 12 weeks.

Other preparations include testosterone patches, which commonly cause local skin irritation, and oral testosterone undecanoate, which has limited efficacy due to poor and variable bioavailability, a short half-life requiring frequent administration, and risk of hepatic injury.

The side-effects of testosterone replacement therapy and its contraindications are summarised in Box 19.4.

Men who desire fertility

Assisted reproductive techniques may be used for men with oligospermia and azoospermia. Intrauterine insemination may be used in couples with mild male infertility. *in vitro* fertilisation is used for the treatment of male infertility in patients with moderate oligospermia.

Intracytoplasmic sperm injection (ICSI) can be used for men with very severe oligospermia and even azoospermia. A single spermatozoon is directly injected into the cytoplasm of a human oocyte (usually obtained from follicles produced under controlled ovarian hyperstimulation). When the ejaculate does not contain any sperm but there are germ cells in the testes, ICSI may be performed with spermatozoa isolated from testicular biopsies or fine needle aspirates.

In men presenting with infertility, 30–40% of cases are due to primary hypogonadism and 1–2% are due to secondary hypogonadism (see below). A total of 10–20% are secondary to post-testicular defects (disorders of sperm transport), and 40–50% are non-classifiable.

Secondary hypogonadism

The underlying cause should be treated if possible. For example, patients with prolactinomas are treated with dopamine agonists. Normal spermatogenesis takes 3 months. Therefore, restoration of a normal sperm count usually does not occur for 3–6 months after the serum prolactin and testosterone levels have normalised.

Men with secondary hypogonadism which does not or cannot respond to treatment of the underlying cause who do not desire fertility should receive testosterone replacement therapy if there are no contraindications (see above).

Men who desire fertility

Men who have secondary hypogonadism due to hypothalamic or pituitary diseases can be treated with gonadotrophins. However, only men with secondary hypogonadism due to hypothalamic disease can be treated with pulsatile GnRH. Both regimens may take up to 2 years to achieve adequate spermatogenesis. Once they are effective, storing several samples of frozen sperm for any future attempts at pregnancy should be considered. Testosterone treatment should be avoided as it may inhibit sperm production.

With *gonadotrophin replacement*, initially human chorionic gonadotrophin (hCG) injections are administered (1000–2000 IU subcutaneously or intramuscularly, three times a week). hCG has the biological activity of LH. The response to therapy is measured on semen analysis and may take 6–12 months. If adequate spermatogenesis is not achieved, human menopausal gonadotrophin or recombinant FSH is added (37.5–75 IU three times a week). It may take 12 months or more for a response to be seen.

Pulsatile GnRH therapy may be given subcutaneously via a catheter attached to a mini-pump. This regimen is suitable in men with a hypothalamic defect with normal pituitary gonadotrophin function.

Follow-up and monitoring

Clinical assessment

Patients should be asked about improvements in symptoms (e.g. libido, erectile/sexual function, energy, stamina, mood and cognition, hair pattern) and symptoms of possible treatment complications – mood swings, features of sleep apnoea (daytime

sleepiness and apnoea witnessed during sleep by a partner) and prostate-related symptoms – every 6–12 months. There is no evidence that testosterone replacement achieving serum concentrations in the physiological range causes prostate cancer, but testosterone treatment is contraindicated in hormonally sensitive cancers (e.g. breast, prostate).

Patients should be assessed for weight gain, peripheral oedema and gynaecomastia at baseline and yearly during follow-up.

For follow-up of patients with secondary hypogonadism due to pituitary disease and hyperprolactinaemia, see Chapters 12 and 14.

Laboratory tests

- *Haemoglobin/haematocrit* should be measured at baseline, after 3 and 6 months, and yearly thereafter to detect polycythaemia.
- *Prostate-specific antigen* (PSA) should be measured at baseline, after 3 and 6 months and yearly thereafter.
- *Liver function tests* and *fasting lipid profile* should be measured before starting therapy and then yearly.
- *Testosterone levels* should be monitored. The timing of testosterone measurement depends on the preparation used. The aim is to maintain testosterone levels in the mid-normal range: (15–20 nmol/L). If it is above 15 nmol/L or below 8 nmol/L, adjust the dosing interval, dose or both.
  - Testosterone gel: levels can be measured at any time after the patient has received treatment for at least 1 week.
  - Testosterone undecanoate injections: measure nadir testosterone levels before each administration.
  - Mixed testosterone ester injections: measure testosterone levels mid-way between injections.

Referral to urologists for further investigation should be considered if patients complain of increasing obstructive symptoms, if digital rectal examination is abnormal or if PSA is increased (>4 ng/mL or an increase of ≥1.0 ng/mL within any 12-month period). PSA measurement should be repeated in patients with a PSA increase of 0.7–0.9 ng/mL.

A sleep study should be performed if obstructive sleep apnoea is clinically suspected. For selected men, bone mineral density monitoring during therapy might be helpful to confirm end-organ effects.

KEY POINTS

- LH stimulates testosterone synthesis by the Leydig cells. Sperm are produced under stimulation from testosterone and FSH.
- Male hypogonadism may result from disease of the testes (primary hypogonadism) or disease of the pituitary or hypothalamus (secondary hypogonadism).
- Klinefelter syndrome is the most common congenital cause of primary hypogonadism. It is caused by one or more extra X chromosomes.
- The clinical presentation depends on whether the onset of hypogonadism is before or after puberty. Hypogonadism occurring before the onset of puberty results in delayed puberty.
- The investigation of patients with hypogonadism should include measurement of serum testosterone, LH, and FSH (high in primary hypogonadism and low or inappropriately normal in secondary hypogonadism), semen analysis, karyotyping in primary hypogonadism (to exclude Klinefelter syndrome), and pituitary function tests and MRI of the hypothalamic–pituitary area in secondary hypogonadism.
- A number of different testosterone preparations are available for testosterone replacement therapy. The choice of preparation depends on local availability and patient preference.

20

Gynaecomastia

Gynaecomastia is a benign proliferation of the glandular tissue of the male breast (Figure 20.1). It is usually bilateral but may be unilateral.

Gynaecomastia must be differentiated from pseudogynaecomastia (due to excessive adipose tissue without glandular proliferation, often seen in obese men) and male breast carcinoma, which is far less common.

Epidemiology

Gynaecomastia is common in infancy, adolescence, and elderly men. A total of 60–90% of infants may have transient gynaecomastia (for 2–3 weeks) due to the high oestrogen levels in pregnancy. The second peak of gynaecomastia occurs during puberty and affects about 65% of boys. Almost all cases regress spontaneously. The third peak of gynaecomastia occurs in 25–65% of middle-aged and elderly men, with the highest prevalence at 50–80 years.

Aetiology

Oestrogens stimulate ductal epithelial growth and proliferation of the periductal fibroblasts.

Conditions (Box 20.1) that cause an increase in the production of oestrogens (and hence their stimulatory effect) and/or a decrease in the production/activity of androgens (and hence their inhibitory effect) result in gynaecomastia.

The factors that define the net oestrogen/androgen balance are:

- the production of oestrogens/androgens or their precursors by the adrenals and testes
- aromatase activity: aromatase is the enzyme that converts androgens to oestrogens in peripheral tissues, for example adipose tissue, liver, skin, muscle, bone, and kidney
- sex hormone-binding globulin (SHBG) levels: SHBG has a higher affinity for androgens than for oestrogens. Thus changes in SHBG levels result in an imbalance in unbound oestrogens and androgens
- the responsiveness of the target cells to androgens and oestrogens.

The histological picture of gynaecomastia changes over time, with early proliferation and inflammation, and later fibrosis.

Box 20.1 summarises the causes of gynaecomastia. During puberty, serum oestradiol rises to adult levels before serum testosterone, and this transient imbalance in oestrogen/testosterone levels may account for pubertal gynaecomastia.

Clinical presentations

Gynaecomastia (enlargement of the glandular tissue) should be differentiated from pseudogynaecomastia (excessive adipose tissue often seen in obese men) and breast cancer.

Ask the patient to lie on his back with his hands behind his head. Place your thumb and forefinger on each side of the breast and slowly bring them together towards the nipple. In gynaecomastia, a rubbery/firm disc of glandular tissue (at least 0.5 cm in diameter) will be felt extending concentrically from the nipple. In pseudogynaecomastia, the fingers will not meet any resistance until they reach the nipple.

Breast cancer tends to be eccentrically positioned (rather than symmetrical to the nipple), tends to be firm to hard in texture, and may be associated with skin dimpling, nipple retraction, discharge, and axillary lymphadenopathy.

A careful history and physical examination are essential in detecting the symptoms and signs of the

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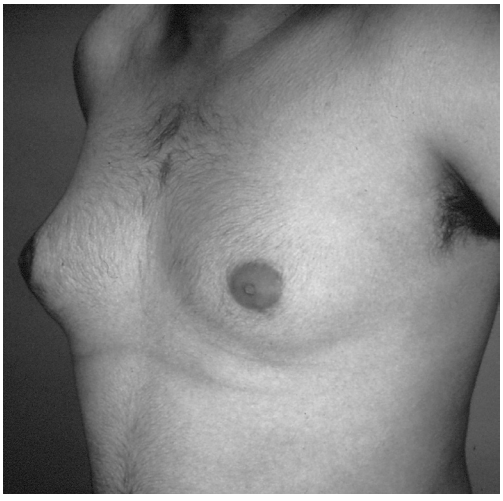

Figure 20.1 Gynaecomastia.

Box 20.1 Causes of gynaecomastia

Physiological
Puberty, persistent pubertal (25% of cases), elderly

Drugs (10–25%)
Oestrogens, antiandrogens, spironolactone (antiandrogenic effects), protease and reverse transcriptase inhibitors, cimetidine, nifedipine, digoxin, herbal products/oils

Hypogonadism (primary 8%, secondary 2%)
Reduced serum testosterone production

Chronic liver disease (8%)
Enhanced aromatisation (many patients are also on spironolactone)

Chronic renal failure (1%)
Reduced serum testosterone due to Leydig cell dysfunction

Thyrotoxicosis (1.5%)
Enhanced aromatisation

Tumours
Testicular germ cell tumours secrete human chorionic gonadotrophin (hCG) resulting in enhanced aromatisation
Testicular Leydig cell tumours secrete increased oestradiol
Other hCG-secreting tumours, e.g. lung, stomach, renal cell and liver
Oestrogen-secreting adrenal tumours.

No detectable abnormality (25%)

Rare causes
Aromatase excess syndrome – rare autosomal dominant disorder of increased aromatase activity
Androgen insensitivity syndrome (testicular feminisation) due to defective/absent androgen receptor in the target tissues. Thus patients are genotypic males but appear to be phenotypic females
Kleinfelter syndrome (47XXY)

underlying cause of gynaecomastia (Box 20.1). Patients should be asked about any of the drugs that can cause gynaecomastia. Look for symptoms and signs of the possible underlying cause, i.e. hypogonadism, hyperthyroidism, chronic liver or chronic renal disease, thyrotoxicosis and testicular or other (hCG- or oestrogen-secreting) tumours.

Investigations

In adolescent boys, gynaecomastia is almost always due to pubertal gynaecomastia and often resolves spontaneously.

Asymptomatic gynaecomastia that is discovered during a physical examination in a patient who does not have one of the possible causative conditions should be re-evaluated in 6 months.

Serum testosterone, luteinising hormone (LH), free thyroxine (T_4), thyroid-stimulating hormone (TSH), oestradiol, and hCG should be measured, particularly if the gynaecomastia is of recent onset or painful (Figure 20.2).

- If *testosterone is low and LH levels are increased*, the diagnosis is primary hypogonadism.
- If *testosterone is low and LH levels are low or inappropriately normal*, the diagnosis is secondary hypogonadism. Serum prolactin should be measured and magnetic resonance imaging (MRI) of the pituitary should be performed.
- If *free T_4 levels are high and TSH is suppressed*, the diagnosis is thyrotoxicosis.
- If the *oestradiol levels are increased and LH levels are low or normal*, testicular ultrasound should be performed to look for a Leydig or Sertoli cell tumour. If the testicular ultrasound is normal, adrenal imaging (CT/MRI) should be performed to look for an adrenal tumour. If the imaging is normal, increased extraglandular aromatase activity is likely.

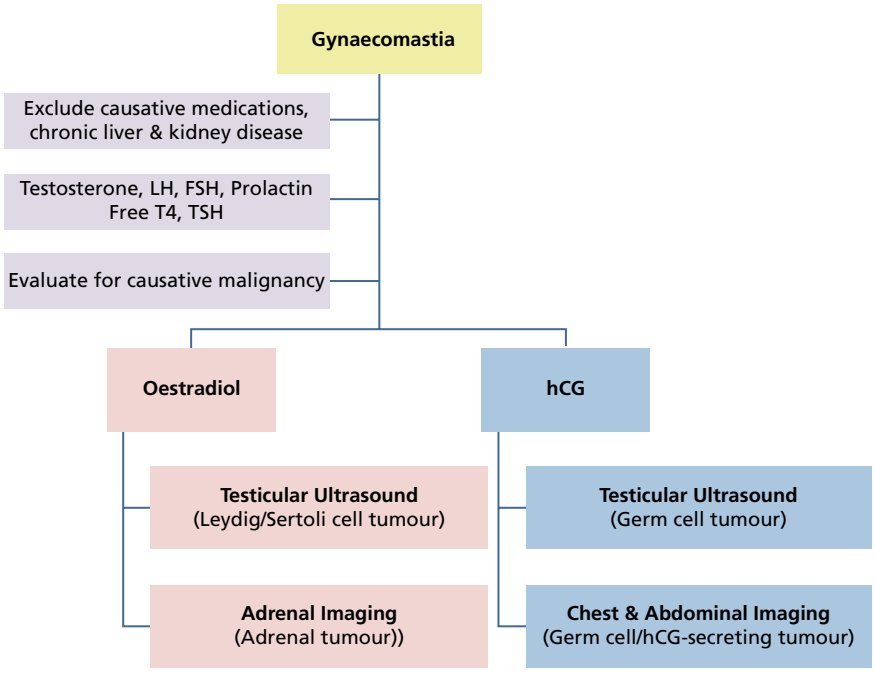

Figure 20.2 Investigation of gynaecomastia. Source: Ali, S. N., et al. 2017/John Wiley & Sons.

- If *hCG is elevated*, a testicular ultrasound scan should be performed to look for a testicular germ cell tumour. If testicular ultrasound is normal, a chest radiograph and abdominal computed tomography (CT) should be done to look for an hCG-secreting tumour.
- If all *tests are normal*, the diagnosis is 'idiopathic gynaecomastia'.

Treatment, follow-up and monitoring

The treatment of gynaecomastia depends on its cause, its severity, the presence of tenderness, and its duration.

Adolescents

Most adolescents with gynaecomastia should be followed up and re-evaluated every 3–6 months. Gynaecomastia usually resolves spontaneously within 6 months to 2 years.

In boys with severe gynaecomastia causing substantial tenderness and/or embarrassment, a 3-month trial of tamoxifen (10 mg twice a day) may be considered. Patients and parents should be told that these drugs are not approved for this purpose.

Adult male

- *Men with an identifiable cause* should be followed up and re-evaluated after the possible cause has been treated.
- *Men with no identifiable cause and tender gynaecomastia persisting for longer than 3 months* may be treated with a 3–6-month trial of tamoxifen (10 mg twice daily). Patients should be told that tamoxifen is not approved for this purpose.
- *Men with persistent gynaecomastia (>1–2 years) who find it psychologically troubling* should be offered surgery, as the breast tissue has probably become fibrotic and medical therapy is unlikely to be effective.
- *Men with advanced prostate cancer who are on antiandrogens* may be given tamoxifen to reduce the risk of developing gynaecomastia. Prophylactic radiation to the chest wall is also an alternative. Tamoxifen may also be tried in men who have already developed gynaecomastia on antiandrogen therapy.

KEY POINTS

- Gynaecomastia is a benign proliferation of the glandular tissue of the male breast.
- Gynaecomastia must be differentiated from pseudogynaecomastia (excessive adipose tissue without glandular proliferation, often seen in obese men) and male breast carcinoma.
- Physiological gynaecomastia is common in infants, adolescents, and elderly men.
- Conditions that cause an increase in the production of oestrogens (and hence their stimulatory effect) and/or a decrease in the production/activity of androgens (and hence their inhibitory effect) result in gynaecomastia.
- Causes of gynaecomastia include hypogonadism, chronic liver disease, chronic kidney disease, thyrotoxicosis, testicular tumours, and other hCG- and oestrogen-secreting tumours.
- Blood tests in patients with gynaecomastia include serum hCG, LH, testosterone, oestradiol, free T_4, and TSH.
- Patients with increased serum hCG or oestradiol require a testicular ultrasound. If this is normal, further imaging is required (chest radiograph and abdominal CT).

21

Female reproductive physiology, amenorrhoea, and premature ovarian insufficiency

The menstrual cycle

The menstrual cycle is divided into two phases.

- The *follicular phase* starts with the onset of menses and ends on the day of the luteinising hormone (LH) surge.
- The *luteal phase* begins on the day of the LH surge and ends at the onset of the next menses.

The average adult menstrual cycle lasts about 28 days, with about 14 days in the follicular phase and about 14 days in the luteal phase. The first day of the cycle is the first day of menses. There is significantly more cycle variability for the first 5–7 years after menarche and for the last 10 years before menopause. The longer menstrual cycles are usually associated with anovulation. There is relatively less cycle variability between the ages of 20 and 40 years. With each normal menstrual cycle, a single mature oocyte is released from a pool of hundreds of thousands of primordial oocytes.

During the early follicular phase, the serum oestradiol and progesterone levels are low (Figure 21.1). The reduced negative feedback effects of oestradiol, progesterone and probably inhibin A (produced by the corpus luteum of the previous cycle) result in increased *gonadotrophin-releasing hormone* (GnRH) pulse frequency, which in turn increases serum *follicle-stimulating hormone* (FSH) levels and *LH* pulse frequency.

The increase in FSH stimulates the recruitment and growth of a cohort of *ovarian follicle*s. The ovarian follicles consist of oocytes surrounded by granulosa cells and theca cells (Figure 21.2a). FSH stimulates the enzyme aromatase (in the granulosa cells of the dominant follicle), which converts androgens (synthesised in the theca cells) to oestrogens (Figure 21.2b).

The increase in oestradiol production initially suppresses serum FSH and LH levels (negative feedback effect on hypothalamic GnRH and pituitary gonadotrophins). Serum inhibin B secreted by the follicles also plays a role in suppressing FSH.

By the late follicular phase, a single dominant follicle is selected and the rest of the growing follicles undergo atresia. The negative feedback effect of ovarian steroids (particularly oestradiol) switches to a positive feedback effect, resulting in an 'LH surge' and a smaller rise in serum FSH concentration. The positive feedback is associated with an increased frequency of GnRH secretion and enhanced pituitary sensitivity to GnRH. Just before ovulation, oestradiol secretion reaches a peak and then falls.

The LH surge stimulates the release of the dominant oocyte from the follicle at the surface of the ovary within 36 hours. The granulosa cells begin to produce progesterone and develop into the corpus luteum. During the luteal phase, LH secretion decreases. This in turn results in a gradual fall in progesterone and oestradiol production by the corpus luteum. As progesterone and oestrogen levels fall near the end of the

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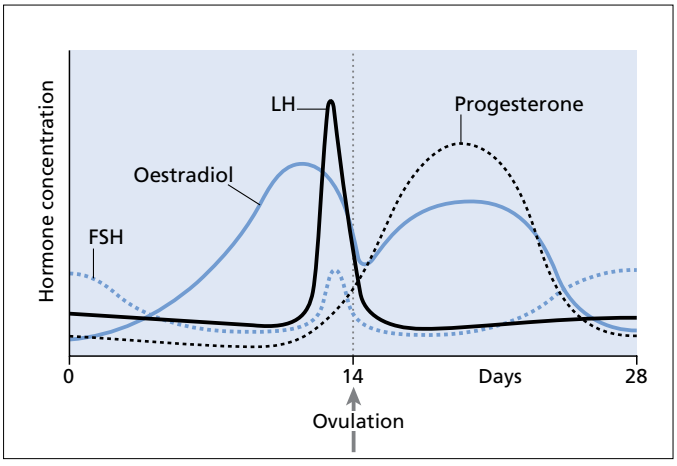

Figure 21.1 Changes in serum luteinising hormone (LH), follicle-stimulating hormone (FSH), oestradiol, and progesterone concentration during the menstrual cycle.

luteal phase, FSH starts to rise to stimulate the development of the next follicle, usually in the contralateral ovary. Inhibin A levels are low in the follicular phase and increased in the luteal phase.

If, however, the oocyte becomes fertilised and is implanted in the endometrium, the early embryo begins to make chorionic gonadotrophin, which maintains the corpus luteum and progesterone production.

Endometrial changes

The endometrium undergoes marked alterations in response to the changing plasma levels of ovarian hormones. The rising serum oestradiol concentrations during the follicular phase of the menstrual cycle result in proliferation of the uterine endometrium and glandular growth. Hence, the follicular phase is also known as the 'proliferative' phase.

After ovulation, increasing serum progesterone secreted by the corpus luteum plays an important role in converting the proliferative endometrium into a secretory lining. Hence, the luteal phase is also known as the 'secretory phase'.

As the corpus luteum function declines and plasma oestrogen and progesterone levels decrease, the arterioles supplying the endometrium undergo vasospasm (caused by locally synthesised prostaglandins), causing ischaemic necrosis, endometrial desquamation and bleeding (the onset of menses at the beginning of the next cycle).

Oestrogens

The principal and most potent oestrogen secreted by the ovary is *oestradiol*. Oestrogens promote the development of secondary sexual characteristics (e.g. breast development), cause uterine growth and play an important role in the regulation of the menstrual cycle (see above).

Oestrogens act by binding to a nuclear receptor (either oestrogen receptor alpha or beta), which binds to specific DNA sequences and regulates the transcription of various genes. There is growing evidence that oestrogen receptors may also alter signal transduction by other mechanisms independent of binding to DNA.

The other oestrogen produced by the ovaries is oestrone, but this is synthesised mainly by the conversion of androstenedione in the peripheral tissues.

Progesterone

Progesterone is the principal hormone secreted by the corpus luteum and is responsible for 'progestational' effects, including induction of secretory activity in the endometrium in preparation for the implantation of a fertilised egg, inhibition of uterine contractions, increased viscosity of cervical mucus, and glandular development of the breasts. Changes in progesterone levels also mediate the changes in basal body temperature during the ovulatory cycle. The basal body temperature increases by 0.3–0.5 °C after ovulation, persists during the luteal phase and returns to normal after the onset of menses.

Other ovarian hormones

Inhibin is a glycoprotein consisting of two disulfide-linked subunits, alpha and beta. The beta subunit can exist in two forms, and therefore there are two forms of inhibin – inhibin A and inhibin B. Inhibin B is secreted by the follicle and inhibits the release of

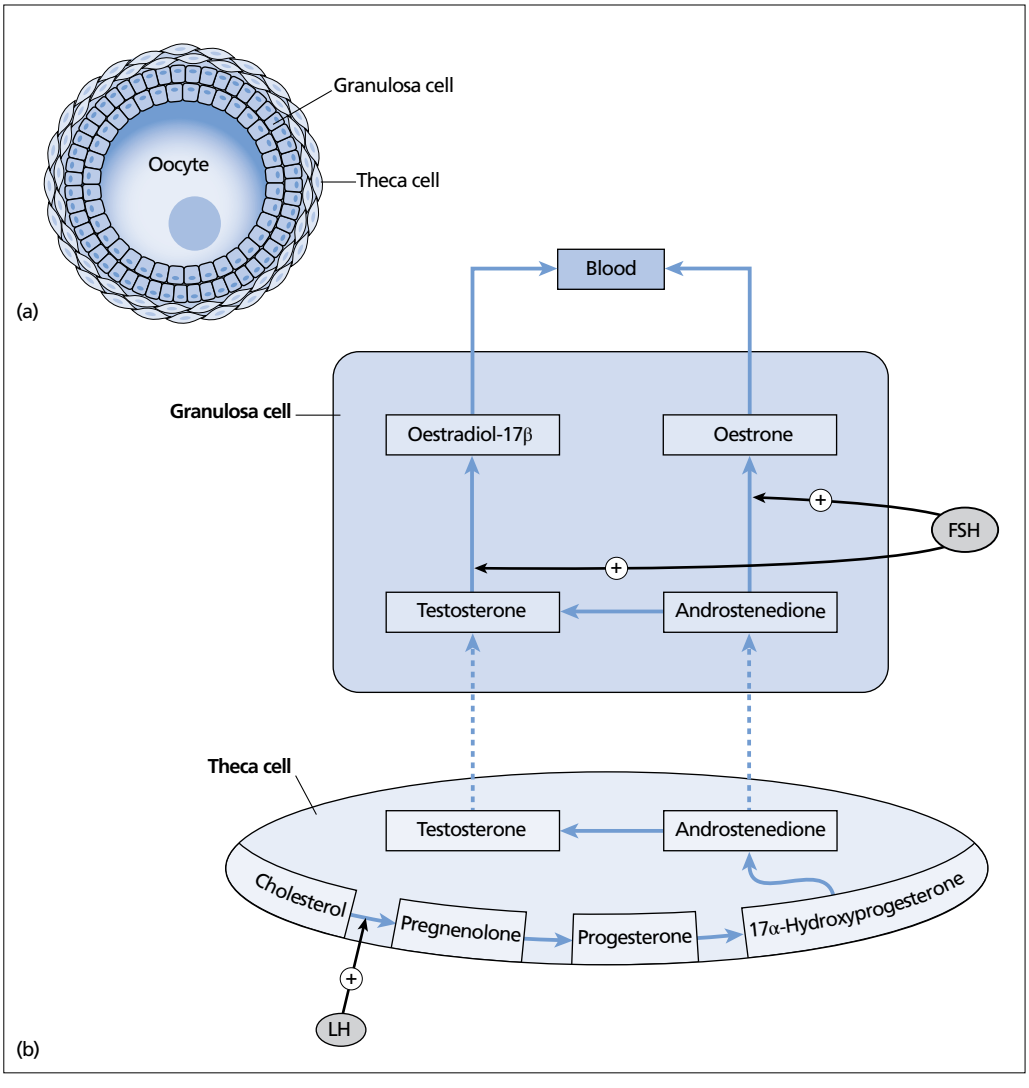

Figure 21.2 (a) Simplified diagram of an ovarian follicle consisting of an oocyte surrounded by granulosa cells and theca cells. (b) Androgens (testosterone and androstenedione) synthesised in the theca cells are converted to oestrogens (oestradiol-17-beta and oestrone) in granulosa cells by the enzyme aromatase, which is stimulated by follicle-stimulating hormone (FSH). Luteinising hormone (LH) stimulates the conversion of cholesterol to pregnenolone.

FSH from the pituitary gland. Inhibin A levels are low in follicular phase and are increased in the luteal phase.

Amenorrhoea

Amenorrhoea is the absence of menstrual periods in a woman during her reproductive years.

Amenorrhoea may be primary or secondary.

- *Primary amenorrhoea* is defined as the absence of menstrual periods by age 14 in a girl without breast development or by age 16 in a girl with breast development.
- *Secondary amenorrhoea* is defined as the absence of menstrual periods for more than 3 months in a woman who has previously had an established menstrual cycle.

Epidemiology

The incidence of primary amenorrhoea is about 0.5–1.2%. The incidence of secondary amenorrhoea is about 5%.

Turner syndrome (see below) occurs in up to 1.5% of conceptions, 10% of spontaneous abortions and 1 in 2000–2500 live births.

Aetiology

Considerable overlap exists between causes of primary and secondary amenorrhoea. All causes of secondary amenorrhoea can also present as primary amenorrhoea.

Amenorrhoea may be due to defects at any level of the reproductive system: hypothalamus, pituitary, ovaries, uterus or vaginal outflow tract. Other causes of menstrual abnormalities include thyroid dysfunction and hyperandrogenism (Box 21.1).

Constitutional delay of puberty is an uncommon cause of delayed puberty and primary amenorrhoea in girls (see Chapter 29). It is difficult to distinguish clinically from congenital GnRH deficiency except that these girls eventually go on to have completely normal pubertal development at a later age.

Box 21.1 Causes of amenorrhoea

Functional hypothalamic amenorrhoea
Stress, weight loss, excessive exercise, eating disorders (anorexia nervosa, bulimia)

Pituitary and hypothalamic tumours and infiltrative lesions
Pituitary adenomas, craniopharyngiomas, haemochromatosis

Hyperprolactinaemia
Prolactinomas or tumours causing pituitary stalk compression

Congenital GnRH deficiency
Kallmann syndrome, idiopathic

Premature ovarian insufficiency (POI)
Chromosomal abnormalities (e.g. Turner syndrome), autoimmune, iatrogenic (surgery, chemotherapy, radiation), *FMR1* gene premutation carriers (CGG repeats of between 55 and 200), galactosaemia

Uterine and vaginal outflow tract disorders
Congenital anatomical abnormalities or acquired (Asherman syndrome)

Thyroid dysfunction
Hypothyroidism or thyrotoxicosis

Hyperandrogenism
Congenital adrenal hyperplasia, polycystic ovary syndrome (PCOS)

Hypothalamic and pituitary disorders

Functional hypothalamic amenorrhoea (Box 21.1) is characterised by abnormal hypothalamic GnRH secretion, resulting in decreased gonadotrophin pulsations.

Pituitary/hypothalamic tumours and other infiltrative disorders (Box 21.1) may cause hypogonadotrophic hypogonadism and amenorrhoea (see Chapter 12).

Hyperprolactinaemia may be due to a prolactin-secreting pituitary adenoma or other tumours causing pituitary stalk compression. This interrupts the transport of dopamine to the anterior pituitary, which normally exerts an inhibitory effect on prolactin secretion. Hyperprolactinaemia can result in hypogonadotrophic hypogonadism by direct inhibition of gonadotrophin release.

Congenital GnRH deficiency is a rare cause of primary amenorrhoea. Patients with congenital GnRH deficiency have apulsatile and prepubertal low serum gonadotrophin levels. Congenital GnRH deficiency associated with anosmia is called Kallmann syndrome. Kallmann syndrome may be due to sporadic or familial mutations of several genes (e.g. *ANOS1*, *CDH7*, *FGF8*, *KAL1*, *FGFR1* [*KAL2*], *PROK2*) required for the migration of GnRH-secreting neurones into the hypothalamus. Other rare causes include Prader–Willi and Laurence–Moon–Biedel syndromes (see Chapter 29). Congenital GnRH deficiency can be inherited as an autosomal dominant, autosomal recessive or X-linked condition. However, more than two-thirds of cases are sporadic.

Premature ovarian insufficiency

Amenorrhoea may be due to POI. POI is defined as primary hypogonadism (lack of folliculogenesis and ovarian oestrogen production) before the age of 40 years. Most cases of POI are idiopathic.

The largest number of patients with primary amenorrhoea and ovarian insufficiency have *Turner syndrome* (45X0) followed by 46XX gonadal dysgenesis and, rarely, 46XY gonadal dysgenesis.

Turner syndrome results from the lack or deletion of part of an X chromosome. The ovaries in Turner syndrome consist of small amounts of connective tissue and no follicles or a few atretic follicles (streak gonads).

The presentation of Turner syndrome is variable and ranges from no pubertal development and

primary amenorrhoea (in most patients) to normal pubertal development and secondary amenorrhoea. Some patients may have no morphological defects. In general, deletions of the long arm of the X chromosome tend to be associated with ovarian insufficiency, and deletions of the short arm of the X chromosome tend to be associated with short stature and somatic anomalies (see 'Clinical presentations' below).

Although X0 is the most frequent abnormality, other X chromosome abnormalities and mosaicism may be present. In subjects with a mosaic karyotype (45X0/46XX), spontaneous menstruation and pregnancy may occur. The presence of a Y chromosome increases the risk of gonadoblastomas, and gonadectomy should be performed.

Acquired ovarian insufficiency may be *iatrogenic* (due to chemotherapy or radiation) or *autoimmune*. Autoimmune ovarian insufficiency is strongly associated with other autoimmune conditions such as adrenal insufficiency and thyroid disease. Around 3% of cases of spontaneous POI develop autoimmune adrenal insufficiency (a 300-fold increase compared with the general population).

Vaginal outflow tract and uterine disorders

Primary amenorrhoea may be due to *Müllerian agenesis* characterised by congenital absence of the vagina with variable uterine development. Patients have normal growth and development of secondary sexual characteristics. This disorder is usually sporadic. However, various genetic aetiologies have been proposed.

The differential diagnosis of Müllerian agenesis includes *androgen insensitivity*, which is caused by mutations in the androgen receptor. The karyotype is XY, but patients are phenotypically female with normal breast tissue.

Primary amenorrhoea may also be due to an imperforate hymen or a transverse vaginal septum between the cervix and hymenal ring, preventing the egress of menses. These patients have normal growth and development of secondary sexual characteristics, and present with abdominal pain due to retained menses. Treatment is surgical.

Secondary amenorrhoea may also be caused by previous pelvic infection, dilation, and curettage or uterine instrumentation resulting in intrauterine scarring and adhesions (Asherman syndrome).

Thyroid dysfunction

Both hypothyroidism and thyrotoxicosis may cause menstrual abnormalities.

Hyperandrogenism

Excessive androgen production is associated with both primary and secondary amenorrhoea and may be due to either ovarian or adrenal sources. The most common cause of primary amenorrhoea with excess androgen production is congenital adrenal hyperplasia (CAH), most commonly 21-hydroxylase deficiency (see Chapter 9).

PCOS classically presents with a peripubertal onset of menstrual disturbances and variable hyperandrogenism. Some patients may present with primary amenorrhoea, but most present with oligomenorrhoea or secondary amenorrhoea (see Chapter 22). PCOS is strongly associated with insulin resistance.

Androgen-secreting ovarian or adrenal tumours should be considered with serum testosterone levels higher than 5 nmol/L and a rapid onset of clinical signs of virilisation and/or hirsutism (see below).

Clinical presentations

After excluding pregnancy, patients should be questioned about the major causes.

- Has there been any recent stress, change in weight, excessive dieting or exercise, or illness that might cause hypothalamic amenorrhoea?
- Is the patient taking any drugs that might be associated with amenorrhoea (e.g. oral contraceptive pills)?
- Are there symptoms of hypothalamic–pituitary disease such as headaches, visual field defects, fatigue or polyuria and polydipsia?
- Is there galactorrhoea (suggestive of hyperprolactinaemia)?
- Are there any symptoms of oestrogen deficiency, for example hot flushes, vaginal dryness, poor sleep, or reduced libido?
- Are there any symptoms of thyrotoxicosis or hypothyroidism?
- Is there a history of hirsutism, acne, or deepening of the voice (suggestive of hyperandrogenism)?
- Is there a history of lower abdominal pain at the time of expected menses in girls with primary amenorrhoea (suggestive of anatomical vaginal outflow tract abnormalities)?
- Is there a history of dilation and curettage, or endometritis that might have caused scarring of the endometrial lining (Asherman syndrome)?

Physical examination should include the following:

- Assessment of pubertal development (Tanner staging).
- Measurements of height and weight, and calculation of body mass index (women with a body mass

index <18.5 kg/m^2 may have functional hypothalamic amenorrhoea).

Signs associated with possible underlying causes include the following.

- *Hypothalamic/pituitary disease*: visual field defects and anosmia (Kallmann syndrome).
- *Ovarian insufficiency:* somatic signs of Turner syndrome (Box 21.2) and signs of other autoimmune diseases, for example hyperpigmentation in Addison disease or vitiligo.
- *Vaginal outflow tract disorders*: evidence of imperforate hymen or haematocolpos in primary amenorrhoea.
- *Thyroid dysfunction*: signs of hypothyroidism or thyrotoxicosis.
- *Hyperandrogenism*: patients with classic CAH may present with ambiguous genitalia at birth.

Signs of hyperandrogenism in patients with non-classic late-onset CAH and PCOS include acne, hirsutism, and alopecia. Patients with androgen-secreting tumours (ovarian or adrenal) may present with progressive virilisation (clitoral enlargement, increased muscle mass, deepening of the voice). Patients with PCOS may have acanthosis nigricans (sign of insulin resistance).

Investigations

Initial tests

A *pregnancy test* (serum or urine human chorionic gonadotrophin tests) should be performed in all women with amenorrhoea.

Box 21.2 Features of Turner syndrome

- Lack of secondary sexual characteristics
- Short stature
- Widely spaced nipples
- Low posterior hairline
- Musculoskeletal: high arched palate, wide carrying angle, short fourth and fifth metacarpals
- Cardiovascular: congenital lymphoedema, aortic dissection, bicuspid aortic valve, coarctation of aorta, hypertension
- Gastrointestinal: angiodysplasia, coeliac disease, abnormal liver function tests
- Renal anomalies: horseshoe kidneys, abnormal vascular supply
- Endocrine: increased risk of hypothyroidism and diabetes mellitus

In patients with primary amenorrhoea, *pelvic imaging* (ultrasound and/or magnetic resonance imaging [MRI]) should be done to demonstrate the presence or absence of the uterus and vagina, and vaginal or cervical outlet obstruction.

Serum FSH levels are elevated in POI (due to reduced inhibition by ovarian oestradiol and inhibin). However, it must be remembered that intermittent follicle development and transient normalisation of serum FSH may occur in ovarian insufficiency. A low or normal serum FSH suggests functional hypothalamic amenorrhoea, congenital GnRH deficiency, or other disorders of the hypothalamic–pituitary axis.

Serum prolactin levels should be measured to exclude hyperprolactinaemia as a cause of secondary hypogonadism. Prolactin levels may be transiently increased by stress or eating. Thus, prolactin should be measured at least twice before MRI of the hypothalamic–pituitary area is performed.

Serum thyroid-stimulating hormone (TSH) and *free thyroxine* (T_4) should be checked as patients with hypothyroidism and thyrotoxicosis can present with menstrual abnormalities.

Serum androgens (dehydroepiandrosterone-sulfate [DHEA-S] and testosterone) should be measured if there are signs of hyperandrogenism.

Follow-up of the initial test

Patients with high FSH levels suggestive of POI should have a *karyotype* to look for chromosomal abnormalities (complete or partial deletion of the X chromosome [Turner syndrome] or the presence of a Y chromosome).

Patients with androgen insensitivity syndrome are phenotypically female but have an XY karyotype and a male-range serum testosterone.

Hypothalamic–pituitary MRI is indicated in women with hypogonadotrophic hypogonadism (low-to-normal FSH) and no clear explanation, and those with visual field defects, headaches, or any other signs of hypothalamic–pituitary dysfunction.

In patients with hyperandrogenism, the differential diagnosis includes PCOS, CAH, and androgen-secreting tumours. CAH is diagnosed with elevated 17-hydroxyprogestrone levels (basal or after adrenocorticotrophic hormone stimulation; see Chapter 9). The diagnostic criteria for PCOS are discussed in Chapter 22. An androgen-secreting tumour of the ovary or adrenal gland should be suspected and further imaging should be done if serum testosterone is >5 nmol/L or DHEA-S is >13.6 µmol/L.

Patients with normal serum prolactin and FSH and a history of uterine instrumentation should be

referred to a gynaecologist to investigate for Asherman syndrome. Cyclic oestrogen–progestin therapy can be given to determine whether a functional endometrium is present. If bleeding does not occur, hysteroscopy or hysterosalpingography should be performed to confirm the diagnosis.

Other investigations

Since pituitary iron deposition can cause secondary hypogonadism, serum transferrin saturation should be measured when hereditary haemochromatosis is suspected. This would apply to patients with an appropriate family history or other suggestive features such as bronzed skin, diabetes mellitus, or unexplained heart or liver disease.

Further investigations should be targeted towards known complications of the disease established as the cause of the ovarian insufficiency.

Around 30% of patients with *Turner syndrome* have congenital heart disease (Box 21.2), and the risk of death from aortic aneurysm is high. Initial evaluation with periodic (3–5 yearly) *echocardiography* and cardiology follow-up are needed. Thirty percent have renal anomalies and a *renal ultrasound scan* should be done at diagnosis. *Thyroid function tests* should be checked every 1–2 years as up to 30% of patients develop thyroid disease. Bone densitometry should be performed every 3–5 years.

Patients with probable autoimmune oophoritis (for which there is no diagnostic measurable autoantibody) have a 10–40% chance of a second autoimmune disease. They should be evaluated for autoimmune adrenal insufficiency (by measuring 21-hydroxylase antibodies and, if positive, an adrenocorticotrophic hormone stimulation test) and for autoimmune thyroid disease (by measuring TSH and free T_4).

In women with unexplained POI, screening for premutation in the *FMR1* gene may be done only after appropriate genetic counselling and informed consent. This is because women with the *FMR1* premutation are at risk of having a child with significant learning difficulties as premutations are unstable when transmitted by females and can expand to a full mutation, causing fragile X syndrome.

Treatment

All women with primary amenorrhoea should be counselled regarding the aetiology and management of amenorrhoea, and their reproductive potential. Treatment of amenorrhoea depends on the underlying cause.

Hypothalamic/pituitary disorders

Functional hypothalamic amenorrhoea can be reversed in most cases by weight gain, reduction in exercise intensity or resolution of illness or stress. Patients may benefit from cognitive behavioural therapy and nutritional or psychological counselling.

Pituitary tumours may require surgery (see Chapter 12). The majority of women with prolactinomas are successfully treated with dopamine agonists (see Chapter 14).

Patients with irreversible gonadotrophin deficiency should receive *oestrogen replacement therapy* and *progesterone* if they have a uterus (see the treatment of ovarian insufficiency below). Hormone replacement therapy is also often started in the setting of hypothalamic dysfunction to optimise bone development.

Women who want to become pregnant may receive either exogenous gonadotrophins or pulsatile GnRH. Pulsatile GnRH is more likely than gonadotrophins to result in the development and ovulation of a single follicle, thereby reducing the risk of ovarian hyperstimulation and multiple gestations.

Kisspeptin (a hormone discovered in 1996) sits at the apex of the hypothalamic–pituitary–gonadal axis. It potently stimulates GnRH secretion and is required for normal pubertal development and fertility (in both sexes), as well as maintenance of regular menstrual cycles in females. Exogenous administration of kisspeptin has been shown to restore LH pulsatility in women with functional hypothalamic amenorrhoea and trigger egg maturation in women undergoing *in vitro* fertilisation treatment for subfertility.

Ovarian insufficiency

In girls with primary amenorrhoea and delayed puberty, oral ethinyloestradiol is started at a low dose (2 µg daily) to promote breast development and adult body habitus. The dose is gradually increased. Cyclical oral progesterone is added with the onset of breakthrough bleeding. Progesterone should not be added until breast growth has plateaued. Premature initiation of progesterone therapy can compromise ultimate breast growth.

Oestrogen–progestin replacement therapy is required for the prevention of osteoporosis and symptomatic control (vasomotor symptoms and vaginal dryness) and possibly the prevention of coronary heart disease.

Adult women with POI may be treated with 100 µg of transdermal oestradiol or 2 mg of oral oestradiol daily. (A dose of 50 µg of transdermal

oestradiol is considered equivalent to 1 mg of oral oestradiol, 5–10 µg of ethinyloestradiol and 0.625 mg of conjugated oestrogens per day.) Sandrena® gel 0.5–2.0 mg applied daily is commonly used as it bypasses the first-pass metabolism and therefore may be associated with reduced risk of venous thromboembolism.

In all women with a uterus, cyclic progesterone must be added to prevent endometrial hyperplasia due to unopposed oestrogen action (e.g. 5–10 mg of medroxyprogesterone or micronised progesterone 100–200 mg for about 10–14 days). Micronised progesterone is metabolically neutral and does not appear to increase the risk of breast cancer or cardiovascular disease so is preferred to medroxyprogesterone.

About 90% of women receiving cyclic regimens have monthly withdrawal bleeding. In the majority of women, the bleeding starts after the last dose of progestin, but some have it while still taking the progestin. Hormone therapy is continued until approximately age 50 years (the average age of normal menopause). At that point, a discussion of potential risks and benefits of postmenopausal hormone therapy should take place (see Chapter 23).

Women who desire fertility can carry a fetus in their uterus following *in vitro* fertilisation of their partner's sperm and donor oocytes.

In patients with Y chromosome material, gonadectomy must be performed to prevent the development of gonadal tumours. In androgen insensitivity syndrome, removal of the gonads may be deferred until immediately after pubertal maturation.

For the treatment of short stature in Turner syndrome, see Chapter 30.

Uterine and vaginal outflow tract disorders

Surgery may be required in patients with congenital anatomical lesions. Surgical correction of a vaginal outlet disorder (e.g. hymenectomy) is essential as soon as the diagnosis is made, to allow passage of menstrual blood. For patients with müllerian duct defects, the creation of a neovagina is usually delayed until the woman is emotionally mature. Asherman syndrome is treated with hysteroscopic lysis of adhesions followed by long-term oestrogen administration to stimulate the regrowth of endometrial tissue.

Women with an absent uterus can have the embryo resulting from *in vitro* fertilisation of their own oocyte transferred to a gestational carrier.

Thyroid dysfunction and hyperandrogenism

For the management of hypothyroidism, thyrotoxicosis, PCOS, and CAH, see the appropriate chapters.

KEY POINTS

- Amenorrhoea may be due to defects at any level of the reproductive system: hypothalamus, pituitary, ovaries, uterus or vaginal outflow tract. Other causes of menstrual abnormalities include thyroid dysfunction and hyperandrogenism.
- The most common cause of primary amenorrhoea is gonadal dysgenesis caused by chromosomal abnormalities, particularly Turner syndrome (due to the lack or deletion of part of an X chromosome).
- Initial investigations in amenorrhoea include a pregnancy test, serum FSH, prolactin, TSH, free T_4 and androgens (DHEA-S and testosterone).
- The underlying cause of amenorrhoea must be identified and treated, for example by weight gain and a reduction in exercise intensity in functional hypothalamic amenorrhoea, and dopamine agonists for prolactinomas.
- Patients with irreversible gonadotrophin deficiency should receive oestrogen replacement therapy (and progesterone if they have a uterus).
- In patients with Y chromosome material, gonadectomy must be performed to prevent the development of gonadal tumours.

22

Polycystic ovary syndrome

The Rotterdam criteria (established in 2003) for the diagnosis of polycystic ovary syndrome (PCOS) include two out of the following three:

- *Oligomenorrhoea/amenorrhoea* (also referred to as oligo-/anovulation)
- *Hyperandrogenism*: clinical (acne, hirsutism, male-pattern hair loss) and/or biochemical (elevated serum androgen levels)
- *Polycystic ovaries on ultrasound* (see 'Investigations' below).

These can be subclassified into four groups, for which the management may differ:

- Oligomenorrhoea/amenorrhoea and hyperandrogenism and polycystic ovaries on ultrasound
- Oligomenorrhoea/amenorrhoea and hyperandrogenism
- Hyperandrogenism and polycystic ovaries on ultrasound
- Oligomenorrhoea/amenorrhoea and polycystic ovaries on ultrasound.

The largest subgroup of these combinations is that of women with oligomenorrhoea/amenorrhoea along with clinical or biochemical hyperandrogenism. The metabolic abnormalities of PCOS are largely absent from those with regular menstrual periods. Those phenotypes that include hyperandrogenism may have higher metabolic risks and poorer fertility outcomes.

PCOS is frequently associated with obesity, *insulin resistance* (impaired glucose intolerance, type 2 diabetes) and dyslipidaemia. Indeed, obesity exacerbates the negative metabolic and reproductive effects of PCOS.

In assessing women with possible PCOS, other causes of menstrual irregularity (e.g. hyperprolactinaemia, thyroid dysfunction) and hyperandrogenism (e.g. congenital adrenal hyperplasia, Cushing syndrome, androgen-secreting tumours) must be excluded.

Epidemiology

Polycystic ovary syndrome is the most common cause of infertility in women. It affects 6–8% of women. The prevalence of PCOS is increased in patients with obesity, insulin resistance, diabetes mellitus, and a positive family history for PCOS among first-degree relatives. PCOS may first become apparent at the onset of puberty. The future risk of developing type 2 diabetes is increased 2–6-fold in women with a history of PCOS, although this risk may be substantially lessened in lean women.

Aetiology

Both environmental factors (e.g. related to diet and development of obesity) and a number of different genetic variants (possibly in genes regulating gonadotrophin, insulin and androgen synthesis, secretion and action, weight and energy regulation) may influence the development of PCOS. Furthermore, prenatal exposure to higher maternal androgen levels may be the main determinant of future PCOS. Although PCOS is associated with familial clusters and the incidence is higher in identical twins than non-identical twins, the exact mode of inheritance remains unclear. The downstream metabolic and endocrine effects seen in PCOS are thought to be the result of a primary ovarian disorder.

Endocrinology and Diabetes: Lecture Notes, Second Edition. Amir H. Sam, Karim Meeran and Neil Hill.
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Clinical presentations

Clinical presentations of PCOS include:

- *menstrual abnormalities*: infrequent or absent menses (oligomenorrhoea or amenorrhoea), infertility (anovulation) and occasionally dysfunctional uterine bleeding resulting from chronic anovulation
- *hyperandrogenism*: acne, hirsutism, and male-pattern hair loss.

Hirsutism (Figure 22.1) is defined as excess hair growing in a male distribution (e.g. on the upper lip and chin, in the midsternum, periareolarly, along the linea alba of the lower abdomen). Hirsutism may cause significant psychological distress. There are familial and ethnic differences in hair growth. Obesity, signs of insulin resistance, for example acanthosis nigricans (hyperpigmented skin, usually in the neck [Figure 22.2], axilla, or groin), impaired glucose intolerance/diabetes mellitus and dyslipidaemia are frequently seen in patients with PCOS. Other clinical manifestations include obstructive sleep apnoea and non-alcoholic steatohepatitis.

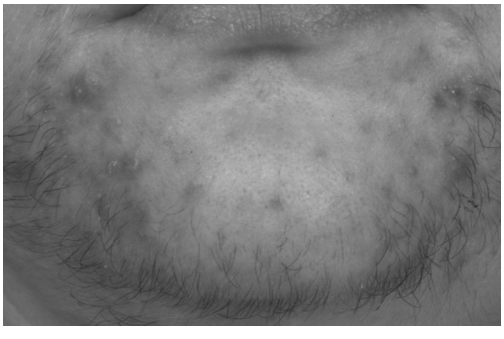

Figure 22.1 Hirsutism and acne in a patient with polycystic ovary syndrome.

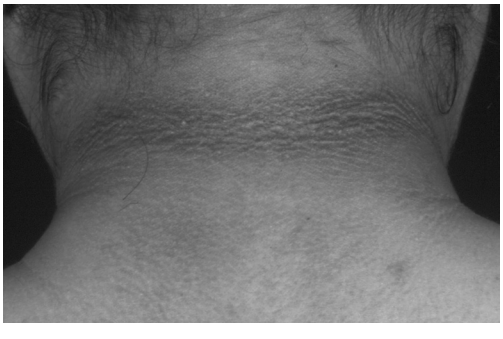

Figure 22.2 Acanthosis nigricans in a patient with polycystic ovary syndrome.

Androgen-secreting ovarian or adrenal tumours and ovarian hyperthecosis (see below) should be suspected in patients with progressive hirsutism, amenorrhoea, and signs of virilisation such as clitoral enlargement, increased muscle mass, and deepening of the voice.

Investigations

- A *pregnancy test* should be done in all women who have missed an expected menstrual period.
- *Luteinising hormone* (LH): high serum LH levels (due to an increased LH pulse frequency and amplitude) and a high (>3) ratio of LH to follicle-stimulating hormone (FSH) are seen in many women with PCOS. However, these are not part of the diagnostic criteria for PCOS. Serum LH levels are affected by the timing of the blood sample relative to the last menstrual period, and may be normal in women with all the diagnostic criteria for PCOS. Raised serum LH levels support (rather than confirm) the diagnosis.
- *FSH*: serum FSH levels should be measured to rule out 'premature ovarian insufficiency' (see Chapter 21).
- *Androgens*: testosterone, androstenedione and dehydroepiandrosterone sulfate (DHEA-S) are usually raised in PCOS. The ovary is the major source of excess androgens; the adrenal cortex may also contribute. It is important to check androgen levels to screen for androgen-secreting ovarian and adrenal tumours (see below).
- *Sex hormone-binding globulin* (SHBG): elevated insulin levels and androgen levels both inhibit the hepatic production of SHBG. Lower SHBG levels (seen in about 50% of patients) result in an increase in circulating free androgens.
- *Anti-müllerian hormone* (AMH) *levels*: secreted by the granulosa cells of preantral or small antral follicles, raised AMH levels support the diagnosis of PCOS because of higher follicle numbers.

Exclude *other causes* of menstrual irregularity or hyperandrogenism by performing the following tests.

- *Hyperprolactinaemia*: serum prolactin.
- *Hypo/hyperthyroidism*: free thyroxine and thyroid-stimulating hormone.
- *Congenital adrenal hyperplasia*: 17-hydroxyprogesterone (9 a.m., follicular phase).
- *Cushing syndrome* (only if there is a high clinical suspicion of Cushing syndrome): two or three 24-hour urine collections for free cortisol measurement, an

overnight dexamethasone suppression test or a late-night salivary cortisol.
- *Androgen-secreting ovarian or adrenal tumours*: serum testosterone levels are nearly always higher than 5 nmol/L. Those with adrenal tumours usually have serum DHEA-S levels above 21 µmol/L, whilst serum LH levels are low.

About 8% of hyperandrogenic patients have no identified cause despite thorough investigation and are said to have idiopathic hyperandrogenaemia.

Look for *impaired glucose tolerance/diabetes mellitus*. About 45% of patients with PCOS have impaired glucose tolerance or type 2 diabetes mellitus. Ideally, an oral glucose tolerance test (OGTT) should be performed in all patients at diagnosis. If this is not practical, a fasting glucose and HbA1c should be done. If either one is abnormal, an OGTT should be performed to distinguish between impaired glucose tolerance and diabetes mellitus. A fasting lipid profile should also be requested in all women with PCOS.

Ultrasound

The presence of 12 or more follicles in each ovary measuring 2–9 mm, and/or an increased ovarian volume of more than 10 mL (calculated by the formula: 0.5 × length × width × thickness) is part of the Rotterdam criteria for the diagnosis of PCOS (Figure 22.3). Ovarian ultrasound may show increased ovarian stroma. The transvaginal approach should be used where possible. However, these ultrasonographic criteria may be difficult to document if an experienced ultrasonographer is not available.

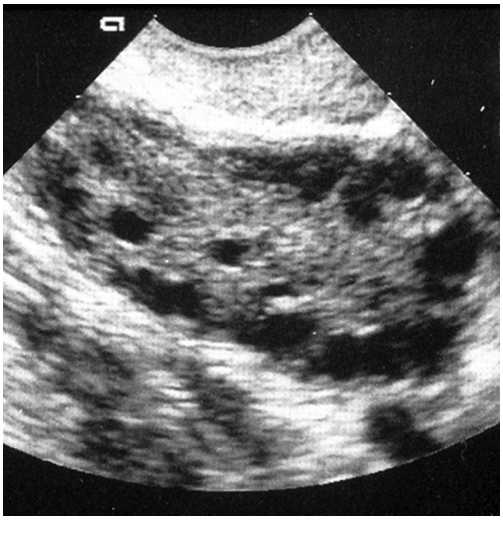

Figure 22.3 Ovarian ultrasound in a patient with polycystic ovary syndrome.

Treatment

The management of PCOS depends on the patient's symptoms (hirsutism, oligomenorrhoea, obesity, glucose intolerance) and goals (e.g. desire to become pregnant).

Hirsutism

The results of pharmaceutical management of hirsutism in PCOS are frequently disappointing. Local removal of hair by means such as shaving, waxing, depilatories, electrolysis, or laser treatment is effective but can be time-consuming, painful, and expensive. Medical management and cosmetic treatments are often combined.

Eflornithine hydrochloride (Vaniqa®) cream is a topical treatment used to inhibit hair growth. Eflornithine inhibits the enzyme ornithine decarboxylase, which regulates cell division.

Oral contraceptive pills are the treatment of choice for hirsutism or other androgenic symptoms. The oestrogen component increases serum SHBG, which binds to and decreases serum free androgen. In addition, inhibition of gonadotrophin secretion by oral contraceptive therapy results in a decrease in ovarian androgen secretion. Adrenal androgen secretion is also reduced, although the exact mechanism of this is not fully understood.

Many endocrinologists start with a preparation containing 30–35 µg of ethinyloestradiol plus a progestin with minimal androgenic effect (e.g. norethindrone, norgestimate, desogestrel) or antiandrogenic effect (e.g. cyproterone acetate, drospirenone). Levonorgestrel-containing preparations should be avoided due to their androgenic activity. In breastfeeding women, progestin-only contraceptives should be used (no earlier than 6 weeks postpartum) as combined oestrogen–progestin contraceptives suppress milk production.

In adolescents, oral contraceptives should be continued for 5 years after menarche or until a substantial amount of excess weight has been lost. At this time, a trial off treatment may be tried to document the persistence of the syndrome.

If the patient is not satisfied with the clinical response after 4–6 months, *spironolactone* may be added. Antiandrogens should not be prescribed to

women of reproductive age without reliable contraception (ideally, an oral contraceptive pill or intrauterine progestogen-only system) due to potential teratogenic effects.

Given the comparable efficacy of all the antiandrogens in the treatment of hirsutism, spironolactone is the first-line treatment chosen by many endocrinologists because of its safety. It inhibits testosterone binding to its receptors and also decreases ovarian androgen production. The usual dose is 50–100 mg twice a day. The effects may be noticeable within 2 months, and reach a peak at 6 months. The side-effects of spironolactone include hyperkalaemia (rarely a problem in those with normal renal function) and gastrointestinal discomfort.

Other antiandrogens used in treatment of hirsutism include the following.

- *Flutamide* also inhibits testosterone binding to its receptors and may be more potent than spironolactone. However, its use may result in hepatotoxicity.
- *Finasteride* inhibits 5-alpha-reductase, which catalyses the conversion of testosterone to dihydrotestosterone. Finasteride is as effective as or less effective than spironolactone.
- *Cyproterone acetate* is a progestin with antiandrogenic activity, and may be given alone or with ethinylestradiol in the contraceptive pill Dianette®. There is a perceived increase in risk of hepatotoxicity.

Oral contraceptives and antiandrogen therapy may also reduce acne, but some women may need antibiotic or other therapy as advised by a dermatologist.

Oligomenorrhoea

Chronic anovulation and resultant long-term unopposed oestrogen are associated with endometrial hyperplasia and possibly increased risk of endometrial cancer. The progestin component of the *oral contraceptive pill* inhibits endometrial proliferation, preventing hyperplasia and the associated risk of carcinoma. The oestrogen component reduces excess androgen, which improves menstrual irregularity and dysfunctional uterine bleeding.

For those who choose not to or cannot take oral contraceptives, intermittent progestin therapy may be given for endometrial protection (10 mg of medroxyprogesterone acetate for 10 days every 1–2 months). Progestin therapy alone will not reduce the symptoms of acne or hirsutism, and will not provide contraception.

Infertility

Patients with PCOS who desire pregnancy and are overweight should be advised to lose weight. This is the most effective way to restore regular menses; weight loss between 5% and 10% of body mass is frequently effective. In patients who are unable to lose weight or in whom modest weight loss does not restore ovulatory cycles, ovulation induction may be initiated with *clomiphene citrate*. Clomiphene is superior to metformin in achieving live birth but it should only be used by specialists with access to serial ultrasound monitoring for at least the first cycle, to reduce the risk of multifollicular growth and multiple births. It binds to oestrogen receptors in the hypothalamus. This is sensed as a state of hypo-oestrogenaemia, resulting in an increased release of gonadotrophin-releasing hormone (GnRH). If this is unsuccessful, other ovulation induction strategies should be considered (see Chapter 21).

Obesity

Lifestyle changes (diet and exercise) and modest weight loss may result in a restoration of ovulatory cycles and an improvement in hyperandrogenism and insulin resistance, reducing the likelihood of developing type 2 diabetes and lessening cardiovascular risk. *Metformin* is a reasonable adjunct to diet and exercise for patients with PCOS who are obese or glucose intolerant. It is associated with a reduction in low-density lipoprotein cholesterol and fasting insulin levels. It also improves ovulation in 50%, and modestly reduces androgen levels.

Diabetes mellitus

Diabetes mellitus and impaired glucose tolerance should be treated as for patients with these disorders who do not also have PCOS.

Other causes of hirsutism

The causes of hirsutism are summarised in Box 22.1.

Congenital adrenal hyperplasia and Cushing syndrome are discussed in separate chapters.

A L G r a w a n y

Box 22.1 Causes of hirsutism

Idiopathic hirsutism
Polycystic ovary syndrome
Congenital adrenal hyperplasia (most often 21-hydroxylase deficiency)
Cushing syndrome
Ovarian tumours (Sertoli–Leydig cell tumours, granulosa–theca cell tumours, hilus cell tumours)
Adrenal tumours
Ovarian hyperthecosis
Drugs (e.g. danazol, oral contraceptives containing androgenic progestins)
Severe insulin resistance syndromes

Ovarian hyperthecosis

Ovarian hyperthecosis is characterised by the presence of islets of luteinised theca cells in the ovarian stroma, resulting in increased production of androgens. Women with hyperthecosis have more severe hirsutism and are much more likely to have clitoral enlargement, temporal balding and deepening of the voice. Ovarian hyperthecosis can occur in postmenopausal women (unlike PCOS, which occurs only during the reproductive years). Increased ovarian secretion of androgen also results in increased peripheral oestrogen production and an increased risk of endometrial hyperplasia.

Patients have high serum testosterone levels (≥7 nmol/L), similar to those seen with androgen-secreting adrenal or ovarian tumours. Pelvic ultrasonography must be performed to exclude virilising ovarian tumours and to measure endometrial thickness. In practice, the diagnosis of ovarian hyperthecosis is made by histological examination of the ovaries following a wedge biopsy performed to rule out virilising ovarian tumours.

The treatment of hyperthecosis includes weight reduction, oral contraceptives, and spironolactone. GnRH agonists may reduce intraovarian androgen levels and restore sensitivity to exogenous gonadotrophins, with subsequent ovulation.

KEY POINTS

- PCOS is characterised by oligomenorrhoea/amenorrhoea and hyperandrogenism.
- PCOS is frequently associated with obesity and insulin resistance.
- Hirsutism is treated with oral contraceptive pills, antiandrogens (e.g. spironolactone), eflornithine cream, and cosmetic therapy.
- Antiandrogens should not be prescribed without reliable contraception due to potential teratogenic effects.
- Menstrual irregularity and dysfunctional uterine bleeding are treated with oral contraceptive pills.
- Metformin is a reasonable adjunct to diet and exercise in women with PCOS who are obese.
- Clomiphene is superior to metformin in achieving live birth.

23

Menopause

Menopause is the time of ovarian failure and cessation of menstrual periods that occurs in normal women at a mean age of 51 years.

Menopause occurs between the ages of 45 and 55 years in 90%, between ages 40 and 45 years in 5% and after age 55 in 5% of women. The reduction in ovarian function will cause symptoms in around half of women, including hot flushes, low mood, night sweats, myalgia, anxiety, vaginal dryness, and reduced libido. About 25% women will have symptoms that significantly affect their personal and/or professional lives.

Endocrinology of menopause

In the early menopausal transition, levels of inhibin B released from the ovaries start to decrease due to a fall in follicular number. This results in an increase in serum follicle-stimulating hormone (FSH) levels due to loss of the negative feedback effect of inhibin B on FSH secretion. Oestradiol levels are initially relatively preserved, possibly due to increased aromatase activity stimulated by the elevated FSH levels (FSH stimulates the aromatisation of androgens to produce oestrogen). It is important to note that, during menopausal transition, there are significant fluctuations in serum FSH and oestradiol levels.

After menopause, when the ovarian follicles are depleted, the ovaries no longer secrete oestradiol but continue to secrete androgens under the continued stimulation of luteinising hormone.

Clinical presentations

The menopausal transition starts with variation in the length of the menstrual cycle (>7 days different from normal cycle length). The menopausal transition ends with the final menstrual period. Menopause is diagnosed clinically as amenorrhoea for 12 months in a woman over age 45 in the absence of other causes.

Menopausal symptoms include:

- *hot flushes*
- *urogenital symptoms*: vaginal dryness, dysuria, frequency, stress incontinence, recurrent urinary tract infections
- *mood changes* and *sleep disturbances*.

Diagnosis and differential diagnoses

The best approach to diagnosing the menopausal transition is to evaluate the menstrual cycle history and menopausal symptoms. Serum FSH levels increase across the menopausal transition. FSH levels increase more than those of luteinising hormone, presumably because of the loss of inhibin as well as the oestrogen negative feedback. However, since serum FSH and oestradiol levels fluctuate during the menopausal transition, a single elevated serum FSH value and even undetectable oestradiol and inhibin levels do not mean that menopause has occurred. Menopause is diagnosed clinically in a woman over age 45 who has had amenorrhoea for 12 months in the absence of other causes. Two FSH results >25 IU/L in amenorrhoeic women age under 45 are also highly suggestive of menopause.

Other causes of menstrual cycle changes such as pregnancy, hyperprolactinaemia and thyroid dysfunction should be ruled out.

Atypical hot flushes and night sweats may also be associated with certain medications, phaeochromocytoma, thyrotoxicosis, carcinoid syndrome, underlying infection or malignancy.

Endocrinology and Diabetes: Lecture Notes, Second Edition. Amir H. Sam, Karim Meeran and Neil Hill.
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Management

Hormone replacement therapy (HRT) with *oestrogen* is the most effective treatment for the relief of menopausal symptoms. However, unopposed oestrogen can result in endometrial hyperplasia and increases the risk of carcinoma, and therefore a *progestin* must be added to the oestrogen in women who have not had a hysterectomy. HRT is not recommended in those with a previous history of breast cancer, coronary heart disease, stroke, or venous thromboembolism, or risk factors for these conditions.

Hormone replacement therapy

Sequential cyclical regimen

In this regimen, oral oestrogen (e.g. 1 mg oestradiol) is given continuously, and a progestin (e.g. micronised progesterone 200 mg) is added for the first 12–14 days of each month. Transdermal oestrogen (e.g. 0.05 mg) may be applied twice weekly instead of oral oestrogen.

Around 90% of women have a monthly withdrawal bleed. Newly postmenopausal or younger women may prefer this regimen to avoid the irregular bleeding caused by the continuous combined regimen (see below). Uterine bleeding usually starts after the ninth day of progestin therapy.

Women with three or more cycles of uterine bleeding before the ninth day of progestin therapy or those with a change in the duration or intensity of uterine bleeding should have a transvaginal ultrasound performed by an experienced sonographer to look at *endometrial thickness*. An endometrial thickness of less than 5 mm excludes disease in 96–99% of cases. If the endometrial thickness is more than 5 mm, an endometrial biopsy is required to exclude carcinoma.

Continuous combined regimen

In this regimen, oral oestrogen (e.g. 1 mg oestradiol) and progestin (e.g. micronised progesterone 100 mg) are taken on a daily basis. Transdermal oestrogen (e.g. 0.05 mg) applied twice weekly can be used instead of oral oestrogen. Uterine bleeding is light but the timing is unpredictable. Uterine bleeding stops within 12 months in 90% of women as daily progestin results in an atrophic endometrium. This regimen is preferred by older women who do not want monthly withdrawal bleeds.

If bleeding is heavy within the first 12 months, if it continues after 12 months or if it starts after a period of amenorrhoea, a transvaginal ultrasound should be performed to assess endometrial thickness (see above).

In any woman with previous long-term exposure to unopposed oestrogen or a previous history of irregular bleeding, a pretreatment biopsy should be performed to rule out atypical endometrial hyperplasia or carcinoma.

HRT risks

Hormone replacement therapy is not recommended in women with history of breast cancer, coronary heart disease, stroke, or venous thromboembolism or risk factors for these conditions. Taking unopposed oestrogen for more than 5 years increases the risk of developing breast cancer, but by less than combined HRT. Furthermore, it appears that excess risk persists for more than 10 years after stopping HRT. However, it is important to note that some studies show alcohol consumption and being overweight confer a greater risk of breast cancer than HRT. In the UK, about 1 in 16 women who have never taken HRT will be diagnosed with breast cancer between the ages of 50 and 69 (baseline risk). For women with a normal body mass index who start HRT in their 40s or 50s, a recent *Lancet* analysis found that the additional risk of breast cancer increases to 1 in 14 (HRT as oestrogen only), 1 in 13 (HRT as oestrogen daily and progestogen for part of each month) and 1 in 12 (HRT as oestrogen and progestogen daily). Furthermore, many studies do not address mortality, and there is some evidence that women who use HRT may have lower cardiovascular death and lower all-cause mortality. Women should be fully counselled on the risks and benefits of HRT to make an informed decision about their treatment.

Hot flushes

Women with mild hot flushes do not usually require any pharmacological treatment. HRT may be given to women with moderate-to-severe symptoms and no history of breast cancer, cardiovascular or thromboembolic disease. HRT may be continued for 1–3 years, but generally not for more than 5 years.

For treatment of hot flushes, oestrogen should be given continuously. The effective daily dose equivalents are:

- 0.625 mg oral conjugated equine oestrogens
- 1 mg oral oestradiol
- 50 µg transdermal oestradiol.

Transdermal patches avoid first-pass hepatic metabolism, and are therefore ideal in women with liver disease or hypertriglyceridaemia. However, 10% of women develop skin reactions.

These doses given daily are sufficient to abolish hot flushes in 80% of women, and to reduce the frequency and severity of hot flushes in the rest. In women who have not had a hysterectomy, oestrogen should always be given in combination with a progestin to prevent the occurrence of endometrial hyperplasia.

HRT does not provide contraception during the menopausal transition. For perimenopausal women between the ages of 40 and 50 years who are troubled by menopausal symptoms and also desire contraception, a low-oestrogen (20 µg of ethinyloestradiol) combined oral contraceptive pill is an appropriate treatment if there are no risk factors for venous and arterial disease. When these women reach 51 years, the oral contraceptive pill is either stopped or changed to HRT if necessary for symptom control.

Recently, neurokinin 3 receptor antagonists have shown promise for ameliorating hot flushes and are now in pharmaceutical development.

Stopping HRT

Many women are able to stop their oestrogen abruptly. If the patient is troubled by recurrent symptoms, HRT may be restarted and a 6-week taper may be tried by reducing by one pill per week. Women who are unable to tolerate this tapering regimen may require resumption of their HRT and a much slower taper, for example over 1 year by reducing one pill every 2 months. Various preparations of transdermal oestradiol can also be used to decrease the dose gradually.

Women with a history of severe hot flushes before starting HRT often require a gradual taper over 6–12 months.

Other treatments

Women in whom oestrogen is contraindicated or not tolerated, and those who experience recurrent symptoms after stopping oestrogen and do not want to be restarted on HRT, may benefit from serotonin–noradrenaline reuptake inhibitors, selective serotonin reuptake inhibitors, or gabapentin (given at bedtime in women with predominantly night-time symptoms). Hot flushes gradually subside in most postmenopausal women, and any drug can be gradually tapered after 1–2 years.

Urogenital symptoms

Women with mild symptoms are treated with regular vaginal moisturising agents and lubricants for use during intercourse. Patients with moderate-to-severe symptoms and no history of breast cancer are treated with low-dose vaginal oestrogen. The choice of vaginal delivery system, i.e. tablet, ring, or cream, depends on the patient's preference.

Osteoporosis

Oestrogen is not the first-line treatment for osteoporosis in postmenopausal women. Bisphosphonates are first-line treatments for postmenopausal osteoporosis (see Chapter 27). In postmenopausal women with osteoporosis who cannot tolerate bisphosphonates, raloxifene or denosumab may be given if there are no fragility fractures. Parathyroid hormone therapy may be considered for those with at least one fragility fracture.

Postmenopausal women with osteoporosis should receive adequate calcium and vitamin D (1000 mg elemental calcium and 800 IU vitamin D daily). Patients should be informed of the importance of relevant lifestyle measures including exercise and smoking cessation, and should receive counselling on fall prevention.

KEY POINTS

- Menopause is the time of ovarian failure and cessation of menstrual periods that occurs in normal women at a mean age of 51 years.
- During menopausal transition, there are significant fluctuations in serum FSH and oestradiol levels.
- Menopausal symptoms include hot flushes, urogenital symptoms, mood changes, and sleep disturbances.
- Women's Health Initiative trials reported that continuous combined oestrogen–progestin therapy increased the risk of breast cancer, coronary heart disease events, stroke, and venous thromboembolism.
- HRT may be given to women with moderate-to-severe symptoms and no history of breast cancer, cardiovascular or thromboembolic disease.
- Oestrogen is not the first-line treatment for osteoporosis in postmenopausal women.

24

Calcium homeostasis, hypercalcaemia, and primary hyperparathyroidism

Most of the body's calcium exists as hydroxyapatite, which is the main mineral component of bone (Figure 24.1). In the plasma, 40% of calcium is bound to albumin, 15% is complexed with citrate, sulfate or phosphate, and 45% exists as the physiologically important free (ionised) calcium.

The plasma concentration of free calcium is regulated by *parathyroid hormone* (PTH) and *vitamin D*. The physiological roles of calcitonin in the regulation of calcium and phosphate balance are incompletely understood.

Parathyroid glands and PTH

Parathyroid hormone is a polypeptide secreted from the parathyroid glands. There are four parathyroid glands (one superior and one inferior gland on each side). They are about 6 mm long in their greatest diameter, and are embedded in the back of the thyroid gland. The superior glands develop from the fourth branchial pouch. The inferior glands develop from the third pouch. The thymus also develops from the third pouch, and may occasionally drag the inferior glands with it to the mediastinum.

PTH release is stimulated by a decrease in plasma free calcium levels (Figure 24.2). Changes in plasma free calcium are sensed by a specific calcium-sensing receptor (CASR) on the plasma membrane of the parathyroid cells. PTH increases plasma calcium by stimulating:

- *bone resorption*, resulting in the release of calcium and phosphate
- *intestinal absorption* of calcium by stimulating 1-alpha-hydroxylation of 25-hydroxyvitamin D in the kidney and the formation of calcitriol (see below)
- *renal reabsorption* of calcium (in the distal tubule and connecting segment).

PTH reduces proximal tubular phosphate reabsorption by decreasing the activity of the type II sodium–phosphate co-transporter.

Vitamin D_3

Vitamin D_3 (cholecalciferol) is a fat-soluble steroid. Sources of vitamin D_3 include diet and synthesis in the skin from 7-dehydrocholesterol in the presence of ultraviolet light (Figure 24.3).

Vitamin D_3 is activated by 25-hydroxylation in the liver followed by 1-alpha-hydroxylation in the kidney. 1,25-dihydroxyvitamin D (calcitriol) is the most active form of vitamin D. 1-Alpha-hydroxylation is stimulated by PTH. Calcitriol stimulates bone resorption, intestinal absorption and renal reabsorption.

Endocrinology and Diabetes: Lecture Notes, Second Edition. Amir H. Sam, Karim Meeran and Neil Hill.
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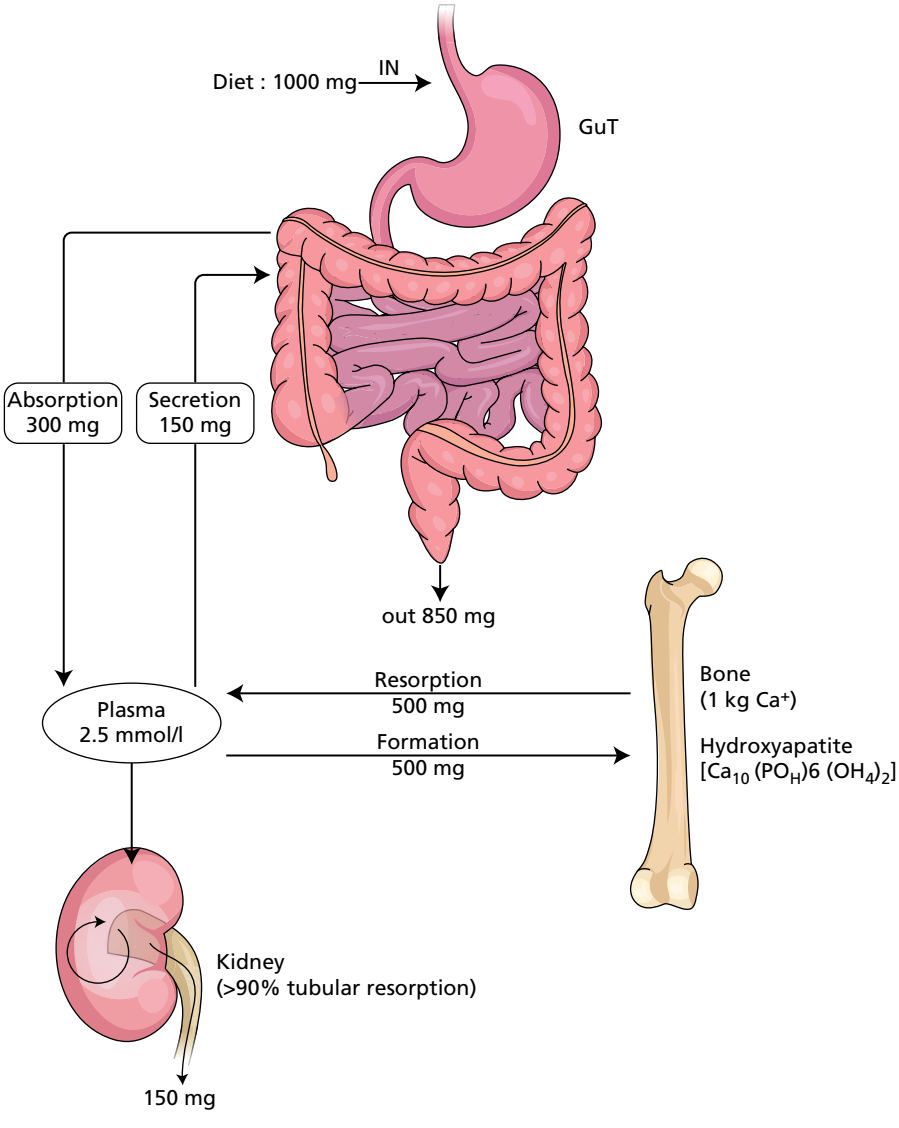

Figure 24.1 Daily physiological flux of calcium.

Hypercalcaemia and primary hyperparathyroidism

Hypercalcaemia

Hypercalcaemia is a relatively common clinical problem. Common causes of hypercalcaemia include the following.

Hyperparathyroidism is the most common cause of hypercalcaemia in ambulatory patients (>90% of cases). The effect of PTH on calcium levels is discussed above. Hyperparathyroidism is discussed in more detail below.

Malignancy is the most common cause of hypercalcaemia among hospitalised patients (about 65% of cases). Hypercalcaemia may be due to a local resorption of bone caused by metastases (mediated by the release of cytokines, tumour necrosis factor, interleukin-1), or the production of PTH-related protein

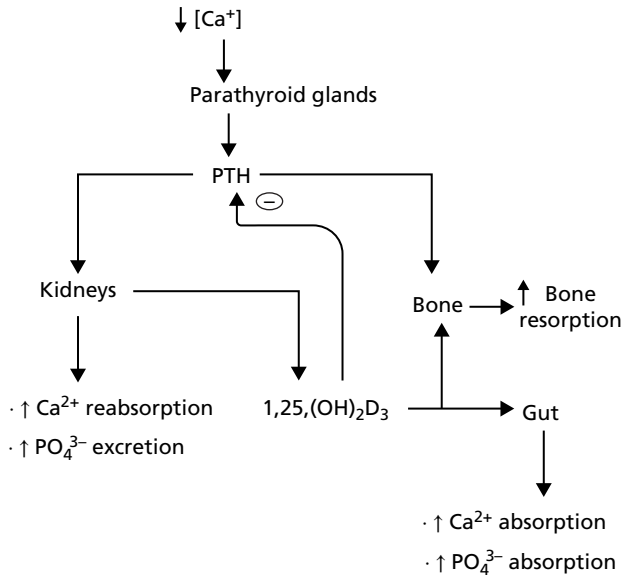

Figure 24.2 Actions of parathyroid hormone (PTH) on calcium and phosphate.

(which activates osteoclasts). PTH- related protein may be secreted by squamous cell carcinomas, breast cancer, and lymphomas due to HTLV-1. PTH levels in malignancy may not be fully suppressed and in the lower half of the normal range.

Familial hypocalciuric hypercalcaemia (FHH) is an autosomal dominant disorder caused by inactivating mutations in the gene encoding the CASR on the parathyroid cells and in the kidneys. This results in mild resistance of the parathyroid cells to calcium, and reduced capacity of the kidneys to increase calcium excretion. Patients have mild hypercalcaemia with inappropriately normal to slightly increased serum PTH concentrations. Although this condition is rare (1 in 100 000 people affected), it *must* be excluded as a differential diagnosis of hyperparathyroidism because patients with this condition have few if any symptoms of hypercalcaemia and require no treatment.

In *hypervitaminosis D*, the source of excess vitamin D may be exogenous (excess intake of supplements, very uncommon) or endogenous (i.e. increased production of calcitriol in chronic granulomatous disorders such as tuberculosis, sarcoidosis and lymphoma). Occasionally, the condition may be idiopathic. The effect of vitamin D on plasma calcium levels is discussed above.

Less common causes of hypercalcaemia include:

- *Drugs:* lithium (causes increased secretion of PTH), thiazide diuretics (causes lower urinary calcium excretion and usually unmasks underlying hyperparathyroidism), theophylline toxicity, ion exchange resins.
- *Immobility:* due to increased bone resorption.
- *Milk-alkali syndrome:* a high intake of milk or calcium carbonate (used to treat dyspepsia) may lead to hypercalcaemia mediated by the high calcium intake plus metabolic alkalosis, which augments calcium reabsorption in the distal tubule.
- *Other endocrine causes:* adrenal insufficiency, acromegaly, phaeochromocytoma (due to concurrent hyperparathyroidism if part of multiple endocrine neoplasia [MEN] type 2 or due to the production of PTH-related protein), thyrotoxicosis, or hypervitaminosis A (due to increased bone resorption).

Primary hyperparathyroidism

Most patients have only small elevations in serum calcium concentrations (<2.75 mmol/L), and many have mostly high-normal values with intermittent hypercalcaemia.

Aetiology

Primary hyperparathyroidism is due to a solitary adenoma (80–85%), multiple adenomas, or four-gland hyperplasia. Parathyroid carcinoma is a very rare cause of primary hyperparathyroidism (<0.5%).

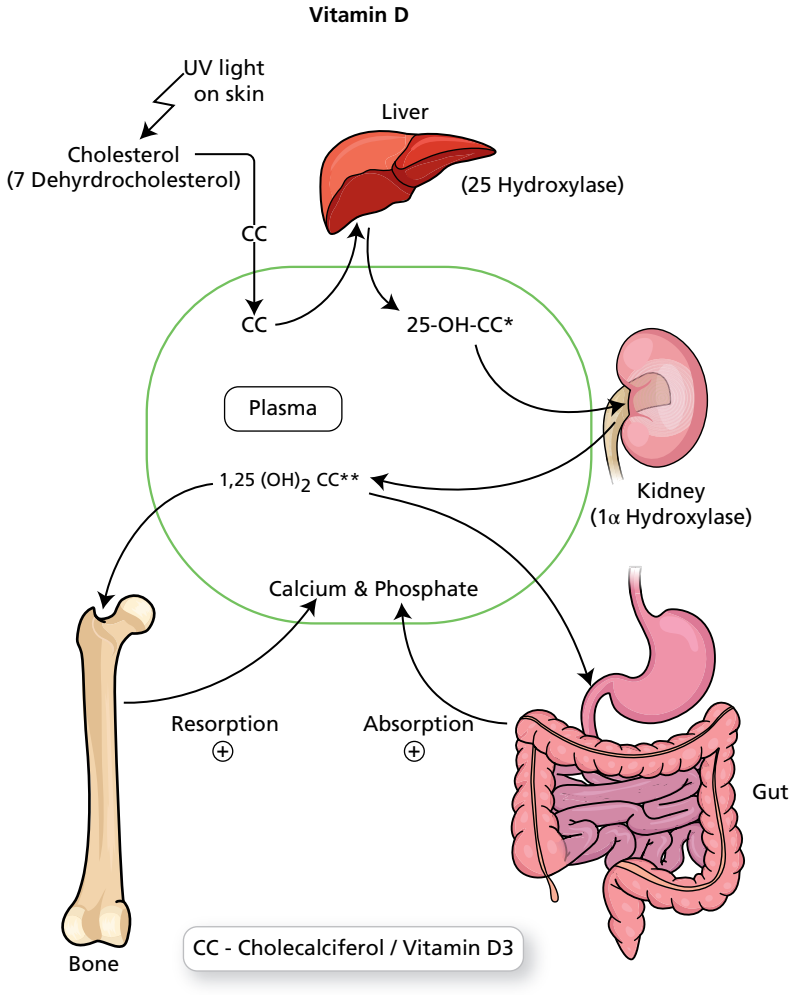

Figure 24.3 Vitamin D activation and actions. *, 25-hydroxyvitamin D; **, 1,25-dihydroxyvitamin D.

Primary hyperparathyroidism is usually sporadic but may be associated with the following inherited syndromes in around 10% of cases:

- *MEN type 1* is characterised by hyperparathyroidism (in 90–95% of patients by the age of 50), pancreatic endocrine tumours (30–80%), and pituitary adenomas (15–50%).
- *MEN type 2a*: up to 25% of patients have parathyroid hyperplasia associated with medullary thyroid carcinoma (100%) and phaeochromocytoma (50%).

Other rare forms of inherited primary hyperparathyroidism usually present at a younger age and include MEN type 4, familial isolated hyperparathyroidism and hyperparathyroidism–jaw tumour syndrome (fibro-osseous tumours of the jaw associated with renal cysts or Wilms tumour). Sporadic parathyroid carcinomas frequently have *HRPT2* mutations that are likely to be of pathogenetic importance.

Epidemiology

The incidence of primary hyperparathyroidism has increased since the introduction of multichannel autoanalysers. More individuals have been diagnosed with primary hyperparathyroidism whose disease would not previously have been recognised simply because serum calcium was not routinely measured. Prevalence is estimated to be 1–3/1000, occurring more commonly in women and in people aged over 50 years.

Clinical presentations

Most patients currently diagnosed with primary hyperparathyroidism have serum calcium levels less than 0.25 mmol/L above the reference range and are usually asymptomatic at diagnosis.

Symptomatic patients generally have serum calcium levels of 3.0 mmol/L or more. Patients may present with nausea, constipation, polydipsia and polyuria, depression and generalised aches and pains ('bones, stones, psychic moans, and abdominal groans'). However, many of these symptoms are common in the general population, and it is not clear whether they are causally related to primary hyperparathyroidism. The abnormalities most directly associated with hyperparathyroidism are nephrolithiasis (seen in 15–20% of newly diagnosed patients) and bone disease (see below).

Osteoporosis is a common feature of primary hyperparathyroidism and affects cortical bone, for example the distal radius, more than trabecular bone such as the vertebral bodies.

Osteitis fibrosa cystica (brown tumours) is now rarely seen (<2% of patients), probably because routine serum calcium checks identify patients with primary hyperparathyroidism before this skeletal complication develops. Osteitis fibrosa cystica is characterised by generalised skeletal demineralisation, subperiosteal bone resorption (e.g. on the radial aspect of the middle phalanges) and brown tumours (osteoclastomas) manifested as lytic lesions.

Calcium levels higher than ~3 mmol/L inhibit the effect of antidiuretic hormone on the renal collecting ducts, causing nephrogenic diabetes insipidus.

Patients with parathyroid carcinomas are more likely to have a marked hypercalcaemia, neck mass and symptoms of bone and kidney disease.

Investigations

In all patients with hypercalcaemia, serum phosphate, vitamin D, and PTH levels should be measured. The diagnosis of primary hyperparathyroidism is biochemical. Patients with primary hyperparathyroidism may have low or low-normal phosphate levels. Vitamin D deficiency should be excluded as the cause of raised PTH levels and may mask the severity of primary hyperparathyroidism.

- In patients with *suppressed PTH*: myeloma, malignancy and granulomatous conditions causing excess production of 1,25-dihydroxyvitamin D (i.e. tuberculosis, sarcoidosis, lymphoma) should be excluded. Measure serum protein electrophoresis and urinary Bence Jones protein (to look for multiple myeloma) and serum angiotensin-converting enzyme (may be raised in sarcoidosis) and request further imaging (to look for malignancy).
- In patients with *high or inappropriately normal PTH levels*: the calcium-to-creatinine clearance ratio should be measured to differentiate between primary hyperparathyroidism (ratio >0.01) and familial hypocalciuric hypercalcaemia (ratio <0.01). These cut-offs are not absolute and are affected by vitamin D status. Repeat measurements may offer clarity; a family history of hypercalcaemia may also help with diagnosing FHH, as may screening for CaSR gene mutations. This is calculated from simultaneous measurements of urine and serum calcium and creatinine concentrations, using the following formula:

$$\frac{\text{Urine calcium}\,(\text{mmol / L}) \times \left[\text{Plasma creatinine}\,(\mu\text{mol / L}) / 1000\right]}{\text{Plasma calcium}\,(\text{mmol}) \times \text{Urine creatinine}\,(\text{mmol / L})}$$

Patients with parathyroid carcinomas are more likely to have a marked hypercalcaemia with very high serum PTH levels.

A 24-hour urine collection should be sent for creatinine clearance and calcium measurement.

Imaging

Patients with confirmed primary hyperparathyroidism should also have a renal ultrasound at baseline to look for renal calculi.

Ultrasound of the neck and ^{99m}technetium sestamibi scan should be performed as part of preoperative localisation only when surgical intervention is indicated (see below).

More extensive preoperative imaging, including magnetic resonance imaging, computed tomography, angiography, and selective venous sampling, may be required in patients with recurrent disease or ectopic parathyroid adenoma (e.g. mediastinal, intrathyroid, lateral neck, retro-oesophageal).

Treatment

The only curative treatment for primary hyperparathyroidism is surgery. However, surgery is not appropriate in all patients. The potential benefits must be weighed against the risks in each case.

Indications for surgery

Guidelines for surgical intervention have been developed based on risk of disease progression and end-organ effects. Parathyroidectomy improves bone

density and may have modest effects on some quality of life symptoms. The Fourth International Workshop on the Management of Asymptomatic Primary Hyperparathyroidism guidelines (2014) suggested that indications for surgical intervention include:

- symptomatic patients
- asymptomatic patients with:
  - age below 50 years (in a study of patients treated conservatively over 10 years, the disease progressed in 27% of asymptomatic patients, most of whom were younger than 50 years, and age was the only predictive index)
  - bone mineral density: T-score less than –2.5 (total hip, femur, lumbar spine, distal 1/3 radius)
  - vertebral fracture (detected by X-ray, CT, MRI, or vertebral fracture assessment)
  - calculi (renal stones) or nephrolithiasis
  - creatinine clearance reduced to <60 mL/min/1.73 m^2
  - elevated serum calcium more than 0.25 mmol/L above the upper limit of normal.

It is important to note that these guidelines do not apply to familial primary hyperparathyroidism syndromes.

Bilateral neck exploration

Parathyroidectomy should be performed only by surgeons who are highly experienced and skilled in this operation. The standard surgical approach for most patients is bilateral neck exploration with identification of all four glands, usually under general anaesthesia. The amount of parathyroid tissue removed varies with the cause of hyperparathyroidism.

- The gland containing a *parathyroid adenoma* is removed. The other glands may be biopsied.
- For *four-gland hyperplasia*, three and one-half glands are removed, leaving one-half of the most normal-appearing gland marked with a clip.
- In patients with *MEN type 1*, total parathyroidectomy may be performed (with surgical implantation of parathyroid tissue in the forearm in some centres) because of the high recurrence rate.

Minimally invasive parathyroidectomy

Minimally invasive parathyroidectomy may be the procedure of choice in patients with unilateral pathology (detected by imaging), with no family history of MEN and in the high-risk elderly.

Minimally invasive parathyroidectomy may be performed if ^{99m}technetium sestamibi and ultrasound scans both show an adenoma in the same location ('concordant' imaging). The location is marked on the skin, and surgery is performed through a 2–4 cm incision under local anaesthetic.

Minimally invasive parathyroidectomy requires an intraoperative test to confirm that the adenoma removed is the only source of abnormal glandular activity. The short plasma half-life of PTH (3–4 minutes) and a rapid assay for PTH make it a useful test for this purpose. A reduction of over 50% in serum PTH measured shortly after the resection compared with preincision levels is considered successful, and the operation is terminated. Alternatively, technetium-labelled sestamibi may be administered intravenously 1–2 hours preoperatively. After the suspected adenoma has been removed, a gamma probe is used to measure the radioactivity of the excised tissue, which is compared with the radioactivity of the surgical bed.

Minimally invasive surgery is not an option for patients with non-concordant imaging, multigland disease, or a history of previous surgery. The cure rates of bilateral neck exploration and minimally invasive parathyroidectomy are similar (95–98%), and complication rates with both are low with an experienced surgeon.

For parathyroid carcinomas, surgery is the initial therapy. Treatment becomes limited to the control of hypercalcaemia with hydration or a bisphosphonate when the tumour is no longer amenable to surgical intervention. Cinacalcet (a calcimimetic agent) has recently been approved for the treatment of hypercalcaemia in patients with parathyroid cancer. Some patients have germline *HRPT2* mutations, and genetic evaluation can play an important role in management of such patients and their family members.

Postoperative hypocalcaemia

Serum corrected calcium and magnesium should initially be checked at least daily. Following parathyroidectomy, calcium starts to fall 4–12 hours after the surgery. The nadir is reached by 24 hours. If the patient becomes hypocalcaemic, it may be due to the following.

- *Functional hypoparathyroidism* (due to the suppression of other parathyroid glands, parathyroid gland ischaemia, hypomagnesaemia): PTH levels checked after day 3 (postoperatively) are detectable. This transient hypoparathyroidism may develop in up to 70% of patients and usually resolves within 1–3 weeks. Patients may require oral calcium supplements and a 1-alpha-hydroxylated vitamin D metabolite.

- *Hungry bone syndrome* causes severe hypocalcaemia, hypophosphataemia and hypomagnesaemia due to extensive skeletal remineralisation.
- *Permanent hypoparathyroidism*: PTH levels checked after day 3 (postoperatively) will be undetectable (<1 pg/mL). Patients with permanent hypoparathyroidism (<2%) require lifelong treatment with a 1-alpha-hydroxylated vitamin D metabolite.

In severe hypocalcaemia (calcium <1.6 mmol/L), intravenous calcium gluconate should initially be given with cardiac monitoring (see Chapter 25). Hypomagnesaemia should be treated with intravenous magnesium sulfate. Oral calcium (e.g. calcium carbonate) is started at a dose of 2.0–2.4 g daily, and calcitriol (or alfacalcidol) is given at a dose of 1 µg per day.

The goal is to relieve symptoms and to achieve a serum calcium concentration in the low-normal range (2.0–2.1 mmol/L). This is because these patients lack the normal stimulatory effect of PTH on renal tubular calcium reabsorption, and therefore excrete more calcium than normal subjects at the same serum calcium concentration. Therefore, completely correcting hypocalcaemia may result in hypercalciuria, nephrolithiasis, nephrocalcinosis and chronic renal insufficiency. The diet also should be limited in phosphate to minimise hyperphosphataemia.

The dose of calcium and vitamin D should be adjusted according to the patient's serum calcium values. Urinary calcium excretion should be measured periodically, and the dose of calcium reduced if it is elevated. Patients are usually weaned off calcium supplementation and calcitriol (or alfacalcidol) is continued.

Medical management

Patients who do not meet surgical criteria or who prefer to avoid surgery are managed conservatively with periodic follow-up (see below). Patients should be advised to take the following steps:

- Avoid factors that can exacerbate hypercalcaemia, including thiazide diuretic and lithium therapy, dehydration, prolonged bedrest and inactivity.
- Maintain adequate hydration (at least 6–8 glasses of water per day).
- Maintain a moderate calcium intake (1000 mg per day). A low-calcium diet may lead to increased PTH secretion and aggravate bone disease. A high-calcium diet may exacerbate hypercalcaemia.
- Maintain moderate vitamin D intake (400–600 IU daily). Vitamin D deficiency stimulates PTH secretion and bone resorption.

About 25% of patients with primary hyperparathyroidism managed conservatively for 10 years develop an indication for surgery (worsening hypercalcaemia, hypercalciuria, renal calculi, osteoporosis) and will benefit from surgical intervention.

In patients with osteopenia or osteoporosis who are not candidates for surgery, bisphosphonates should be given to preserve bone mass.

Thiazide diuretics (which reduce renal calcium excretion) may be used to prevent stone formation.

Cinacalcet is a calcimimetic agent that increases the sensitivity of the CASRs to extracellular calcium, resulting in reduced PTH secretion. Cinacalcet may be used to treat patients who are not candidates for surgery and improves biochemical abnormalities without affecting bone mineral density at 12 months.

Follow-up and monitoring

Patients with primary hyperparathyroidism who are managed conservatively should have:

- a baseline 24-hour urine collection for calcium and creatinine clearance measurement
- a baseline renal ultrasound to look for renal calculi
- serum calcium measured every 6 months
- serum creatinine measured once a year
- a dual-energy X-ray absorptiometry scan every 2 years.

Management of severe hypercalcaemia

Patients with severe symptomatic hypercalcaemia require rehydration with 3–6 L 0.9% saline in the first 24 hours. Once rehydrated, 0.9% saline infusion is continued. Furosemide should only be given to treat fluid overload. Potassium must be added to fluids to avoid hypokalaemia if furosemide is used.

If rehydration fails to correct symptoms or the calcium level remains above 2.8 mmol/L, or if there is a known underlying malignancy at the outset, a bisphosphonate may be given. Zolendronic acid (4 mg over 15 minutes) or ibandronic acid (2–4 mg) or pamidronate can be used. The dose of pamidronate depends on the level of hypercalcaemia (30 mg over 2 hours with calcium <3 mmol/L or significant renal impairment, 60 mg over 4 hours with calcium 3.0–3.4 mmol/L, and 90 mg over 6 hours with calcium >3.4 mmol/L). The use of intravenous bisphosphonates results in a decrease in plasma calcium over 3–5 days.

Doses should not be repeated sooner than a minimum of 7 days. Patients with humoral hypercalcaemia of malignancy due to production of PTH-related protein by the tumour may have a better response to zoledronic acid or gallium nitrate.

Bisphosphonates are not necessary in patients with hypercalcaemia secondary to primary hyperparathyroidism as they often respond to rehydration. Bisphosphonates should particularly be avoided if parathyroid surgery is imminent as their use can cause profound hypocalcaemia postoperatively. Glucocorticoids (prednisolone 40–60 mg per day orally) should be considered if hypercalcaemia is secondary to sarcoidosis, hypervitaminosis D, or myeloma.

Calcitonin, calcimimetics and the novel antiresorptive denosumab have been used to treat hypercalcaemia and are included as footnotes in some guidelines.

KEY POINTS

- The plasma concentration of free calcium is regulated by PTH and vitamin D.
- Malignancy is the most common cause of hypercalcaemia among hospitalised patients.
- Hyperparathyroidism is the most common cause of hypercalcaemia in ambulatory patients.
- Primary hyperparathyroidism may be due to a solitary adenoma (85%), multiple adenomas, or four-gland hyperplasia.
- Hyperparathyroidism may be part of MEN type 1 or 2a.
- The only curative treatment for primary hyperparathyroidism is surgery.
- The accepted criteria for parathyroid surgery include symptoms, age below 50 years, osteoporosis, reduced creatinine clearance, and renal calculi.
- Parathyroid surgery may be complicated by hypocalcaemia.
- Patients who do not meet surgical criteria or who prefer to avoid surgery are managed conservatively with periodic follow-up and adequate oral fluid intake.

25

Hypocalcaemia

Hypocalcaemia may be caused by either decreased calcium entry into the circulation or increased loss of free calcium from the circulation (due to deposition in the tissues or increased binding of calcium in the serum).

Aetiology

Causes of decreased calcium entry into the circulation include:

- *Vitamin D deficiency* (decreased vitamin D synthesis, intake or action): the role of vitamin D in calcium homeostasis is discussed in Chapter 26. Hypocalcaemia is seen with chronic, severely low vitamin D levels; mild vitamin D deficiency does not typically result in low serum calcium levels. Causes of vitamin D deficiency are summarised in Box 25.1.
- *Hypoparathyroidism* (decreased secretion or action of parathyroid hormone [PTH]): the role of PTH in calcium homeostasis is discussed in Chapter 26. Causes of hypoparathyroidism are summarised in Box 25.1. Magnesium depletion may cause reduced PTH secretion and bone resistance to PTH.
- *Pseudohypoparathyroidism*: characterised by target organ (kidney and bone) resistance to PTH.

Causes of extravascular calcium deposition include:

- *Rhabdomyolysis* and *tumour lysis syndrome*: excess tissue breakdown results in acute hyperphosphataemia and consequently calcium deposition, mostly in bone but also in extraskeletal tissue.
- *Acute pancreatitis*: calcium soaps (calcium bound to free fatty acids) are precipitated in the abdominal cavity.
- *Widespread osteoblastic metastases* (e.g. breast or prostate cancer): calcium is deposited in the metastases.
- *Hungry bone syndrome*: calcium is deposited in bone after parathyroidectomy in patients with primary hyperparathyroidism.

Causes of increased intravascular calcium binding include:

- *Acute respiratory alkalosis*: elevated extracellular pH results in increased binding of calcium to albumin and lower plasma free calcium levels.
- *Massive blood transfusion*: the citrate used to inhibit coagulation in banked blood chelates calcium in the serum.
- *Foscarnet* (used to treat cytomegalovirus): chelates calcium in the serum.

Hypocalcaemia may be caused by a number of drugs (see Box 25.1). *Sepsis* can be associated with hypocalcaemia due to impaired secretion of both PTH and calcitriol, and due to end-organ resistance to the action of PTH (probably due to hypomagnesaemia). These may be mediated by the action of inflammatory cytokines on the parathyroid glands, kidneys and bone. In addition, increased lactate levels in sepsis chelate calcium in the serum.

Rarer causes of hypocalcaemia include CaSR gene mutations (autosomal dominant) or autoantibodies directed against the calcium-sensing receptor, resulting in hypocalcaemia and hypercalciuria.

Pseudohypocalcaemia may be seen in patients who have had some of the gadolinium-based contrast agents for magnetic resonance angiography, due to interference with the colorimetric assays for calcium.

Clinical presentations

The clinical manifestations of hypocalcaemia are the result of neuromuscular excitability, which relates to both the rate at which hypocalcaemia

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Box 25.1 Causes of hypocalcaemia

Vitamin D deficiency
- Lack of sun exposure
- Poor intake or malabsorption (e.g. coeliac disease)
- Liver failure (decreased 25-hydroxylation of vitamin D), medications increasing vitamin D metabolism, e.g. phenytoin
- Chronic kidney disease
- Target organ resistance due to mutations in the vitamin D receptor gene (vitamin D-dependent rickets type 2) has an autosomal recessive inheritance and may lead to childhood alopecia along with high PTH and alkaline phosphatase levels. Treatment is with high-dose vitamin D and calcium
- Impaired activation of vitamin D due to mutations in the 1-alpha-hydroxylase gene (vitamin D-dependent rickets type 1) treated with calcitriol

Hypoparathyroidism
- Following thyroid or parathyroid surgery (hypoparathyroidism may be transient or permanent)
- Autoimmune, e.g. part of autoimmune polyglandular syndrome type 1 (see Chapter 6)
- Infiltrative diseases of the parathyroid glands: haemochromatosis, Wilson disease, granulomas, metastatic cancer
- Congenital: DiGeorge syndrome or 22q11.2 deletion syndrome (defective development of the pharyngeal pouch system, resulting in cardiac defects, cleft palate and abnormal facies, hypoplastic thymus, learning difficulties and hypoparathyroidism)
- Genetic: autosomal dominant hypocalcaemia type 1 is caused by an activating mutation in the calcium sensing receptor (CaSR) leading to hypocalcaemia, normal or low PTH levels, high or high normal urinary calcium excretion and renal stones and/or nephrocalcinosis; a different phenotype results in renal salt-wasting with hypokalaemic metabolic alkalosis (similar to a Barter syndorme phenotype). Gain-of-function mutations of G alpha 11 are seen in autosomal dominant hypocalcaemia type 2. An autoimmune variant (with autoantibodies directed against the calcium-sensing receptor) has been described.
- Hypomagnesaemia: due to malabsorption, chronic alcoholism, prolonged parenteral fluid administration, diuretics, aminoglycosides, proton pump inhibitors and cisplatin
- HIV infection

Pseudohypoparathyroidism (end-organ PTH resistance): type 1a, type 1b, type 2

Extravascular calcium deposition
- Hungry bone syndrome
- Pancreatitis
- Rhabdomyolysis
- Tumour lysis syndrome
- Widespread osteoblastic metastases

Increased intravascular calcium binding
- Respiratory alkalosis
- Massive blood transfusions

Sepsis

Drugs
- Combination chemotherapy with 5-fluorouracil and leucovorin (decreases calcitriol production)
- Fluoride poisoning (inhibits bone resorption)
- Bisphosphonates (suppress the formation and function of osteoclasts, especially in people with pre-existing vitamin D deficiency in which case bone resorption is inhibited despite high PTH levels)

develops and the extent to which serum calcium levels fall. Box 25.2 summarises the clinical manifestations of hypocalcaemia.

Pseudohypoparathyroidism

Pseudohypoparathyroidism is characterised by tissue PTH resistance usually caused by mutations in the *GNAS* gene (encoding the alpha subunit of the G protein, coupled to the PTH receptor), resulting in an inability of PTH to activate adenylate cyclase.

- In *type 1a disease*, patients with maternally inherited mutations have hypocalcaemia (due to PTH resistance in the kidney) as well as phenotypic abnormalities (short stature, obesity, round face, short fourth/fifth metacarpals [Figure 25.1], subcutaneous calcification, occasionally mental retardation), known as Albright hereditary osteodystrophy (AHO). Patients with paternally inherited mutations have the phenotypic abnormalities of AHO (due to impaired PTH action in bone) but have normal serum calcium levels (pseudo-pseudohypoparathyroidism). This is an example of tissue-specific genetic imprinting.

Box 25.2 Clinical presentations of hypocalcaemia

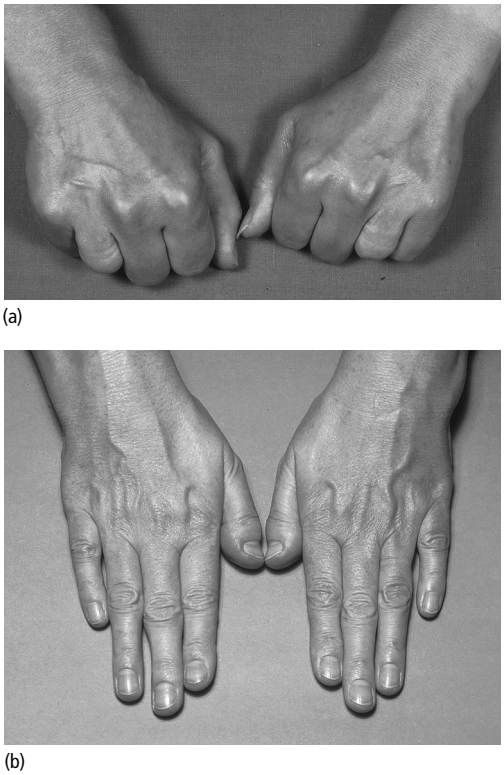
Musculoskeletal
Tetany, muscle spasms/cramps, paraesthesia (perioral/peripheral), myopathy
Chvostek's sign: tapping the facial nerve in front of the ear causes contraction of the facial muscles ipsilaterally
Trousseau's sign: inflating the blood pressure cuff to above systolic blood pressure causes carpal spasm

Neuropsychiatric/eyes
Seizures, fatigue, depression, anxiety, in children mental retardation
Movement disorders: dystonia, hemiballismus, basal ganglia calcifications
Eyes: cataracts, papilloedema with severe hypocalcaemia, keratoconjunctivitis

Cardiovascular
Cardiac failure, hypotension, prolonged QT interval, decreased digoxin effect

Gastrointestinal
Reduced gastric acid secretion, steatorrhoea

Skin
Dry and coarse skin and hair, brittle nails


(a)

(b)

Figure 25.1 Shortening of the fourth (a) and fifth (b) fingers due to short metacarpals.

- *Type 1b* is characterised by hypocalcaemia but not the phenotypic abnormalities of AHO (as PTH resistance is confined to the kidney).
- *Type 2*: the molecular defect in the rare type 2 pseudohypoparathyroidism has not been identified (see 'Investigations' below).

Investigations

Total serum calcium is the sum of free (ionised) calcium and calcium bound to albumin. Changes in serum albumin result in a change in the amount of bound calcium and total calcium, but not free (ionised) calcium. Therefore, the 'total serum calcium' measurement should always be adjusted for albumin levels.

Approximately 40% of circulating calcium is bound to albumin in a ratio of 0.02 mmol/L of calcium per 1.0 g/L of albumin. Therefore, to calculate 'adjusted' (corrected) total calcium: add 0.02 mmol/L to total calcium levels for every g/L of albumin below 40 and subtract 0.02 mmol/L from total calcium for every g/L of albumin over 40.

Useful tests for determining the cause of hypocalcaemia include intact *PTH*, serum *phosphate*, *magnesium*, *alkaline phosphatase* (ALP), *creatinine*, *alanine transaminase*, a *coeliac screen*, *25-hydroxyvitamin D* and *1,25-dihydoxyvitamin D* (Figure 25.2). In hypoparathyroidism, phosphate levels may be normal or high, and PTH is low or inappropriately normal despite low serum calcium. In vitamin D deficiency, serum phosphate levels are low or normal, urinary calcium excretion may be low, bone-specific alkaline phosphatase is elevated and PTH is raised (secondary hyperparathyroidism). It is important to recall that raised serum ALP may reflect bony metastases (albeit typically seen with hypercalcaemia). In acute hypocalcaemia, an ECG should be obtained to look for a prolonged QT interval.

In patients with type 1 pseudohypoparathyroidism, the infusion of PTH fails to induce an increase in urinary cyclic AMP and phosphate excretion (the Ellsworth–Howard test). Patients must be vitamin D replete before the test. In rare type 2 pseudohypoparathyroidism, there is a normal cyclic AMP response without a concomitant increase in phosphate excretion.

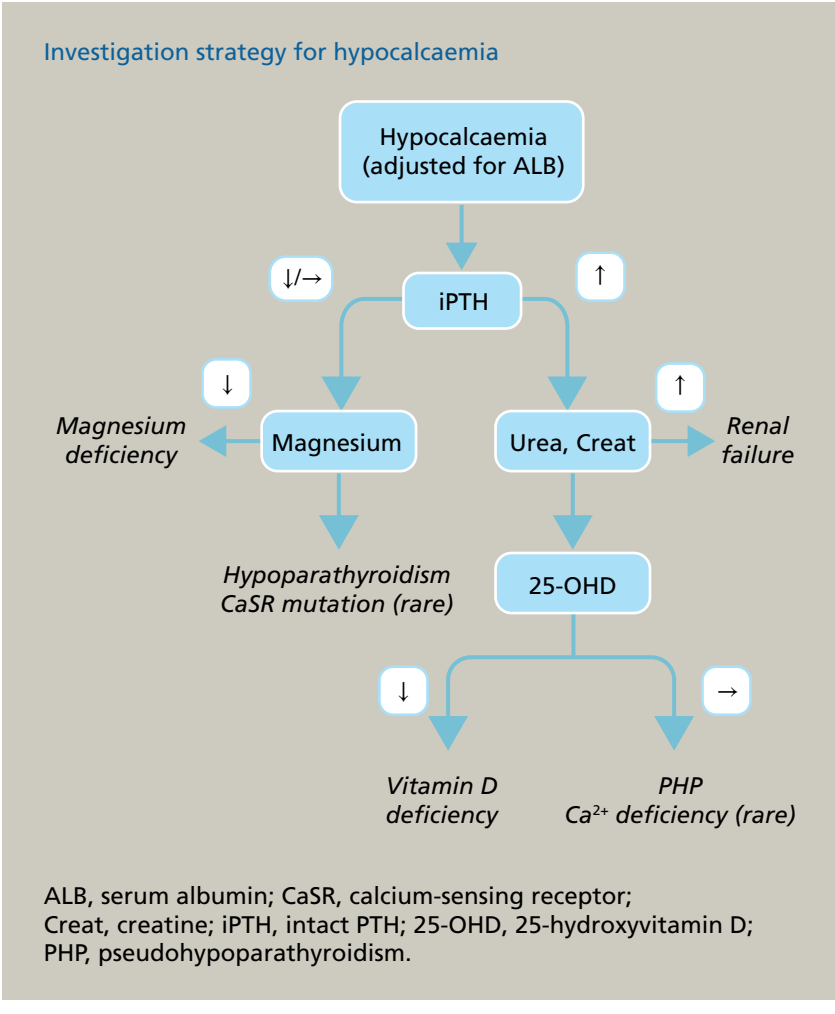


Figure 25.2 Investigation of hypocalcaemia. Source: Hassan-Smith Z, Gittoes N. Hypocalcaemia. Medicine 20212;49(9):562–566.

Treatment

Patients with an adjusted total calcium of more than 1.9 mmol/L are usually asymptomatic and can be treated by increasing dietary calcium intake by 1 g per day or oral calcium supplementation (except in those with hyperphosphataemia).

Many patients become symptomatic when serum total calcium concentration is less than 1.9 mmol/L. Intravenous calcium is required particularly in patients with tetany, seizures, ECG changes and reduced cardiac function.

Calcium gluconate is preferred over calcium chloride as it causes less local tissue necrosis. If the patient is symptomatic, treatment is started with 10 mL 10% w/v calcium gluconate (diluted in 100 mL 0.9% saline or 5% dextrose) infused over 10–20 minutes (with cardiac monitoring). This will increase the serum calcium levels for 2–3 hours, and should be followed by a slow infusion of calcium. A dose of 100 mL 10% calcium gluconate is added to 1 L of 0.9% saline (or 5% dextrose). The infusion may be started at 50 mL per hour and titrated to maintain serum calcium in the low-normal range.

A solution of 10% calcium gluconate contains 10 g of calcium gluconate in 100 mL, and 10 g of calcium gluconate contains about 900 mg of elemental calcium. Therefore, adding 100 mL of 10% calcium to 1 L of fluid gives a preparation close to 1 mg/mL of elemental

calcium. Calcium infusion is usually given at 0.5–1.5 mg/kg per hour of elemental calcium.

Concomitant hypomagnesaemia should be corrected with intravenous magnesium sulfate. Magnesium sulfate 2 g (8 mmol) is given over 10–20 minutes, followed by another 4 g in the next 4 hours if necessary.

Intravenous calcium should be continued until the patient is receiving an effective regimen of oral calcium and vitamin D. Calcitriol (1,25-dihydroxycholecalciferol) is the preferred preparation of vitamin D for patients with severe acute hypocalcaemia because of its rapid onset of action. Calcitriol should be started immediately at a dose of 0.5–1 μg per day. The doses of calcitriol and oral calcium are adjusted to maintain serum calcium in the low-normal range (2.0–2.1 mmol/L). This is because patients with hypoparathyroidism have decreased calcium reabsorption in the distal tubules. Raising plasma calcium above 2.1 mmol/L may result in marked hypercalciuria and calcium stone formation.

In stable patients, serum and urinary calcium should be checked every 6 months to check for hypercalcaemia and hypercalciuria. Bendroflumethiazide may be an adjunct treatment for people with hypocalcaemia and hypercalciuria (as it reduces urinary calcium excretion).

In patients with the rare mutations in the calcium-sensing receptor, vitamin D results in further hypercalciuria, nephrocalcinosis, and renal impairment. Therefore, asymptomatic patients are generally left untreated.

KEY POINTS

- The ‘total serum calcium’ measurement should always be adjusted for albumin levels.
- Clinical presentations of hypocalcaemia include tetany, paraesthesia, cardiac dysfunction and seizures.
- Hypocalcaemia may be caused by either decreased calcium entry into the circulation (e.g. due to hypoparathyroidism or vitamin D deficiency) or increased loss of free calcium from the circulation (due to deposition in tissues or increased binding of calcium in serum).
- Investigation of hypocalcaemia should include serum phosphate, magnesium, alkaline phosphatase, creatinine, 25-hydroxyvitamin D, and PTH levels.
- Symptomatic patients or those with calcium levels below 1.9 mmol/L should receive intravenous calcium gluconate. Chronic hypocalcaemia, for example due to hypoparathyroidism, is treated with calcitriol and calcium supplements.
- The goal of treatment in chronic hypocalcaemia is to maintain serum calcium in the low-normal range without causing hypercalciuria.

26

Osteomalacia

Osteomalacia is a disorder of *mineralisation* of bone matrix ('osteoid'). Rickets is a disorder of defective mineralisation of cartilage in the epiphyseal growth plates of children.

Aetiology

Osteoclasts begin the bone remodelling cycle by excavating a cavity on the bone surface. Osteoblasts lay down the organic matrix ('osteoid').

The process of bone mineralisation begins in the 'matrix vesicles', which are extracellular organelles derived from the plasma membrane of chondrocytes. Calcium is transported from the extracellular space into the matrix vesicles. Phosphatases (e.g. alkaline phosphatase) increase the inorganic phosphate levels inside the matrix vesicles. The increase in intravesicular calcium and phosphate results in a deposition of calcium phosphate, which undergoes conversion to hydroxyapatite. The hydroxyapatite crystals are subsequently released from the matrix vesicles.

Defective bone mineralisation in osteomalacia is mostly due to reduced calcium and phosphate levels in the extracellular fluid. This may be due to *vitamin D deficiency* or *phosphate deficiency* secondary to primary renal phosphate wasting.

Vitamin D deficiency

Vitamin D_3 (cholecalciferol) may either be taken in the diet (e.g. fish, eggs) or synthesised in the skin from 7-dehydrocholesterol by the ultraviolet light in sunshine (Figure 26.1). Vitamin D is activated by hydroxylation in the liver (25-hydroxylation) and the kidneys (1-alpha-hydroxylation), resulting in 1,25-dihydroxyvitamin D.

Causes of vitamin D deficiency are summarised in Box 26.1.

The exact concentrations of 25-hydroxyvitamin D associated with osteomalacia are still not entirely clear. 25-Hydroxyvitamin D concentrations less than 8 ng/mL (20 nmol/L) are generally associated with osteomalacia. Vitamin D deficiency is defined as 25-hydroxyvitamin D levels less than 20 ng/mL (<50 nmol/L). Vitamin D levels between 20 and 30 ng/mL (50–75 nmol/L) are termed 'insufficient'.

Vitamin D insufficiency is extremely common and may contribute to the development of osteoporosis, falls and fractures.

Renal phosphate wasting

Primary renal phosphate wasting can occur in:

- *Renal tubular acidosis* (type 2) due to defective proximal tubular transport. This may be congenital (Fanconi syndrome, Wilson disease, cystinosis) or acquired (e.g. in patients with multiple myeloma).
- *X-linked hypophosphataemic rickets*: mutations in a gene named *PHEX*, which codes for a cleaving enzyme, result in reduced inactivation of hormone-like substances ('phosphatonins') such as fibroblast growth factor-23 (FGF23) that promote phosphate excretion.
- *Autosomal dominant hypophosphataemic rickets*: mutations in the gene for FGF23 interfere with its cleavage.
- *Oncogenic (tumour-induced) osteomalacia*: excess FGF23 is produced by the tumour (usually mesenchymal tumours).

Rarer causes

These include inadequate alkaline phosphatase activity (hypophosphatasia), inhibition of mineralisation by excess fluoride ingestion, and abnormal bone matrix, for example in osteogenesis imperfecta or fibrogenesis imperfecta.

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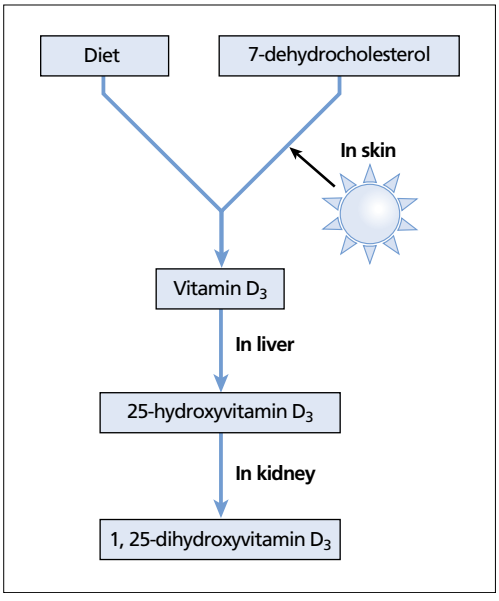

Figure 26.1 Vitamin D_3 may either be taken in the diet or synthesised in the skin from 7-dehydrocholesterol by the effect of ultraviolet light in sunshine. Vitamin D_3 is activated by hydroxylation in the liver and kidneys.

Box 26.1 Causes of osteomalacia

Vitamin D deficiency

Reduced synthesis, intake or absorption

Inadequate sunlight exposure (exacerbated in people with increased skin pigmentation)

Malabsorption: small bowel disease (e.g. coeliac disease, inflammatory bowel disease), extensive bowel surgery, gastrectomy, pancreatic insufficiency, phytate excess (found in chapaties)

Dietary lack of vitamin D

Reduced 25-hydroxylation of vitamin D

Liver disease

Anticonvulsants

Reduced 1-alpha-hydroxylation

Chronic kidney disease

Hypoparathyroidism (reduced stimulation of vitamin D 1-alpha-hydroxylation by PTH)

Vitamin D-dependent rickets type 1 (an autosomal recessive disorder caused by mutations in the gene encoding the enzyme 1-alpha-hydroxylase)

Vitamin D-dependent rickets type 2 (an autosomal recessive disorder caused by mutations in the gene encoding the vitamin D receptor, resulting in target organ resistance to vitamin D)

Primary renal phosphate wasting

Type 2 renal tubular acidosis: Fanconi syndrome, multiple myeloma

Hereditary hypophosphataemic rickets (X-linked and autosomal dominant)

Oncogenic osteomalacia

Rarer causes

Abnormal bone matrix: osteogenesis imperfecta, fibrogenesis imperfecta

Hypophosphatasia (associated with periodontal disease)

Mineralisation inhibitors: high doses of fluoride (e.g. in certain teas), aluminium hydroxide antacids, bisphosphonates

Clinical presentations

Osteomalacia may be asymptomatic and present radiologically as osteopenia. In osteomalacia, the bone is biomechanically unsound and therefore at risk of pathological fractures or 'bowing'. Clinically, patients with osteomalacia may present with diffuse bone pain and tenderness, fractures with little or no trauma (typically in the ribs, vertebrae, and long bones) and proximal muscle weakness, which may be associated with a waddling gait.

History and physical examination should look for symptoms and signs of the possible underlying cause. This should include a detailed dietary history and sensitive questioning about possible disordered eating and laxative abuse.

Children with rickets may present with hypotonia, growth retardation, and skeletal deformities.

The laying down of uncalcified osteoid at the metaphases leads to widening of the ends of the long bones. This may be seen as 'rachitic rosary' in the ribs (enlarged ends of the ribs resembling beads at the costochondral junction) and at the level of the ankle and wrist. Other skeletal deformities include frontal bossing, pectus carinatum, and bowing of the long bones.

Investigations

Radiographic findings

A *spine X-ray* may show decreased bone density, with blurring and deformity of the spine that makes the films appear of low quality. Concavity of the vertebral bodies is seen in more advanced disease.

Looser's zones or 'pseudofractures' are the characteristic radiological finding in osteomalacia. These are narrow radiolucent lines (2–5 mm in width) with sclerotic borders that often lie perpendicular to the cortical margins of the bones. They are usually found at the femoral neck, on the medial part of the femoral shaft and on the pubic rami. They may also occur at the ulna, scapula, clavicle, rib, and metatarsal bones. It has been proposed that Looser's zones may represent stress fractures that have been repaired by inadequately mineralised osteoid. They have also been suggested to be the result of erosion by arterial pulsations.

More severe disease can lead to shortening and bowing of the tibia, fractures and coxa profunda hip deformity (in which the femoral head comes deeply into the pelvis).

Laboratory findings

Patients with vitamin D deficiency may have:

- low plasma phosphate levels
- low-normal to low plasma calcium levels
- an increased alkaline phosphatase level
- low levels of 25-hydroxyvitamin D
- increased PTH (secondary hyperparathyroidism).

Patients with primary renal phosphate wasting have:

- low plasma phosphate levels
- increased phosphate excretion: if the renal phosphate wasting is not the cause of the hypophosphataemia, the fractional excretion of phosphate should be well below 5%
- a normal anion gap (hyperchloraemic) metabolic acidosis if the patients have renal tubular acidosis.

Patients with hypophosphatasia have low alkaline phosphatase levels but normal plasma calcium and phosphate concentrations.

In patients with tumour-induced osteomalacia, a thorough search for the tumour must be undertaken with magnetic resonance imaging or technetium scans.

Osteomalacia can be accurately diagnosed by bone biopsy using double tetracycline labelling. Tetracycline is deposited at the mineralisation front as a band. After two courses of tetracycline (separated by a period of days), the distance between the bands of deposited tetracycline is reduced in osteomalacia. However, despite its accuracy, bone biopsy is not usually performed as osteomalacia can be diagnosed from the history, examination, laboratory, and radiological studies.

Treatment

Treatment should include reversal of the underlying disorder (e.g. a gluten-free diet in coeliac disease) and supplementation with vitamin D and calcium (at least 1000 mg per day). Vitamin D replacement reduces fracture rate and improves bone tenderness and muscle weakness.

Vitamin D replacement

Patients with nutritional vitamin D deficiency may initially be treated with 20 000–50 000 IU of oral vitamin D_2 (ergocalciferol) or D_3 (cholecalciferol) once a week for 6–12 weeks, followed by maintenance doses of 800–1000 IU of vitamin D_3 daily. Vitamin D_2 is made by ultraviolet irradiation of ergosterol obtained from yeast. A dose of 300 000 IU of intramuscular ergocalciferol in one or two doses per year is an alternative option when poor compliance is suspected.

25-Hydroxyvitamin D concentrations should be measured approximately 3 months after initiating therapy. The dose of vitamin D may require adjustment depending upon individual absorption.

In patients with a gastrectomy or malabsorption, high doses of vitamin D (10 000–50 000 IU daily) may be necessary. The adequacy of the calcium and vitamin D supplementation should be confirmed by measurements of serum calcium, phosphate, 25-hydroxyvitamin D and parathyroid hormone (PTH).

Vitamin D-deficient and -insufficient pregnant women are treated more slowly, with 800–1000 IU of vitamin D_3 daily. Urinary calcium excretion increases in pregnancy, and it should be monitored when treating vitamin D deficiency, particularly in women with a history of renal stones.

Patients with defective vitamin D_3 hydroxylation (e.g. due to chronic renal failure or liver disease) are treated with alfacalcidol or calcitriol (0.25–1.0 µg per day), which have a rapid onset of action and a shorter half-life (around 6 hours).

Patients with hereditary hypophosphataemic rickets are treated with a combination of oral phosphate supplementation and calcitriol.

Patients with vitamin D insufficiency may be treated with 800–1000 IU of vitamin D_3 daily. Vitamin D replacement in patients with co-existing vitamin D insufficiency and primary hyperparathyroidism is controversial. A small study of vitamin D replacement in patients with co-existing vitamin D insufficiency

and primary hyperparathyroidism (with mild hypercalcaemia) showed a decrease in PTH level and no increase in mean calcium concentrations.

Follow-up and monitoring

In hypocalcaemic patients, serum calcium is monitored every 2 weeks until normocalcaemic (to permit early detection of hypercalcaemia from excessive dosing). The 24-hour urinary calcium should be monitored initially after 3 months and less frequently as plasma calcium stabilises. Maintenance of normal urinary calcium levels often indicates that treatment is effective.

Serum calcium, phosphate, alkaline phosphatase, PTH levels and vitamin D (25-hydroxyvitamin D or 1,25-dihydroxyvitamin D depending on the aetiology of the osteomalacia) should be rechecked after 3 months of therapy and at regular intervals thereafter. The dose of vitamin D should be adjusted accordingly.

KEY POINTS

- Osteomalacia is a disorder of decreased mineralisation of bone matrix.
- Defective mineralisation in osteomalacia is mostly due to reduced calcium and phosphate levels in the extracellular fluid, which may be caused by vitamin D deficiency or primary renal phosphate wasting.
- Osteomalacia may present with diffuse bone pain and tenderness, fractures and proximal muscle weakness.
- Looser's zones or 'pseudofractures' are the characteristic radiological finding in osteomalacia.
- Patients with osteomalacia may have low plasma phosphate, low plasma calcium, increased alkaline phosphatase, and low levels of 25-hydroxyvitamin D or increased phosphate excretion.
- Treatment should include reversal of the underlying disorder and supplementation with vitamin D and calcium.
- Patients with hereditary hypophosphataemic rickets may be treated with a combination of oral phosphate supplementation and calcitriol.

27

Osteoporosis

Bone remodelling

Bone is continuously being formed and resorbed. This 'remodelling' process is important in the prevention of fatigue damage and the maintenance of calcium homeostasis. Around 10% of the skeleton is 'remodelled' each year in adults.

The bone remodelling cycle consists of three phases (Figure 27.1).

- *Resorption:* osteoclasts remove matrix and mineral on the trabecular surface or within the cortical bone.
- *Reversal:* mononuclear cells, possibly of monocyte/macrophage lineage, appear on the bone surface and may provide signals for osteoblast differentiation and migration.
- *Formation:* osteoblasts lay down bone to replace resorbed bone.

Cellular signals regulating bone remodelling

Cells of the osteoblast lineage express a factor called RANKL (receptor activator of nuclear factor kappa B ligand), which interacts with a receptor on osteoclast precursors called RANK and results in the activation and differentiation of osteoclasts.

Osteoporosis

Osteoporosis is a skeletal disease characterised by reduced bone mass and microarchitectural deterioration, resulting in increased bone fragility and fracture risk.

Epidemiology

According to the International Osteoporosis Foundation, osteoporosis affects approximately 1 in 3 women and 1 in 8 men worldwide. After the age of 50 years, the risk of osteoporotic fractures is 40% in women and 15% in men. This is termed the 'lifetime fracture risk.' In both men and women, the incidence of hip fractures increases exponentially with age, although the increase begins approximately 5–10 years later in men. This is because oestrogen levels fall after the menopause, accelerating bone loss, whereas men are relatively protected by higher testosterone levels.

Aetiology

Osteoporosis is characterised by increased bone turnover. However, an imbalance between rates of bone formation and resorption results in bone loss and consequent trabecular thinning and perforation, with loss of bone strength.

Bone mineral density (BMD) changes with age (Figure 27.2). The maximum BMD ('peak bone mass') is achieved by the age of 30–40 years. Thereafter, bone is lost in both men and women at a rate of about 1% per year. Women experience a phase of accelerated bone loss for 3 years after the menopause. A decrease in spine BMD of 1 standard deviation (or 12%) doubles the risk of fracture. Box 27.1 summarises the factors that increase the rate of bone loss.

Clinical presentations

Osteoporosis does not cause pain or deformity per se but increases the risk of fractures that can then result in pain, deformity, increased dependence, and mortality. Osteoporosis-related fractures associated with minor trauma (fragility fractures) tend to occur

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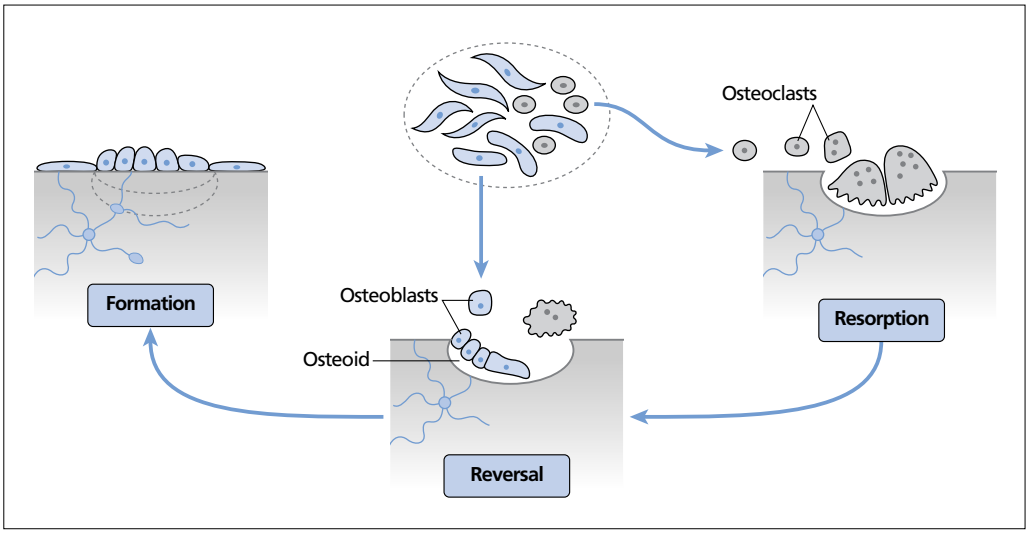

Figure 27.1 The process of bone remodelling. Osteoclast precursors are attracted to the site to be resorbed. They differentiate and fuse to form multinucleated osteoclasts, which resorb bone by secreting acid and proteolytic enzymes. Osteoblast precursors are attracted to the site that has undergone resorption. They differentiate and lay down uncalcified bone matrix (osteoid), which then calcifies to form mature bone.

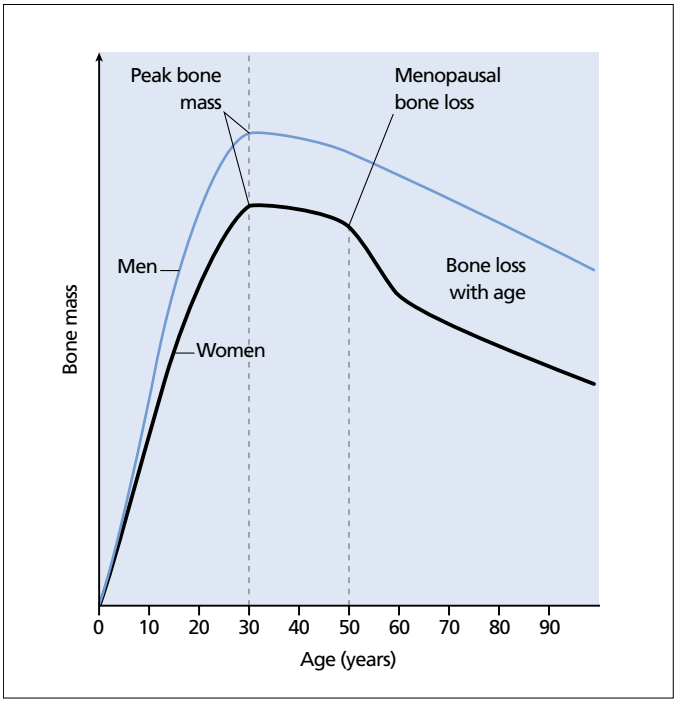

Figure 27.2 Changes in bone mass with age in men and women.

Box 27.1 Factors associated with increased bone loss

Family history
Lifestyle: reduced exercise, excess alcohol, smoking
Drugs: corticosteroids, cyclosporine, cytotoxic agents, heparin
Endocrine causes: hypogonadism, hyperparathyroidism, Cushing syndrome, osteomalacia, thyrotoxicosis
Malabsorption: coeliac disease
Myeloma
Liver disease
Renal disease
Anorexia nervosa
Rheumatoid arthritis and other inflammatory conditions

at sites comprising more than 50% trabecular bone (i.e. less than 50% cortical bone). These sites include the:

- *Vertebral bodies*: these fractures result in backache that usually subsides after 3 months. Chronic pain may occur due to secondary osteoarthritis. Vertebral fractures also result in kyphosis, loss of height, and abdominal protrusion. Vertebral fractures may appear as wedge deformity (loss of anterior height), endplate deformity (loss of middle height), or compression deformity (loss of anterior, posterior and middle height).
- *Proximal femur*: mortality is increased by 20% in the first year following a hip fracture.
- *Distal radius* (Colles fracture): may have a significant deleterious effect on independence

Investigations

Diagnosis

In patients presenting with osteoporosis-related fractures, BMD is measured using *dual-energy X-ray absorptiometry* (DEXA). It is worthwhile measuring BMD in patients with low-trauma fractures and those with strong risk factors, for example taking long-term corticosteroids.

Low doses of X-rays of two different energy levels are directed towards areas of interest (lumbar spine, proximal femur, distal radius) and are absorbed to different extents by bone and soft tissue. This principle is used to calculate bone density in g/cm^2.

The *T-score* compares the patient's BMD with that of a young reference population. The World Health Organization (WHO) has selected a T-score of –2.5 or less to define osteoporosis in healthy postmenopausal women and men aged 50 years and older. The diagnosis of osteoporosis is made by DEXA using the lowest T-score of the lumbar spine (L1–L4), proximal femur, or distal radius. A T-score of between –2.5 and –1.0 is referred to as osteopenia.

The *Z-score* compares the patient's BMD to that of an age-matched reference population. In premenopausal women and younger men, the relationship between BMD and risk of fracture is not well established. For premenopausal women and men under age 50 years, Z-scores rather than T-scores should be used. In these patients, a clinical diagnosis of osteoporosis may be made in the presence of a fragility fracture, or when there is low BMD and risk factors for fracture, such as long-term steroid therapy or hyperparathyroidism.

Secondary causes

Patients with osteoporosis-related fractures resulting from minor trauma should be investigated to look for secondary causes (Box 27.2).

Other investigations

Markers of bone turnover (such as osteocalcin and N-terminal telopeptides) can be used to predict those at risk of osteoporosis. Furthermore, the effects of drug treatment on osteoporosis can be quantified and monitored in a shorter timeframe (maximal effect at ~6 months, compared to 2 years for DEXA).

Box 27.2 Investigations for secondary causes of osteoporosis

Endocrine causes

Hypogonadism: luteinising hormone, follicle-stimulating hormone, oestradiol (premenopausal women), testosterone (men)
Primary hyperparathyroidism: calcium, phosphate, PTH
Osteomalacia: calcium, phosphate, alkaline phosphatase, 25-hydroxyvitamin D, 1,25-dihydroxyvitamin D (if indicated)
Thyrotoxicosis: thyroid-stimulating hormone, free thyroxine
Cushing syndrome: 24-hour urine free cortisol or overnight dexamethasone suppression test (if clinically indicated)

Myeloma

Erythrocyte sedimentation rate, serum protein electrophoresis, urinary Bence Jones protein

Malabsorption

Full blood count, coeliac screen

Bone biopsy is rarely used but can be helpful in unusual forms of osteoporosis in young adults. It may provide information about the presence of rare secondary forms of osteoporosis (e.g. systemic mastocytosis).

Treatment

The aims of treatment are:

- alleviation of pain (with adequate analgesics)
- restoration of vertebral height may be attempted (within 6 weeks of fracture) by percutaneous vertebroplasty (injecting bone cement into the vertebral body) or balloon kyphoplasty (inflating a balloon within the vertebral body then adding bone cement)
- reduction of the risk of further fractures (currently available drugs for osteoporosis reduce the incidence of fractures by up to 50%)
- treatment of the underlying cause: this often leads to a partial recovery of bone mass.

All patients with low BMD should receive adequate calcium (1200 mg per day), vitamin D (800 U per day), advice regarding lifestyle modifications, i.e. weight-bearing exercise, smoking cessation and avoidance of excessive alcohol use, and falls prevention counselling.

WHO Fracture Risk Assessment Tool (FRAX)

The *FRAX* calculator (www.sheffield.ac.uk/FRAX/tool.aspx?country=1) may be used to calculate the 10-year probability of hip fracture and major osteoporotic (clinical spine, forearm, hip, shoulder) fracture. The FRAX calculator requires information regarding age, sex, weight, height, previous fractures, parental fractured hip, current smoking, alcohol (≥3 units per day), glucocorticoids (>3 months at a dose of prednisolone ≥5 mg per day), rheumatoid arthritis, secondary osteoporosis (due to untreated long-standing hyperthyroidism, hypogonadism, chronic malnutrition/malabsorption, chronic liver disease, type 1 diabetes, osteogenesis imperfecta in adults), and BMD at the femoral neck (if available).

If the fracture risk is calculated in the absence of BMD, the patient may be classified to be at low, intermediate, high or very high risk (Figure 27.3):

- *For patients at low risk:* reassure, give lifestyle advice and re-evaluate in 5 years or less depending on the clinical context.
- *For patients at intermediate risk:* measure BMD and recalculate the fracture risk to determine whether an individual's risk lies above or below the intervention threshold (see below).
- *For patients at high risk:* consider pharmacological treatment.
- *For patients at very high risk:* consider specialist referral and treatment with teriparatide.

When the BMD of the femoral neck is available, it can be included in the calculation of the fracture risk to determine whether the individual lies above or below the intervention threshold. Treatment should be strongly considered in individuals with probabilities of a hip fracture and/or major osteoporotic fracture above the intervention threshold. Where both probabilities fall below the treatment threshold, a further assessment is recommended in 5 years or less depending on the clinical context.

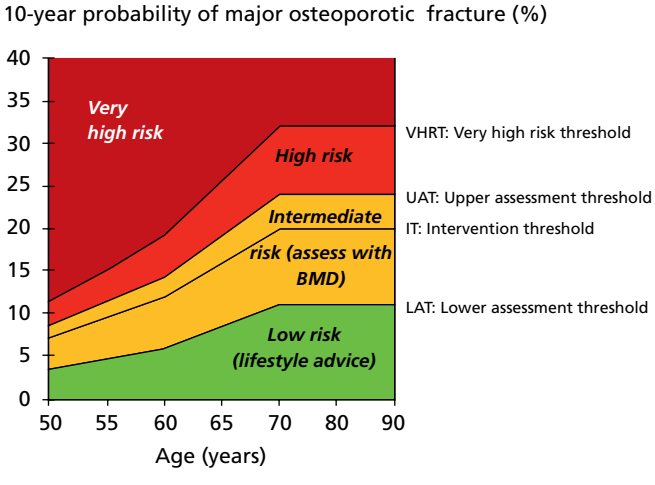

Figure 27.3 Intervention Thresholds.

Antiresorptive drugs

Bisphosphonates

Alendronate (70 mg weekly) or *risedronate* (35 mg once weekly) are often recommended as first-line therapy. If the patient's diet does not contain sufficient calcium, a calcium supplement (700 mg per day) should be given in the evening. Bisphosphonates must be taken with a full glass of water half an hour before breakfast to help absorption. Patients must be advised not to lie down after taking the tablet in order to avoid oesophagitis. These strict dosing instructions may reduce compliance. Bisphosphonates prevent fracture of the hip, spine, and forearm.

Intravenous zoledronic acid may be used in patients who cannot tolerate oral bisphosphonates, or cannot comply with administration instructions (e.g. an inability to sit upright for 30–60 minutes).

Vitamin D insufficiency/deficiency should be treated before initation of parenteral anti-osteoporosis treatment.

Bisphosphonates have an excellent safety record although there is a small increased risk of osteonecrosis of the jaw and atypical femoral fractures. It is recommended that oral therapy and intravenous therapy are paused after 5 and 3 years, respectively, if BMD has increased above –2.5. Bone turnover markers and/or DEXA can then be measured every 2 years until bone loss recurs. If the BMD remains below –2.5, bisphosphonates can be continued for up to 10 years, and should then be stopped.

Raloxifene

Another alternative in postmenopausal women with osteoporosis is raloxifene (a selective oestrogen receptor modulator), which may be given in a dose of 60 mg per day. It reduces the risk of spine (but not other) fractures. Raloxifene may reduce the risk of breast cancer and increase the risk of deep vein thrombosis.

Denosumab

A human anti-RANK ligand monoclonal antibody, which inhibits osteoclasts, denosumab is administered by subcutaneous injections every 6 months. It reduces spine, hip and non-vertebral fracture. Upon stopping denosumab, bone turnover markers increase, so another drug should be started to prevent this and the subsequent risk of vertebral fractures.

Hormone replacement therapy

Hormone replacement therapy is no longer a first-line treatment for osteoporosis but may be used in women with premature menopause up to the age of 50 (see Chapter 23).

Anabolic treatment

Teriparatide is a recombinant fragment of parathyroid hormone (PTH) that is administered subcutaneously (20 µg per day). It increases BMD and reduces fracture risk. It is recommended in patients with severe osteoporosis (T-score <–2.5 and at least one fragility fracture) who do not tolerate bisphosphonates or do not respond to them (i.e. who continue to have fractures after 1 year of therapy).

Previous or current bisphosphonate use blunts the response to PTH so PTH should be started about 3 months after bisphosphonates have been discontinued. PTH treatment should be continued for 24 months; it is not effective beyond this and there are concerns about the potential for development of osteosarcomas with long-term therapy (based on rodent studies). For patients at high risk of subsequent fracture after discontinuing PTH, a bisphosphonate may be started after the PTH has been discontinued. The high cost of PTH restricts its use to those at very high risk.

Romosozumab is a monoclonal antibody that inhibits sclerostin. Sclerostin is produced by osteocytes and inhibits bone formation. Romosozumab (administered by monthly subcutaneous injections) may be given to patients with multiple fragility fractures, and those at high risk for fracture who cannot tolerate or fail other treatments. Therapy is limited to 12 months.

Premenopausal women

In premenopausal women, isolated low bone mass may or may not be associated with a decrease in bone strength or quality. However, those with secondary causes of low bone mass are more likely to have an increased risk of fracture. Therefore, a secondary cause of low BMD should be determined and treated. A DEXA scan should be repeated in 1 year. Those with no accelerated bone loss or fragility fractures and no known secondary cause may not require any pharmacological treatment.

Men

Secondary causes of osteoporosis are commonly found among men. Therefore, men should be thoroughly investigated, and a secondary cause of low BMD should be determined and treated.

Men with osteoporosis and hypogonadism should receive testosterone replacement therapy. Bisphosphonates remain a reasonable alternative in these men. PTH therapy may be considered for men with severe osteoporosis (T-score <–2.5 and at least one fragility fracture) who are unable to tolerate

bisphosphonates or who continue to have fractures after 1 year of bisphosphonate therapy.

Preventing osteoporosis

Prevention of osteoporosis should aim to maximise peak bone mass and reduce the rate of bone loss. Preventive measures include using adequate calcium (at least 1000 mg per day) and vitamin D intake (400–800 IU per day), regular (although not excessive) weight-bearing exercise, and avoidance of smoking and alcohol. Hip fractures can be prevented in elderly patients by the use of hip protectors.

The need for bisphosphonates depends on the fracture risk, determined by a combination of low BMD and risk factors (advanced age, prior fragility fracture, a parental history of hip fracture, corticosteroid use, excess alcohol intake, rheumatoid arthritis, current cigarette smoking).

Markers of bone turnover may be useful in predicting the rate of future bone loss and risk of fractures in patients with osteopenia. Patients with osteopenia (a T-score between –2.5 and –1) may be treated if their bone turnover markers are above the upper limits of normal for premenopausal women. Bone density measurement should be repeated after 2 years in patients with osteopenia.

Follow-up and monitoring

There is no consensus on the optimal monitoring for osteoporosis. However, most guidelines recommend follow-up DEXA scan (of the hip and spine) 1 year after starting treatment. The same DEXA instrument should be used for serial BMD testing whenever possible, as it is not possible to make quantitative comparisons of BMD measured on different instruments unless a cross-calibration study has been done. If BMD is stable or improved, the frequency of monitoring may be reduced thereafter.

Biochemical markers of bone turnover (which include urine cross-linked N-terminal telopeptides of type 1 collagen [NTX] or serum cross-linked C-terminal telopeptides of type 1 collagen [CTX]) may be used to monitor the response to antiresorptive treatment, particularly if a repeat DEXA scan cannot be performed at 1 year. A 50% decrease in fasting urinary NTX or serum CTX 6 months after treatment indicates compliance with antiresorptive treatment.

Monitoring patients on PTH treatment should include measurement of serum calcium, renal function and uric acid prior to initiation of therapy and at least once during the course of treatment.

KEY POINTS

- Osteoporosis is characterised by reduced bone mass and microarchitectural deterioration resulting in increased bone fragility and fracture risk (particularly of the hip, vertebrae, and distal radius).
- The WHO definition of osteoporosis is based on a T-score of –2.5 or less (measured using DEXA) in healthy postmenopausal women and men age 50 years and older.
- Secondary causes of osteoporosis include hypogonadism, hyperparathyroidism, osteomalacia, thyrotoxicosis, and Cushing syndrome.
- The WHO FRAX tool may be used to calculate the 10-year probability of hip and major osteoporotic fractures and helps in treatment decision plans.
- Alendronate or risedronate is often used as the first-line therapy for osteoporosis. Other therapies include strontium ranelate and raloxifene.
- Teriparatide should be considered in patients with a T-score less than –2.5 and at least one fragility fracture who do not tolerate bisphosphonates or continue to have fractures after 1 year of bisphosphonate therapy.

28

Paget Disease of Bone

Paget disease of bone is a skeletal disorder characterised by increased bone turnover.

Epidemiology

It is difficult to estimate the incidence of Paget disease of bone because most patients are asymptomatic. Studies of autopsies and plain radiographs of unselected patients admitted to hospitals have shown Paget disease in 3–4% of patients over the age of 40 years. The incidence appears to increase with age, but overall incidence is falling. Men are affected more often (1.4:1).

Paget disease is more common in areas of the world with large concentrations of people of Anglo-Saxon origin, and it is rare in Asia, Africa, and Scandinavia.

Aetiology

The aetiology of Paget disease is unknown. Genetic factors and viral infection (possibly canine distemper virus) may play a role, as suggested by familial and pathological studies.

Excessive bone resorption by abnormally large osteoclasts is followed by increased bone formation by osteoblasts in a disorganised fashion. This results in an abnormal ('mosaic') pattern of lamellar bone. The marrow spaces are filled by an excess of fibrous tissue with a marked increase in blood vessels.

Clinical presentations

Around 90% of patients with Paget disease are asymptomatic. The diagnosis is usually suspected from a plain radiograph obtained for some other reason, or from routine biochemistry screen showing an elevated serum alkaline phosphatase (ALP). Any part of the skeleton may be involved but the most commonly affected areas are the pelvis, spine, skull, and long bones (proximal and distal areas). Single (monostotic) or multiple (polyostotic) bone involvement may occur.

The changes of Paget disease spread through individual bones (at an annual rate of about 1 cm). However, it is rare for the disease to move between bones. Therefore, when patients present with Paget disease, the distribution within their skeleton is likely to remain fixed.

Pain

Pain may be due to periosteal stretching caused by bone enlargement, microfractures, or secondary degenerative arthritis. Bone pain often worsens upon weight bearing and at night. Patients may complain of headache due to skull involvement. Pain may also arise from complications including nerve impingement or osteosarcoma. Increased blood flow in the affected areas may also cause a warm sensation.

Deformities

The bone changes result in enlarged and abnormally contoured bones, for example anterior bowing of the tibia and anterolateral bowing of the femur. Involvement of the skull may be seen as enlargement of the frontal (bossing) and occipital areas.

Fractures

The abnormal bone is weak and prone to fractures. Fractures may be associated with substantial acute blood loss.

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Osteosarcoma

Osteosarcomas occur in up to 1% of cases. These may present with increased pain with or without an enlarging mass. Such patients have a poor prognosis, with a 5-year survival rate of 10–15%.

Neurological complications

Nerve compression may be caused by enlarging bones. Compression of the eighth, seventh and second cranial nerves can result in hearing loss, facial palsy and visual disturbance respectively. Involvement of the base of the skull can lead to invagination of the skull by cervical vertebrae (platybasia), and possibly to hydrocephalus due to blockage of the aqueduct of Sylvius.

Involvement of the spine can result in nerve impingement. Increased blood flow to highly vascularised and hypermetabolic pagetic bone may cause ischemic myelitis (vascular 'steal syndrome').

Cardiac complications

High-output cardiac failure can occur in Paget disease with involvement of more than 20% of the skeleton. Signs of calcific aortic stenosis and conduction abnormalities are more common in patients with severe Paget disease (with ≥75% involvement of three or more major bones).

Investigations

Laboratory findings

Patients with Paget disease have an elevated concentration of the bone isoform of serum ALP (a marker of increased bone formation), although this may be normal in monostotic disease. ALP can be used as a marker of disease activity. Serum calcium, phosphate, and 25-hydroxyvitamin D concentrations are normal. Hypercalcaemia can occur with immobilisation or fracture due to an unopposed increase in bone resorption.

Patients with polyostotic Paget disease have an increased urinary excretion of hydroxyproline (a reflection of accelerated bone resorption), but this test is not readily available.

Radiographs

The diagnosis of Paget disease is primarily based on plain radiographs. In the early stages, bone resorption at localised areas may be seen as lytic areas. Later, chaotic new bone formation results in a lack of distinction between the cortex and medullary bone. The affected bones are expanded (Figure 28.1). This feature is helpful in differentiating Paget disease from sclerotic metastases, in which the bone is of normal size.

Plain radiographs also show the adjacent joints, fractures and extent of deformity. Involvement of the skull begins with radiolucent areas (osteoporosis circumscripta) followed, many years later, by a 'cotton wool' appearance due to disruption of normal bone architecture.

Radioisotope bone scan

Radioisotope bone scanning is recommended for determining the extent of skeletal involvement, but is not specific for diagnosis. Pagetic bone lesions are seen as focal areas of markedly increased uptake ('hot spots').

Differentiating Paget disease from metastatic bone disease is sometimes difficult. Previous laboratory tests and radiographs can be helpful. If, for example, laboratory and radiographic studies from the previous year were normal, the diagnosis of Paget disease is unlikely. In rare cases, usually affecting a single vertebra, distinguishing between Paget disease and metastasis may require computed tomography-guided biopsy.

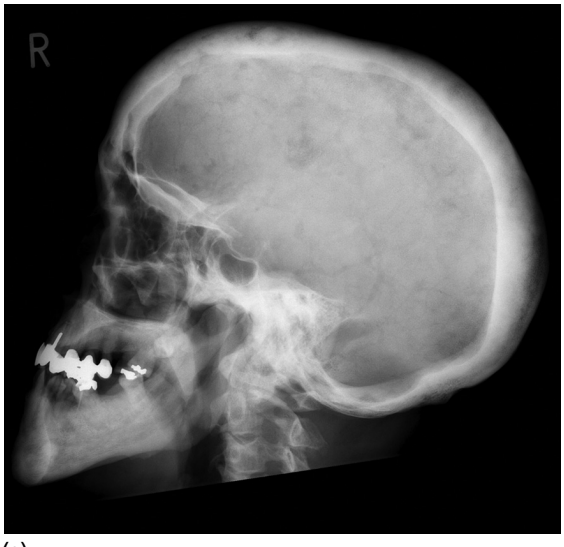
Treatment

The primary indication for treatment in Paget disease is the presence of symptoms rather than radiological signs or elevated ALP, unless affecting the skull base or long bones.

Long-term studies are needed to determine whether treatment prevents complications. However, many endocrinologists also treat patients with involvement of sites where there is an increased risk of complications, i.e. the skull (deafness), long bones (deformity, fracture, arthritis) and spine (cord compression, vascular steal syndrome).

If there is doubt regarding the origin of pain when both Paget disease and osteoarthritis are present, the arthritis may be treated first with paracetamol or non-steroidal anti-inflammatory drugs.

All drugs used to treat Paget disease suppress osteoclastic activity. Many endocrinologists use bisphosphonates as first-line therapy because of their superior efficacy compared with calcitonin and their minimal side-effects.



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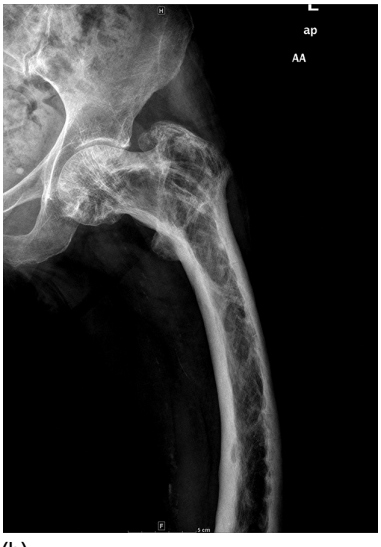

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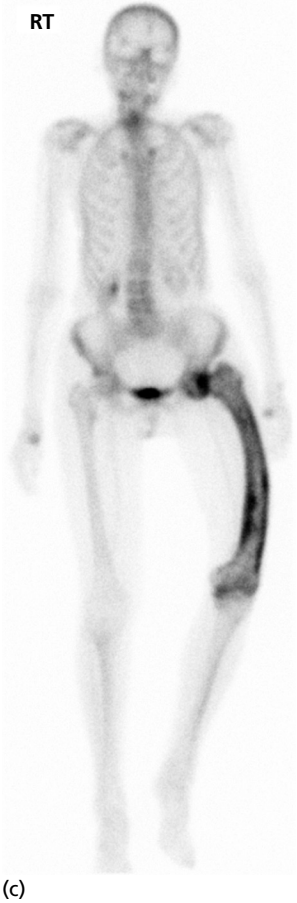

(c)

Figure 28.1a Paget's disease of skull and mandible (note the bone expansion).
Figure 28.1b Paget's disease of the left femur. There is bony expansion, cortical thickening and coarsening of the trabeculation.
Figure 28.1c Bone scintigraphy confirming monostotic Paget's disease of the left femur.

Bisphosphonates

Bisphosphonates are considered the first-line treatment for bone pain in Paget disease and may be considered as part of a treatment package for associated neurological complications. Zoledronic acid is the recommended first-line agent, a dose of 5 mg intravenously is administered annually.

Side-effects of bisphosphonates include low-grade fever and flu-like symptoms in the first 1–2 days in 20% of patients. Hypocalcaemia may occasionally occur, and can be ameliorated by the administration of 1000 mg calcium per day for 1–2 weeks. Rarer side-effects include ocular complications (conjunctivitis, uveitis, scleritis) and osteonecrosis of the jaw.

Calcitonin

Evidence for the use of calcitonin in Paget disease is weak but it may be considered in people with bone pain or neurological complications. Salmon calcitonin may be given initially at a dose of 100 U per day subcutaneously at bedtime. Biochemical improvement (a 50% reduction in serum ALP) occurs in 3–6 months. The dose is then reduced to 50–100 U every other day. The optimum duration of treatment has not been established. Intermittent therapy may be tried. Patients with severe disease may require indefinite treatment.

Around 20% of patients become resistant to salmon calcitonin due to the development of antibodies. Human calcitonin has been developed to avoid this problem, but is somewhat less potent than salmon calcitonin. Both salmon and human calcitonin are expensive, and 20% of patients have side-effects such as nausea, facial flushing, and a metallic taste. Rare side-effects include diarrhoea, abdominal pain, and allergic reactions.

Surgery

Elective surgery for joint replacement, tibial osteotomy, and internal fixation of pathological fractures may benefit patients with refractory pain. Patients with spinal cord compression, spinal stenosis, or basilar invagination complicated by neural compromise may require decompression procedures. Pretreatment with calcitonin or bisphosphonates (for a minimum of 2–3 months) may prevent excessive bleeding and postoperative hypercalcaemia (again, evidence for this is lacking).

Follow-up and monitoring

Patients should be clinically monitored for an improvement in symptoms such as pain and symptoms of nerve compression. Effective therapy results in a reduction in serum ALP and urinary hydroxyproline levels. Serum ALP should be measured initially every other month and, once stabilised, once or twice a year as long as there is a good clinical response.

Repeat bone scans and radiographs are not necessary unless the patient has new or progressive symptoms. Neurological complications may improve with early treatment. Bowed extremities will not change.

KEY POINTS

- Paget disease of bone is a skeletal disorder characterised by increased bone turnover.
- Ninety percent of patients with Paget disease are asymptomatic. The diagnosis is usually suspected from a plain radiograph obtained for some other reason, or from a routine biochemistry screen showing an elevated serum ALP.
- Complications of Paget disease include pain, deformities, fractures, osteosarcoma, nerve compression (e.g. eighth cranial nerve), and high-output cardiac failure.
- The diagnosis of Paget disease is primarily based on plain radiographs, which may show lytic areas (in the early stages), a lack of distinction between cortex and medullary bone and expanded bones.
- The primary indication for treatment in Paget disease is the presence of symptoms.
- Many endocrinologists use bisphosphonates as first-line therapy.

29

Disorders of puberty

Puberty

Puberty is the process of acquisition of secondary sexual characteristics and attainment of reproductive function. Puberty is associated with a growth spurt (accelerated linear growth). Secondary sexual characteristics include the development of genitalia, pubic and axillary hair in boys and girls, the development of breasts in girls, and an increase in testicular volume in boys.

Normal puberty occurs between the ages of 8 and 13 years in girls and 9 and 14 years in boys, and usually lasts for 3–4 years. During puberty, girls gain an average 22 cm height and boys 27 cm.

During puberty, there are also significant neurological and psychosocial changes which includes the capacity for abstract thinking, development of identity, and adoption of health behaviours.

Endocrinology of puberty

The first step in initiation of puberty is activation of the hypothalamic *gonadotrophin-releasing hormone (GnRH) pulse generator* and the pulsatile secretion of GnRH. This results in an increase in plasma concentrations of luteinising hormone (LH), follicle-stimulating hormone (FSH), and sex steroids, i.e. testosterone in boys and oestradiol in girls.

The initial change in gonadotrophin secretion during the early stages of puberty is a nocturnal increase in serum LH levels during sleep. In the later stages of puberty, daytime LH levels also increase, gradually changing to the adult pattern of one pulse every 90 minutes throughout the day and night.

The activation of the GnRH pulse generator and onset of puberty is likely to be influenced by multiple neuronal and hormonal signals that are not completely understood.

It has been proposed that a critical body weight or composition is necessary for the development of puberty. *Leptin* is a hormone produced largely in adipocytes and may act as a signal of the availability of the metabolic reserve necessary for pubertal development.

Kisspeptin is a hypothalamic neuropeptide that binds to the GPR54 receptor. Kisspeptin/GPR54 signalling has also been shown to be crucial for the development of puberty. Mutations in GPR54 cause autosomal recessive hypogonadotrophic hypogonadism in humans.

Separately, there is enlargement of the zona reticulosa of the adrenal gland around 18 months before central puberty commences. Adrenal androgens are subsequently released. The clinical significance of adrenarche is not fully understood.

Tanner staging

Normal puberty occurs between the ages of 8 and 13 years in girls, and 9 and 14 years in boys. Although girls enter puberty at an earlier chronological age than boys, their onset of fertility is usually later.

The sequence of pubertal changes in secondary sexual characteristics may be categorised into five *Tanner stages*. Box 29.1 describes the five Tanner stages for the development of pubic hair (both males and females), breasts (in girls), and genital changes (in boys).

- In *girls*, the first sign of puberty is the onset of *breast development* (thelarche). Breast enlargement is followed by the development of pubic hair (pubarche). Menarche occurs 2–3 years after the onset of puberty, usually at breast stage 5. The first 1–2 years following menarche involve anovulatory cycles associated with irregular and usually painful periods. Peak growth velocity (the growth spurt) occurs within the first year after the onset of puberty and is limited after menarche.

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Box 29.1 Tanner staging of pubertal changes

Boys

Genital changes

Stage 1: Prepubertal
Stage 2: Scrotum and testes enlarge, and scrotum skin reddens and changes in texture
Stage 3: Penis enlarges (length at first) and the testes grow further
Stage 4: Size of the penis increases with a growth in breadth and development of the glans; the testes and scrotum become larger, and the scrotum skin becomes darker
Stage 5: Adult genitalia

Pubic hair

Stage 1: Prepubertal (velus hair similar to the abdominal wall)
Stage 2: Sparse growth of long, slightly pigmented hair, straight or curled, at the base of the penis
Stage 3: Darker, coarser and more curled hair, spreading sparsely over the junction of the pubes
Stage 4: Hair adult in type but covering a smaller area than in the adult, and no spread to the medial surface of the thighs
Stage 5: Adult in type and quantity

Girls

Breast development

Stage 1: Prepubertal
Stage 2: Breast bud stage with elevation of breast and papilla; enlargement of the areola
Stage 3: Further enlargement of the breast and areola; no separation of their contour
Stage 4: Areola and papilla form a secondary mound above the level of the breast
Stage 5: Mature stage with projection of papilla only, related to recession of the areola

Pubic hair

Stage 1: Prepubertal (velus hair similar to the abdominal wall)
Stage 2: Sparse growth of long, slightly pigmented hair, straight or curled, along the labia
Stage 3: Darker, coarser and more curled hair, spreading sparsely over the junction of the pubes
Stage 4: Hair adult in type but covering a smaller area than in adult; no spread to the medial surface of the thighs
Stage 5: Adult in type and quantity

- In *boys*, the first sign of puberty is an increase in *testicular volume* (≥4 mL). Testicular enlargement is followed by penile and pubic hair development. Spermatogenesis begins at Tanner stage 3 (see below). Peak growth velocity occurs 2 years after the onset of puberty (Tanner stage 3–4, at a testicular volume of about 12 mL). Boys experience a greater peak height velocity than girls.
- In both sexes, puberty progresses through distinct stages in an orderly and consistent manner.

Delayed puberty

Delayed puberty is defined as the absence or incomplete development of secondary sexual characteristics by an age at which 95% of children of that sex and culture have initiated sexual maturation.

- In boys, delayed puberty may be diagnosed when there is no testicular enlargement by age 14.
- In girls, delayed puberty may be diagnosed when there is no breast development by age 13.

Aetiology

Causes of delayed puberty are summarised in Box 29.2.

Constitutional delay of growth and puberty

Constitutional delay of growth and puberty (CDGP) is one of the most common conditions presenting to paediatric endocrinologists. It is a normal variant of growth and puberty, and is characterised by a delayed onset of puberty, pubertal growth spurt, and skeletal maturation (i.e. delayed bone age). CDGP is uncommon in girls and other causes should be investigated.

In the years preceding the expected time of puberty, the growth pattern of these children is normal (usually along the lower growth percentiles). The height of the child begins to drift from the growth curve because the onset of the pubertal growth spurt is delayed. However, the child's height is appropriate for the bone age. Physical examination and biochemical investigations are normal and prepubertal.

Patients often have a family history of late onset of puberty in one or both parents. The predicted height for the child is in the appropriate range for the parental heights. It may be difficult to distinguish between CDGP and congenital GnRH deficiency as gonadotrophin levels are low in both conditions, and the diagnosis may only be made with time and serial observations. Persistent hypogonadism beyond age 18 is highly suggestive of congenital GnRH deficiency.

Box 29.2 Causes of delayed puberty

Constitutional delay of growth and puberty

Hypogonadotrophic hypogonadism

Pituitary/hypothalamic tumours and other sellar/parasellar disorders
Adenomas, cysts, craniopharyngiomas, germinomas, meningiomas, gliomas, astrocytomas
Infiltrative diseases (haemochromatosis, granulomatous diseases, histiocytosis)
Trauma
Pituitary apoplexy
Functional gonadotrophin deficiency
Anorexia nervosa, excessive exercise
Systemic illness, malnutrition
Hyperprolactinaemia
Hypothyroidism
Congenital GnRH deficiency
Idiopathic without anosmia
May be associated with anosmia (Kallmann syndrome), congenital adrenal hypoplasia, or learning difficulties/obesity (Laurence–Moon–Biedl and Prader–Willi syndrome)

Hypergonadotrophic hypogonadism

Congenital
Chromosomal abnormalities: 45X0 in girls (Turner syndrome), 47XXY in boys (Klinefelter syndrome)
Acquired
Gonadal damage: infection, trauma, iatrogenic (chemotherapy, radiotherapy), autoimmune

Hypogonadotrophic hypogonadism

Hypogonadotrophic (or secondary) hypogonadism is due to impaired secretion of hypothalamic GnRH and/or impaired FSH and LH levels. Hypogonadotrophic hypogonadism may be acquired or congenital (see Box 29.2).

Congenital hypogonadotrophic hypogonadism may be associated with the following:

- *Anosmia:* in *Kallmann syndrome,* which is usually X-linked (although autosomal dominant transmission can also occur). Kallmann syndrome may be due to the sporadic or familial mutations of several genes (e.g. *KAL1*, FGFR1 [*KAL2*], *PROK2*) encoding cell surface adhesion molecules or their receptors required for the migration of GnRH-secreting neurones into the brain and hypothalamus. Kallmann syndrome may be associated with midline facial abnormalities (e.g. cleft palate), red–green colour blindness, hearing loss, urogenital tract abnormalities and synkinesis (mirror movements of the hands).
- *Learning difficulties and obesity:* in Prader–Willi syndrome (caused by deletion of part of paternally derived chromosome 15q) and Laurence–Moon–Biedl syndrome (also associated with polydactyly and retinitis pigmentosa).
- *Congenital adrenal hypoplasia:* due to a mutation of the *NROB1* (DAX-1) gene.

Hypergonadotrophic hypogonadism

Hypergonadotrophic (or primary) hypogonadism may be associated with high FSH and LH levels due to a lack of negative feedback of the sex steroids. Hypergonadotrophic hypogonadism may be congenital or acquired (Box 29.2).

Clinical evaluation

History should enquire about the features associated with the possible underlying causes of delayed puberty (Box 29.2).

Physical examination should include the following:

- Assessment of secondary sex characteristics and staging according to the Tanner criteria (see Box 29.1). Testicular volume is measured using a Prader orchidometer, which comprises a series of plastic ellipsoids with a volume from 1 to 25 mL (Figure 29.1). The symmetry of the testes must be carefully examined as gonadal tumours

Figure 29.1 Prader orchidometer.

may present at puberty with asymmetrical gonadal development and defects in sexual maturation.
- Measurement and plotting of height on a growth chart that includes normal growth patterns with centiles. Height velocity must be documented for at least 6 months.
- Measurement of weight and calculation of body mass index.
- General examination to look for any features of an underlying cause, for example visual field defects due to a pituitary tumour, systemic illness or Kallmann, Turner or Klinefelter syndromes (Box 29.2).

If the first signs of puberty (i.e. breast buds in girls and a testicular volume of more than 4 mL in boys) are present, normal spontaneous puberty usually occurs in more than 95% of patients. However, follow-up is essential since some children with genetic causes of idiopathic hypogonadotrophic hypogonadism can exhibit cessation after some initial signs of pubertal development.

Investigations

The investigation of patients with delayed puberty should include:

- full blood count, urea and electrolytes, liver function tests, erythrocyte sedimentation rate and/or C-reactive protein
- serum LH and FSH, oestradiol (girls) or testosterone (boys)
- prolactin
- free thyroxine and thyroid-stimulating hormone
- karyotype (to evaluate the possibility of Klinefelter syndrome in boys and Turner syndrome in girls).

Bone age is determined by comparison of a radiograph of the patient's bones in the left hand and wrist with the bones in a standard atlas, usually 'Greulich and Pyle'. Bone age allows an assessment of skeletal maturation and the potential for future skeletal growth.

Brain magnetic resonance imaging (MRI) should be performed if there are associated neurological symptoms or signs, or if the blood tests suggest a pituitary/hypothalamic disease.

Pelvic or testicular ultrasonography should be performed when an ovarian or testicular mass is detected on the physical examination. Pelvic ultrasound determines the presence or absence of a uterus (the uterus is absent in patients with androgen insensitivity and disorders of the Müllerian duct system).

Treatment

Treat the underlying disorder if identified, for example levothyroxine for hypothyroidism, a dopamine agonist for prolactinomas and excision of craniopharyngiomas. Patients with features of chronic illness or anorexia nervosa should be referred to the appropriate specialist teams.

CDGP and congenital GnRH deficiency

It is difficult to distinguish between CDGP and congenital GnRH deficiency. The initial therapeutic approach may be similar for both disorders. The history is critical (e.g. anosmia, cranial pathology, etc.) but frequently the diagnosis can only be made with serial observations.

In patients with significant psychosocial concerns, a short-term (6-month) course of low-dose sex steroid therapy may be given to promote secondary sexual characteristics and growth without inducing premature closure of the epiphyses. Boys may be treated with 50 mg testosterone enanthate or cypionate intramuscularly monthly. Girls may be treated with 2 µg ethinyloestradiol orally daily.

Patients should be assessed after cessation of therapy. Spontaneous pubertal development (an enlargement of testicular volume in boys and spontaneous menstruation in girls) indicates CDGP. In contrast, patients with hypogonadotrophic hypogonadism show little pubertal development. These patients need replacement therapy with sex steroids (i.e. testosterone in boys, and oestrogen and progesterone in girls). It is important to remember the normal timescale of pubertal development.

Treatment should be started with low doses of sex steroid replacement (as above), the dose being increased gradually at appropriate intervals. In boys, the dose of testosterone is gradually increased to the adult dose (50 mg intramuscularly monthly for the first 6 months). The side-effects of testosterone therapy include acne.

In girls, the dose of oestrogen is gradually increased. Cyclical oral progesterone is added with the onset of breakthrough bleeding. Progesterone should not be added until breast growth has plateaued. Premature initiation of progesterone therapy can compromise ultimate breast growth.

Primary (hypergonadotrophic) hypogonadism

Primary (hypergonadotrophic) hypogonadism must also be treated with a gradually increasing dose of sex steroids over 2–3 years to complete puberty.

Precocious puberty

Precocious puberty in Europe is defined as the onset of secondary sexual characteristics before the age of 8 years in girls or 9 years in boys.

Children with untreated precocious puberty have increased growth velocity, advanced bone age, and smaller predicted final adult heights due to epiphyseal fusion at an early age.

Epidemiology

The incidence of precocious puberty is 20 per 10 000 girls and fewer than 5 per 10 000 boys (using the above diagnostic age limit).

Aetiology

Precocious puberty may be GnRH dependent or GnRH independent (Box 29.3). Obesity is associated with earlier puberty, possibly because of hyperinsulinaemia. Adoption may trigger GnRH-dependent puberty, especially in girls.

GnRH-dependent ('central') precocious puberty

Gonadotrophin-releasing hormone-dependent ('central') precocious puberty is caused by earlier activation of the hypothalamic–pituitary–gonadal axis. Pubertal development is 'consonant' with normal puberty, i.e. patients have a normal sequence and pace of pubertal milestones. The secondary sexual characteristics are appropriate for the child's gender ('iso-sexual'). Children with GnRH-dependent precocious puberty may have a central nervous system disorder, but 80% have no identifiable cause. Boys are more likely to have occult intracranial pathology.

GnRH-independent precocious puberty

Gonadotrophin-releasing hormone-independent precocious puberty is caused by the autonomous endogenous secretion of sex steroids from the gonads or adrenal glands or excess exogenous sex steroids. Human chorionic gonadotrophin-secreting germ cell tumours can also increase testosterone production via activation of the LH receptors on the Leydig cells.

In these children, pubertal development may not be consonant with normal puberty (i.e. there may be deviations from the normal sequence and pace of puberty) because of the unregulated pattern of sex steroid secretion. The sexual characteristics may be appropriate for the child's gender ('iso-sexual precocity') or inappropriate, with the virilisation of girls and feminisation of boys ('contrasexual precocity').

Testotoxicosis is an autosomal dominant disorder caused by an activating mutation of the LH receptor gene, resulting in premature Leydig cell maturation and increased testosterone secretion in boys.

McCune–Albright syndrome is a rare disorder characterised by precocious puberty, café-au-lait skin

Box 29.3 Causes of precocious puberty

Gonadotrophin-releasing hormone-dependent (central precocious) puberty

Central nervous system disorders
Hydrocephalus
Hamartomas (containing GnRH neurones)
Tumours (astrocytomas, ependymomas, pineal tumours, gliomas)
Trauma
Radiotherapy
Inflammatory disease
Congenital midline defects (e.g. septo-optic dysplasia)
Idiopathic (80–90%)

Gonadotrophin-releasing hormone-independent precocious puberty

Increased sex steroids secreted from the ovaries
Ovarian cysts and tumours (granulosa cell tumours and gonadoblastomas)
Increased testosterone secreted from the testes
Leydig cell tumours (benign testosterone-secreting tumours)
Human chorionic gonadotrophin-secreting germ cell tumours (gonadal, pineal, hepatic, retroperitoneal, mediastinal)
Testotoxicosis
Increased sex steroids secreted from the adrenal glands
Congenital adrenal hyperplasia
Adrenal (androgen- and oestrogen-secreting) tumours
McCune–Albright syndrome
Exogenous sex steroids

pigmentation and fibrous dysplasia of bone. It is due to an activating mutation of the gene (*GNAS*) encoding the alpha subunit of the stimulating G protein that couples transmembrane receptors to adenylate cyclase. The mutation may result in continued stimulation of LH/FSH receptors (causing precocious puberty). It may be associated with activation of a number of pituitary hormone receptors, resulting in other endocrinopathies such as gigantism, Cushing syndrome, and thyrotoxicosis.

Incomplete precocity

Premature thelarche (breast development with no other signs of puberty) and premature adrenarche (the appearance of pubic and/or axillary hair with no other signs of puberty) are variants of normal puberty. Growth velocity and bone age are normal. Close monitoring is essential, as a significant number of these children will develop central precocious puberty.

Isolated breast development may be a presentation of primary hypothyroidism. Increased thyrotrophin-releasing hormone may stimulate FSH, causing ovarian cyst development and increased oestradiol secretion.

Clinical evaluation

The evaluation of patients includes a thorough medical history, a physical examination and a range of investigations to determine the aetiology of precocious puberty.

Medical history

Medical history should enquire about:

- Details of pubertal development: when the initial pubertal changes were first noted (for the patient, as well as for his/her parents and siblings). Deviation from the normal sequence and pace suggests a GnRH-independent cause.
- A previous history of central nervous system disease, radiotherapy, trauma, or presence of any neurological symptoms, such as headaches or seizures.
- A history of exposure to exogenous androgens or oestrogens.
- The presence of abdominal pain (ovarian disease).

Physical examination

Physical examination should include the following:

- Measurements of height and height velocity (cm per year) to look for accelerated linear growth.
- Pubertal (Tanner) staging: staging breast development in girls, testicular volume (and symmetry) and penile size in boys, and pubic hair development in both sexes. Physical examination also determines whether the secondary sexual characteristics are iso-sexual (appropriate for the patient's gender) or contrasexual – virilisation in females (hirsutism, cliteromegaly, deepening of the voice) or feminisation in males. Boys who have an adrenal cause will not have testicular enlargement (i.e. testicular volume will be <4 mL).
- Neurological examination including fundoscopy (to look for papilloedema, a sign of increased intracranial pressure) and visual field assessment.
- Dermatological examination to look for café-au-lait spots (associated with McCune–Albright syndrome).

Investigations

Investigation of a patient with precocious puberty should include the following:

- *Bone age* (determined from a radiograph of the left hand/wrist): to look for advanced skeletal maturation, i.e. bone age higher than chronological age. Children with incomplete precocity (see above) have a normal bone age.
- *Sex steroid* (oestrogen and testosterone) levels are often uninformative, and low levels do not exclude precocious puberty.
- *LH and FSH levels*: in GnRH-dependent (central) precocious puberty, basal levels of LH and FSH are at pubertal levels and will increase with GnRH stimulation (increment >3–4 IU/L for LH and >2–3 IU/L for FSH). In GnRH-independent precocious puberty, baseline LH and FSH levels are low and will not increase with GnRH stimulation.
- *Thyroid function tests* should be performed in all girls presenting with early breast development to exclude primary hypothyroidism.
- *GnRH-dependent (central) precocious puberty*: a brain MRI scan is indicated to determine whether there is an identifiable central nervous system cause. Pelvic ultrasonography may show multicystic ovaries and an enlarging uterus in girls.
- *GnRH-independent precocious puberty*: measure testosterone, oestradiol, dehydroepiandrosterone sulfate (elevated in adrenal tumours) and 17-hydroxyprogesterone (elevated in the common form of congenital adrenal hyperplasia).
- Pelvic ultrasound may identify the presence of an ovarian cyst or tumour in girls.

Treatment

Central precocious puberty

If a cause has been found, it should be treated appropriately. If there is no identifiable cause, the decision to treat depends on the child's age (younger), the rate of pubertal progression, predicted adult height (from bone age) and height velocity.

GnRH analogue therapy (monthly leuprorelin acetate or goserelin given intramuscularly) is effective and safe. It induces the downregulation of pituitary GnRH receptors and results in the suppression of pulsatile gonadotrophin secretion. It slows accelerated puberty and improves final height. Bone density should be monitored during therapy.

GnRH-independent precocious puberty

The underlying pathology should be treated, i.e. surgical removal of tumours of the testis, adrenal gland or ovary. Children with human chorionic gonadotrophin-secreting tumours may require some combination of surgery, radiotherapy and chemotherapy depending on the site and histology.

Children with congenital adrenal hyperplasia should be treated with glucocorticoids (see Chapter 9).

Patients with McCune–Albright syndrome are treated with drugs that inhibit gonadal steroid synthesis or action rather than surgery, in order to preserve fertility. Girls may be treated with testolactone (which inhibits the aromatisation of androgen to oestrogen). Successful treatment has also been achieved with tamoxifen (an anti-oestrogen). Boys may be treated with ketoconazole (which inhibits androgen synthesis) or a combination of spironolactone (which inhibits androgen action) and testolactone. Bone pain and increased fractures caused by the fibrous dysplasia of bone may improve with intravenous pamidronate.

Incomplete precocity

Patients with premature thelarche or premature adrenarche do not require any treatment but should be followed up regularly to detect possible progression to central precocious puberty.

KEY POINTS

- Normal puberty occurs between the ages of 8 and 13 years in girls and 9 and 14 years in boys, and usually lasts for 3–4 years.
- The first step in the initiation of puberty is activation of the hypothalamic GnRH pulse generator and the pulsatile secretion of GnRH.
- Leptin is a hormone produced largely in adipocytes that may act as a signal of the availability of the metabolic reserve necessary for pubertal development.
- Kisspeptin/GPR54 signalling has also been shown to be crucial for the development of puberty.
- The sequence of pubertal changes in secondary sexual characteristics may be categorised into five Tanner stages.
- Delayed puberty may be diagnosed when there is no testicular enlargement by age 14 in boys or no breast development by age 13 in girls.
- Delayed puberty may be due to CDGP, hypogonadotrophic hypogonadism, or hypergonadotrophic hypogonadism.
- Precocious puberty may be GnRH dependent or GnRH independent (due to increased sex steroids secreted from the gonads or adrenal glands, McCune–Albright syndrome, or exogenous sex steroids).

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Growth and stature

Normal growth

There are three phases of postnatal growth.

- The *infantile phase* is characterised by rapid but decelerating growth during the first 2 years of life. Infants often cross percentile lines in the first 2 years and settle onto their childhood centile position at age 2–3 years. Overall growth during this period is about 30–35 cm. Nutrition is an important factor for growth in this phase.
- The *childhood phase* is characterised by growth at a relatively constant velocity of 5–7 cm per year. There is often a slight slowing later in childhood. Normal children do not cross percentile lines. Growth hormone (GH) is the most significant endocrine factor for growth in this phase.
- The *pubertal phase* is characterised by a growth spurt of 8–14 cm per year due to the synergistic effects of increasing gonadal steroid and GH secretion. Bone maturation occurs during puberty, and growth stops as the epiphyses fuse. Limb growth ceases before spinal growth.

Children with normal growth settle on a centile line by 2–3 years of age and grow along this line until they reach puberty. Short or tall children growing at normal velocity are unlikely to have an underlying pathological condition. Children often grow faster during the summer.

Prediction of height potential

About 80% of adult height is determined by genetic factors. The height of parents and siblings can be a guide for future adult height, but genetic variation means some healthy normal children will have short stature relative to their parents.

Mid-parental height

The mid-parental height can be used to estimate a child's adult height.

- For *boys*, 13 cm is added to the mother's height and averaged with the father's height.
- For *girls*, 13 cm is subtracted from the father's height and averaged with the mother's height.

The 13 cm represents the average difference in height of men and women. For both girls and boys, 8.5 cm on either side of this calculated value represents the 3rd to 97th percentiles for anticipated adult height.

Mid-parental height is useful in assessing genetic influences on height. However, it is important to remember that illnesses or other factors in parents may have prevented them from reaching their genetic potential. The mid-parental height is less accurate than the *bone age* method (see below), because it does not reflect environmental contributions to growth or disease processes.

Bone age

Bone age is a measure of skeletal maturity. It is obtained by assessing the appearance and shape of the bones of the hand and wrist from a radiograph. The methods used most commonly for determining bone age are the 'Greulich and Pyle' atlas and the Tanner–Whitehouse method.

At any given bone age, an individual is at a certain percentage of adult height. Thus, multiplying the present height by the reciprocal of this percentage (of adult height) predicts the adult height (although accuracy is limited, especially if an underlying condition is affecting growth).

Endocrinology and Diabetes: Lecture Notes, Second Edition. Amir H. Sam, Karim Meeran and Neil Hill.
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Short stature

Short stature is defined as a height 2 standard deviations or more below the mean height for children of that gender and chronological age. This translates into being below the 3rd percentile for height.

Concerns about short stature are a common reason for referral to a paediatrician. However, most children referred are found to be normal. Studies investigating the psychosocial effect of short stature show mixed results, with some suggesting a reduced health-related quality of life and others demonstrating no effect.

Aetiology

Causes of short stature are summarised in Box 30.1 and the relative frequency of short stature according to growth centile in Box 30.2.

Low birth weight and illnesses in infancy

Children with low birth weight or loss of growth potential in infancy due to various illnesses have short stature but normal growth velocity.

Box 30.1 Causes of short stature

Low birth weight and illnesses in infancy

Familial

Constitutional delay of growth and puberty

Endocrine abnormalities
Thyroid disease
Growth hormone or insulin-like growth factor-1 (IGF-1) deficiency or insensitivity
Cushing syndrome
Vitamin D deficiency or resistance

Dysmorphic syndromes associated with abnormal skeletal growth
Turner syndrome
Noonan syndrome
Down syndrome
Achondroplasia

Chronic illness, malnutrition

Psychosocial problems

Idiopathic

Box 30.2 Relative frequency of short stature

Growth centile	Standard deviation from mean	Number shorter than
16th	–1	1 in 6
3rd	–2	1 in 44
0.1	–3	1 in 750
–	–4	1 in 31250

Familial short stature

Children with *familial (genetic) short stature* have short parent(s) with a history of normal puberty. These children have normal growth velocity, timing of puberty and bone age.

Constitutional delay of growth and puberty

Constitutional delay of growth and puberty (CDGP) is the one of the most common conditions presenting to paediatric endocrinologists. It is a normal variant of growth and puberty, and is characterised by a delayed onset of puberty, the pubertal growth spurt and skeletal maturation (i.e. delayed bone age).

The growth chart and growth velocity of a boy with CDGP is shown in Figure 30.1. In the years preceding the expected time of puberty, the growth pattern of these children is normal (usually along the lower growth percentiles). The height of the child begins to drift from the growth curve because the onset of pubertal growth spurt is delayed. However, the child's height is appropriate for his bone age. Physical examination and biochemical investigations are normal and prepubertal. Patients often have a family history of late onset of puberty in one or both parents. The predicted height for the child is in the appropriate range for the parental heights.

Endocrine abnormalities

Children with abnormalities in the *endocrine* control of growth have reduced growth velocity and are usually overweight for height.

GH deficiency

Growth hormone deficiency is the most common endocrine cause of short stature. GH deficiency may be isolated or associated with other pituitary hormone deficiencies (see Chapters 12 and 13).

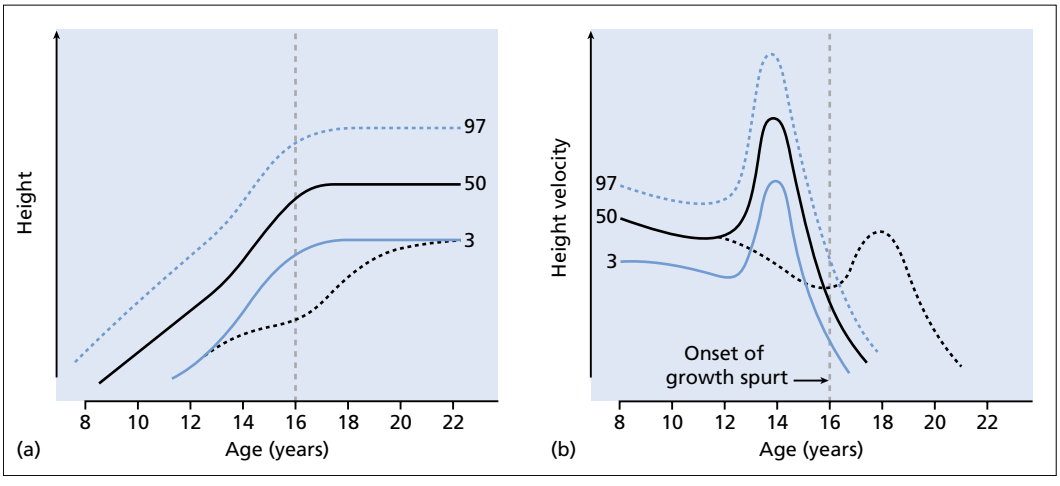

Figure 30.1 (a) Serial height measurements of a boy with constitutional delay of growth and puberty (CDGP; dotted black line) are plotted on a growth chart with 3rd, 50th and 97th percentile lines. Note that the height of the child falls below the 3rd percentile line during the early teenage years because of the delay in onset of the pubertal growth spurt. (b) Growth velocity of a boy with CDGP (dotted black line) is plotted on a growth velocity chart with 3rd, 50th and 97th percentile lines. Note the delayed onset of the growth spurt (arrow) and reduced peak height velocity.

GH secretion is stimulated by hypothalamic growth hormone-releasing hormone (GHRH). GH stimulates epiphyseal prechondrocyte differentiation and linear bone growth in children. It also stimulates skeletal growth through stimulation of the hepatic synthesis and secretion of IGF-1, which is a potent growth and differentiation factor. GH deficiency usually results from a deficiency of GHRH, but can be secondary to sellar and parasellar tumours such as germinoma.

Rare causes of short stature include an inactivating mutation of the GHRH receptor inherited in an autosomal recessive manner, homozygous GH gene deletion, abnormalities of the GH receptor (Laron syndrome) and abnormal IGF-1 secretion or action.

Hypothyroidism

Hypothyroidism is a well-recognised cause of short stature. The skeletal age is usually as delayed as the height age, and as a result many children with hypothyroidism have a reasonably normal growth potential.

Cushing syndrome

Cushing syndrome in children is usually iatrogenic, due to glucocorticoid therapy for asthma, inflammatory bowel disease or immunological renal disease. Endogenous Cushing syndrome is rare but should be considered if the child has both weight gain and growth retardation. Bone age is normal at diagnosis in most patients.

Dysmorphic syndromes associated with abnormal skeletal growth

Abnormalities in skeletal growth are features of certain syndromes such as Turner syndrome (see Chapter 21), Down syndrome (trisomy 21) and achondroplasia (caused by an autosomal dominant mutation in the gene encoding fibroblast growth factor receptor-3, resulting in abnormal cartilage formation).

Malnutrition or chronic illness

Malnutrition or chronic illnesses such as congenital heart disease, asthma, cystic fibrosis, coeliac disease, inflammatory bowel disease, chronic kidney disease, vitamin D deficiency, or HIV infection can result in short stature. These children are usually underweight for height.

Psychosocial problems

Psychosocial problems in childhood can contribute to short stature. These children have reduced growth velocity.

Idiopathic

Idiopathic short stature is the term applied to children with short stature in whom no endocrine, metabolic or other diagnosis can be made. These children have normal (often at the lower limit) growth velocity. Mutations in the short stature homeobox (*SHOX*) gene are responsible for up to 15% of cases of apparent 'idiopathic' short stature.

Clinical evaluation

A full medical history should be taken to determine:

- birth weight and history of any illnesses during infancy/childhood
- the parents' height (heights reported by adults may be inaccurate and should be measured)
- the stage of puberty
- a family history of delayed puberty
- nutrition and any features of systemic illness
- psychosocial problems.

A thorough clinical examination should be performed to look for the following.

- *Reduced growth velocity*: accurate serial measurement of height and plotting of the measurements on a growth chart are essential to determine the growth velocity (Figure 30.2).
- *Underweight/overweight*: children with systemic illness or malnutrition are usually underweight for height, whereas children with endocrine abnormalities are overweight for height.
- *Pubertal development* (see Chapter 29).
- *Dysmorphic features*: particularly features of Down syndrome and Turner syndrome (see Chapter 21). Patients with achondroplasia have short stature with disproportionately short arms and legs, a large head and characteristic facial features with frontal bossing and mid-face hypoplasia.
- *Features of chronic illness*.
- *Features of endocrine abnormalities* (GH deficiency, hypothyroidism, Cushing syndrome).

Investigations

Children with reduced growth velocity should be thoroughly investigated for the following conditions.

- *Systemic illness:* initial blood tests should include full blood count, urea and electrolytes, liver function tests, bone profile, glucose, coeliac serology, erythrocyte sedimentation rate and/or C-reactive protein.
- *Turner syndrome:* a *karyotype* analysis should be performed in girls.
- *GH deficiency or resistance:* serum IGF-1 and *insulin-like growth factor-binding protein-3* (IGFBP-3) should be measured, and bone age determined. If bone age and height velocity are normal, GH deficiency is effectively excluded. If IGF-1 and IGFB-3 levels are low, provocative GH testing (e.g. using insulin-induced hypoglycaemia or arginine) may be performed. However, provocative GH testing has a number of limitations, including the arbitrary cut-off level of 'normal' (GH concentration of 10 μg/L), variable accuracy of the GH assays, the risk of insulin-induced hypoglycaemia, and inadequate documentation of test reproducibility. Children with GH insensitivity (Laron syndrome) have high serum GH concentrations but low serum IGF-1 and IGFBP-3 concentrations. When sellar/parasellar disorders are suspected, pituitary function tests and *magnetic resonance imaging* (MRI) scan of the hypothalamic–pituitary area should be performed.
- *Hypothyroidism:* serum *thyroid-stimulating hormone* and free *thyroxine* should be measured. It is important to remember that if the child is hypothyroid, provocative GH testing should be postponed until thyroxine has been adequately replaced.
- *Cushing syndrome:* investigations (see Chapter 16) should only be performed if there is a high clinical suspicion.

The bone age can be determined from a radiograph of the left hand and wrist (using a scoring system of epiphyseal maturation). This is useful in estimating adult height (see above) and differentiating children with familial short stature (normal bone age) and CDGP (delayed bone age).

Treatment

Affected children may miss important psychosocial milestones if they continue to differ from their peers with respect to stature and degree of adolescent development.

Growth rate can be improved by treating the underlying condition. For example, thyroxine replacement in hypothyroidism and a gluten-free diet in coeliac disease result in normal growth if the child is compliant with the treatment.

Recombinant GH is administered as a daily subcutaneous injection and is usually continued until the

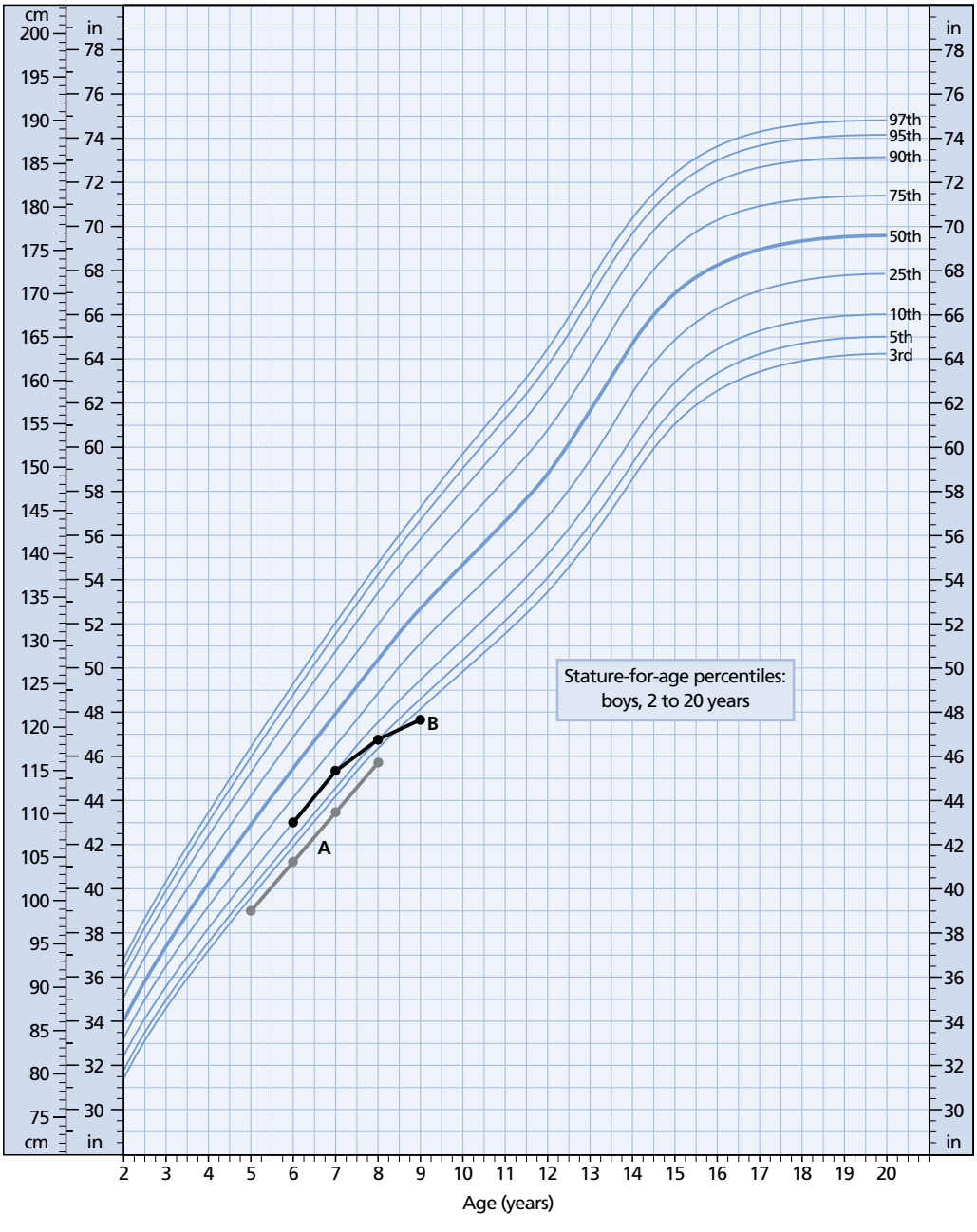

Figure 30.2 The serial height measurements of two boys with short stature are plotted on the growth chart for boys. Child A has normal growth velocity. Child B has reduced growth velocity.

growth rate slows at the end of puberty. Only a small proportion may benefit from GH replacement therapy as adults. Thus, it is mandatory to retest GH-deficient children after completion of growth. Children with multiple pituitary hormone deficiencies rarely recover the ability to secrete GH as an adult.

Few adverse events have been reported during treatment. Headache is the most commonly reported complication of GH therapy. Benign intracranial hypertension (around 1 in 1000) and carpal tunnel syndrome may occur, possibly due to sodium and water retention. Slipped capital femoral epiphysis

may occur soon after GH therapy is initiated; hip and/or knee pain and changes in gait should be urgently investigated. Other adverse effects include pancreatitis and an increase in the growth and pigmentation of naevi. Glucose intolerance and type 2 diabetes mellitus may occur in children receiving GH therapy, but the absolute risk appears to be low.

There are several indications for GH replacement therapy, described below.

GH deficiency

Growth hormone therapy (25–50 µg/kg per day) is monitored using the growth response and IGF-1 levels. The goal is to achieve IGF-1 levels of about 1 standard deviation above the mean for age and/or Tanner stage of pubertal development. With adequate replacement, adult height should be within the parental target range. Girls often need higher doses of GH, especially if having oral oestrogen replacement.

Turner syndrome

Children with Turner syndrome are treated with slightly higher doses of GH (45–50 µg/kg per day) because they have a degree of GH resistance. GH therapy should be started as soon as the height of a girl with Turner syndrome falls below the 5th percentile for age (usually between 2 and 5 years of age). In girls 9–12 years of age, combination therapy with GH and oxandrolone (an anabolic steroid) at a dose of 0.0625 mg/kg per day is recommended. GH therapy is continued until growth slows to less than 2 cm per year and the bone age exceeds 15 years. The usual increment in adult height is 4–6 cm, meaning many women with Turner syndrome will be short as adults in spite of GH treatment.

Growth failure associated with chronic kidney disease

Treatment with GH has been shown to stimulate growth in prepubertal children with renal failure. GH should be considered in children with height between the 3rd and 10th percentiles who have low height velocity (below the 25th percentile) with stabilisation of other factors contributing to uraemic growth failure.

Children with chronic kidney disease are treated with slightly higher doses of GH (45–50 µg/kg per day), because they have a degree of GH resistance. The response to GH is better in children with preterminal chronic kidney disease than those on renal replacement therapy. Therefore. GH therapy should be commenced well before the need for dialysis. GH therapy is continued until final height is reached or a well-functioning renal transplant has been achieved. The minimal therapeutic aim is a height greater than the 3rd percentile of the general population.

Children born small for gestational age

It is critical to discuss realistic expectations with the patient and family. GH therapy is likely to result in only modest gains in height compared with no treatment (an increase in adult height of approximately 4–6 cm, provided the treatment is started early and continued for at least 7 years). Adult height will usually be below average despite therapy. GH is started at doses of approximately 40 µg/kg per day based on ideal body weight. The dose is adjusted to maintain IGF-1 levels at approximately 1 standard deviation above the mean.

Prader–Willi syndrome

Growth hormone treatment (35 µg/kg per day) should be offered to all children and adolescents with clinical evidence of growth failure, unless there are contraindications (severe obesity, respiratory compromise, severe sleep apnoea). Sudden deaths have been reported in severely obese children with Prader–Willi syndrome shortly after starting GH.

GH therapy improves linear growth, body composition, and bone density. The treatment may be continued until the epiphyses have closed. The optimal age to begin treatment has not been established. Patients should be closely monitored for the development of respiratory obstruction, particularly during the first few months of treatment.

Idiopathic short stature

Growth hormone is licensed in the USA for use in children with idiopathic short stature. Although the adult height is increased, the reported gains are small.

Mutations in the GH receptor

Children with mutations in the GH receptor (Laron syndrome) or with other defects in IGF-1 production may be treated with recombinant IGF-1.

Tall stature

Most tall children are normal children of tall parents. Causes of tall stature are summarised in Box 30.3.

Box 30.3 Causes of tall stature

Normal growth velocity
Constitutional tall stature
Obesity
Klinefelter syndrome
Marfan syndrome
Homocystinuria
Soto syndrome

Increased growth velocity
Precocious puberty (central or peripheral)
Growth hormone-secreting pituitary adenoma
Thyrotoxicosis

Obesity may be accompanied by an early onset of puberty and modest overgrowth. Obese children often have diminished overall GH production but high normal serum IGF-1 and GH-binding proteins, resulting in tall stature for age prior to puberty.

Klinefelter syndrome is characterised by the presence of one or more extra X chromosomes (most commonly 47XXY). Prepubertal boys have relatively long legs and are often tall for their age. Other features of Klinefelter syndrome include gynaecomastia, small testes, and learning disabilities (mainly expressive language).

Marfan syndrome is an autosomal dominant condition caused by mutations in the gene encoding fibrillin-1. Features of Marfan syndrome include upward lens dislocation, arm span exceeding height, arachnodactyly (long thin fingers), skeletal abnormalities, and aortic dilation/regurgitation.

Homocystinuria is an autosomal recessive condition caused by deficiency of the enzyme cystathionine synthetase. Features of homocystinuria include downward lens dislocation, learning difficulties, thromboembolic phenomena, and osteoporosis.

Causes of tall stature associated with increased growth velocity include *precocious puberty* (central or peripheral), *GH-secreting pituitary adenoma* and *thyrotoxicosis*.

Children with precocious puberty have accelerated childhood growth and epiphyseal maturation (i.e. accelerated bone age). These children have precocious sexual development and high serum sex steroid hormone levels (for their age). If their growth is not halted, these tall children will be short adults as early epiphyseal closure stops linear growth.

A GH-secreting pituitary adenoma is suspected when increased growth velocity is seen without manifestations of premature puberty. An arm span larger than standing height suggests an onset of disease before fusion of the epiphyses.

Investigations

A *karyotype* analysis should be performed in boys to look for Klinefelter syndrome (47XXY). *Genetic tests* for the inherited conditions associated with tall stature (e.g. Marfan syndrome) may be carried out if clinically suspected. *IGF-1* and *IGFBP-3* levels are elevated in children with GH-secreting adenomas. An oral glucose tolerance test will show a failure of GH suppression in these children. If a GH-secreting pituitary adenoma is suspected, a pituitary *MRI* should be performed. Serum *free thyroxine* and *thyroid-stimulating hormone* should be measured to exclude thyrotoxicosis.

Treatment of tall stature

The underlying disorder should be corrected if possible. The treatment of tall children and adolescents is controversial, and treatment is discouraged except in extreme cases. Psychosocial problems influence the final decision about treatment.

Sex steroids promote premature epiphyseal fusion by a direct effect at the epiphysis and an indirect action mediated by the GH–IGF-1 axis.

In *girls*, oestrogen (in the form of oestradiol or ethinyloestradiol) may be started before a bone age of 14–15 years (usually when the bone age is 10–12 years) at a dose of 15–30 µg per day, and increased to 50 µg per day if well tolerated and clinically indicated. Cyclic progestin therapy is indicated if breakthrough bleeding occurs. Treatment should be continued until the epiphyses fuse.

The risk–benefit ratio of oestrogen therapy must be discussed with the child and parents. Adverse effects include nausea, weight gain, oedema, and hypertension. Oestrogen treatment may also have a negative impact on later fertility.

In *boys*, androgens also accelerate epiphyseal fusion, presumably via aromatisation to oestrogens. Testosterone therapy as a treatment of constitutional tall stature in boys is extremely uncommon.

KEY POINTS

- Short stature is defined as a height 2 standard deviations or more below the mean height for children of that gender and chronological age. This translates into being below the 3rd percentile for height.

- Causes of short stature include familial, CDGP, endocrine abnormalities (thyroid disease, GH or IGF-1 deficiency or insensitivity, Cushing syndrome), dysmorphic syndromes associated with abnormal skeletal growth (e.g. Turner syndrome, Down syndrome, achondroplasia), chronic illness, malnutrition, and psychosocial problems.
- Initial investigations in children with reduced growth velocity should include blood tests to look for systemic illness, karyotype analysis (in girls), serum IGF-1 and IGFBP-3, and thyroid function tests.
- When sellar/parasellar disorders are suspected, an MRI of the hypothalamic–pituitary area should be performed.
- The bone age is a measure of skeletal maturity and is determined from a radiograph of the left hand and wrist (using a scoring system of epiphyseal maturation).
- Indications for GH replacement therapy include GH deficiency, Turner syndrome, growth failure associated with chronic kidney disease, children born small for gestational age, and Prader–Willi syndrome.
- Most tall children are the normal children of tall parents.

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Endocrine disorders of pregnancy

Disorders of thyroid function

Thyroid function during normal pregnancy

Maternal thyroid function

It is important to recognise the physiological changes that occur in the maternal thyroid function during normal pregnancy. These include:

- Increased serum 'total' thyroxine (T_4) and triiodothyronine (T_3) levels due to an increase in serum T_4-binding globulin production. This is caused by elevated oestrogen levels.
- A slight increase in serum free T_4 and T_3 levels (usually within the normal range), and appropriate reductions in serum thyroid-stimulating hormone (TSH) levels in the first trimester. This is caused by human chorionic gonadotrophin (hCG, produced by the placenta), which is a weak stimulator of the TSH receptor. TSH reference ranges by trimester vary according to local and national guidelines. A transient subclinical hyperthyroidism (normal free T_4 and suppressed TSH) may be seen in 10–20% of normal women during the period of highest serum hCG levels (10–12 weeks' gestation).

Thyroid hormone requirements increase during pregnancy. This may be due to:

- increased weight
- placental deiodinase activity
- transfer of T_4 to the fetus.

Fetal thyroid function

Maternal TSH does not cross the placenta. However, maternal thyroid hormones cross the placenta in small quantities, and are important for fetal growth and cognitive development during early pregnancy. Fetal TSH appears around the 10th week of gestation. However, little thyroid hormone synthesis occurs until the 18–20th week.

Overt hypothyroidism in pregnancy

Significance

Hypothyroidism in pregnancy is associated with several complications, including early pregnancy loss, placental abruption, pre-eclampsia, preterm delivery, low birth weight, perinatal mortality, and neuropsychological impairment.

Treatment and follow-up

If hypothyroidism has been diagnosed *before* pregnancy, the preconception levothyroxine dose should be adjusted to reach a TSH level of less than 2.5 mU/L, although the original evidence for this threshold was from a small study. As mentioned above, T_4 requirements increase during pregnancy. However, women with hypothyroidism are unable to increase their T_4 and T_3 secretion. Therefore, the dose of levothyroxine should be increased by 30–50% by 4–6 weeks' gestation.

Serum TSH should be measured 4–6 weeks after conception, 4–6 weeks after any change in the dose of levothyroxine, and at least once each trimester.

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Further dose changes are based on serum TSH concentrations.

If overt hypothyroidism is diagnosed during pregnancy, levothyroxine should be started, and titrated rapidly to reach and thereafter maintain serum TSH concentrations within trimester-specific ranges.

Earlier suggestions that subclinical hypothyroidism (high serum TSH with a normal free T_4) in mothers caused neurodevelopmental delay in their children have not been substantiated; furthermore, treating subclinical hypothyroidism has not been shown to improve outcomes. Women with a TSH level more than 4.0 mU/L should be treated with levothyroxine to bring TSH to within the reference range. After delivery, the dose of levothyroxine can be reduced to pre-pregnancy levels. However, serum TSH should be measured 4–6 weeks later to confirm that the reduction in dose was appropriate.

Screening

Universal screening for thyroid dysfunction in asymptomatic women is not advised for pregnant women or those hoping to become pregnant, unless there is known thyroid dysfunction or a high clinical suspicion.

Hyperthyroidism in pregnancy

Significance

Poorly controlled hyperthyroidism in pregnancy is associated with an increased risk of pregnancy loss, premature labour, low birth weight, pre-eclampsia and maternal cardiac failure.

Diagnosis

The clinical diagnosis of hyperthyroidism during pregnancy may be difficult as many of the symptoms of hyperthyroidism (e.g. heat intolerance, increased sweating) are similar to the non-specific symptoms associated with pregnancy. In addition, high serum hCG levels during early pregnancy and in women with hyperemesis gravidarum (see below) or multiple pregnancies may result in transient subclinical or rarely overt hyperthyroidism. Hyperthyroidism in these cases rarely requires antithyroid drugs.

Although hyperthyroidism from any cause can complicate pregnancy, Graves disease is the most common cause. Patients with Graves disease may have ophthalmopathy, a family history of Graves disease and a history of other autoimmune conditions.

The diagnosis of hyperthyroidism in pregnant women should be based primarily on a *serum TSH less than 0.01 mU/*L and a *high serum free* T_4 and/or free T_3. Radio-isotope administration is contraindicated in pregnancy.

Measurement of TSH receptor antibodies (TRAbs) may be helpful in making the diagnosis of Graves disease during pregnancy. In addition to mothers with current Graves disease, TRAbs should also be measured before pregnancy or by the end of the second trimester in those with a history of Graves disease and treatment with radio-iodine or thyroidectomy, or with a previous neonate with Graves disease (see 'Fetal and neonatal assessment' below).

Treatment and follow-up

Overt hyperthyroidism due to Graves disease or hyperfunctioning thyroid nodules should be treated with antithyroid drugs. Patients should be reviewed at 4-week intervals with measurements of free T_4 levels. The dose of antithyroid drug should be adjusted appropriately. A block and replace regime (with high-dose antithyroid drug and levothyroxine) must not be used as it will result in fetal hypothyroidism.

Antithyroid drugs

Both propylthiouracil (PTU) and carbimazole are associated with serious side-effects but it should be emphasised that these are rare and the risk of adverse outcomes with uncontrolled hyperthyroidism is far greater. PTU is usually used as a first-line drug and should be used in the preconception period. Carbimazole is very rarely associated with congenital anomalies (aplasia cutis), but may be given to patients who have had an adverse reaction to PTU. Some guidelines recommend swapping from PTU to carbimazole during the second trimester due to the increased risk of maternal liver failure seen with PTU during this period. This must be balanced against the risk of destabilising thyroid control during the swap-over and in clinical practice, many clinicians recommend continuing with PTU throughout the pregnancy.

In patients with severe hyperthyroidism, an initial PTU dose of 150 mg twice a day (or carbimazole 30 mg once a day) may be given to normalise thyroid function. The dose is then adjusted according to the free T_4 levels measured every 2–4 weeks. The aim is to maintain the maternal free T_4 levels in the high-normal range. As pregnancy progresses, most patients require lower PTU doses (50 mg twice a day or less).

Antithyroid drugs may be stopped in women who have been euthyroid for at least 4 weeks on the lowest dose, and thyroid function tests should be monitored every 4 weeks. Antithyroid drugs are usually not

stopped during pregnancy in women with ophthalmopathy and a large goitre (i.e. those with a high chance of recurrence).

Graves disease usually becomes less severe during the later stages of pregnancy, possibly due to a fall in TRAb levels. It is possible to discontinue the antithyroid drug during the third trimester in one-third of women. However, Graves hyperthyroidism can worsen post partum. A beta-blocker (propranolol 20–40 mg three times a day) may be used for a few weeks in women with moderate-to-severe symptoms.

There is no evidence that the treatment of subclinical hyperthyroidism improves pregnancy outcome, and treatment could potentially adversely affect fetal outcome.

Breast-feeding mothers should be treated with the lowest possible dose of PTU or carbimazole.

Surgery

Subtotal thyroidectomy may be indicated in hyperthyroid women during pregnancy who cannot tolerate antithyroid drugs because of allergy or agranulocytosis. The optimal timing of surgery is in the second trimester. Radio-iodine treatment is absolutely contraindicated in pregnancy.

Fetal and neonatal assessment

Thyroid-stimulating hormone receptor antibodies can cross the placenta. The fetuses of women treated with antithyroid drugs and those with elevated TRAbs should be monitored by sonography for signs of fetal thyrotoxicosis (fetal heart rate >160 beats per minute, goitre, growth restriction). Treatment is by giving antithyroid drugs to the mother and monitoring fetal heart rate (aiming for <140 beats per minute), growth, and goitre size.

Around 1–5% of neonates born to women with Graves disease have hyperthyroidism due to the transplacental transfer of TSH receptor-stimulating antibodies. The incidence is unrelated to maternal thyroid function. All newborns of mothers with Graves disease should be evaluated for thyroid dysfunction and treated if necessary.

Hyperemesis gravidarum

Hyperemesis gravidarum is characterised by nausea, vomiting, and weight loss (≥5%) during early pregnancy. It may be caused by high serum hCG and oestradiol concentrations, or the secretion of hCG with increased biological activity. Many women with hyperemesis gravidarum have either subclinical or mild overt hyperthyroidism. Features that distinguish the transient hyperthyroidism of hyperemesis gravidarum from Graves disease are the vomiting, absence of goitre and ophthalmopathy, and absence of the symptoms and signs of thyrotoxicosis (diarrhoea, muscle weakness, tremor). TRAbs should be measured in women with hyperemesis gravidarum to help to differentiate from Graves disease. In addition, in hyperemesis gravidarum serum free T_4 is minimally elevated and serum T_3 is usually not elevated.

The hyperthyroidism in hyperemesis gravidarum does not require treatment with antithyroid drugs and resolves as hCG production falls. Patients are treated with intravenous fluids, antiemetics, a beta-blocker (e.g. propranolol), and nutritional support. If overt hyperthyroidism persists for more than several weeks or beyond the first trimester, it is probably not hCG mediated and may be due to coincident Graves disease, which should be treated with antithyroid drugs.

Trophoblastic disease

Human chorionic gonadotrophin-mediated hyperthyroidism also occurs in about 60% of women with a hydatidiform mole or choriocarcinoma. The hyperthyroidism may be severe, and is primarily treated by evacuation of the mole or therapy directed against the choriocarcinoma.

Goitre, thyroid nodules, and cancer

Iodine depletion (due to increased maternal renal clearance and fetal uptake of iodide) may lead to mild thyroid enlargement. However, significant thyroid growth during pregnancy should be considered abnormal, requiring further investigation.

A pregnant woman with a thyroid nodule should be evaluated in the same way as if she were not pregnant (i.e. with fine needle aspiration and cytological examination). Thyroid radio-isotope uptake scanning is absolutely contraindicated. Women with benign nodules are followed up. Those whose thyroid nodules enlarge should have another fine needle aspiration.

Women with malignant or suspicious cytology require surgery. The safest time for surgery during pregnancy is the second trimester. However, because of the usually indolent nature of most well-differentiated thyroid cancers, some delay surgery until the postpartum period.

Prolactinomas in pregnancy

Prolactinomas usually result in infertility due to the inhibitory effect of prolactin on gonadotrophin secretion. However, treatment of hyperprolactinaemia enables most women to become pregnant.

Increased oestrogen levels in pregnancy cause lactotroph hyperplasia. In normal pregnant women, pituitary size increases throughout pregnancy (more than double). In patients with prolactinomas, the increase in the size of the tumour may result in compression of the optic chiasm and visual impairment.

The management of women with prolactinoma during pregnancy varies according to the size of the adenoma.

Microprolactinomas (<1 cm)

The risk of a clinically important enlargement of a microprolactinoma during pregnancy is small (1.5–5.5% may develop neurological symptoms). Patients are treated with dopamine agonists prior to pregnancy.

Bromocriptine was historically preferred by some endocrinologists because of greater experience with it, but cabergoline is safe in women trying to conceive and is now preferred. Women can attempt to become pregnant when the serum prolactin concentration is normal and menstrual periods have occurred regularly for a few months. When periods have resumed, patients should be advised to have a pregnancy test as soon as they miss a period. The dopamine agonist should be discontinued as soon as pregnancy has been confirmed.

Monitoring and follow-up

Pregnant women with microprolactinomas should be followed up every 3 months to enquire about headaches and changes in vision. Patients who develop these symptoms should be investigated with formal visual field testing and pituitary magnetic resonance imaging (MRI).

Serum prolactin levels are difficult to interpret as they are elevated during normal pregnancy. Serum prolactin should be measured 2 months after the delivery or cessation of breast feeding, and if it is similar to the pretreatment value, dopamine agonist therapy can be resumed. If serum prolactin levels are higher than pre-pregnancy levels, the size of microprolactinomas should be assessed by MRI.

Macroprolactinomas (≥1 cm)

Before conception, patients should be advised of the higher risk of clinically important tumour enlargement during pregnancy (neurological symptoms may occur in up to 36%).

If the adenoma does not elevate the optic chiasm

The patient should be treated with cabergoline to shrink the tumour substantially before she can attempt to become pregnant. The dopamine agonist may be stopped when pregnancy has been confirmed.

The patient should be carefully monitored with monthly visual field testing. If she develops symptoms of tumour enlargement (headache, visual impairment), a pituitary MRI should be performed. If the adenoma has enlarged, the woman should be treated with cabergoline throughout the remainder of her pregnancy. Cabergoline and bromocriptine are safe in pregnancy but are contraindicated in breast feeding as they inhibit milk production.

In patients who do not respond to dopamine agonist therapy, and whose vision is severely compromised, trans-sphenoidal surgery may be considered in the second trimester. Surgery for persistent visual symptoms in the third trimester should be deferred until delivery if possible because of the difficulty of anaesthetising and ventilating a heavily pregnant woman.

MRI should be performed in the postpartum period to look for tumour growth.

If the adenoma is very large, elevates the chiasm, or is unresponsive to dopamine agonists

Pregnancy should be strongly discouraged until the patient has been treated by trans-sphenoidal surgery and perhaps by postoperative radiotherapy and dopamine agonists. This approach reduces the risk of symptomatic expansion during pregnancy to 4–7%.

Breast feeding

Breast feeding does not increase the risk of lactotroph adenoma growth. Therefore, breast feeding is an option for women with micro- and macroadenomas that remained stable in size during pregnancy.

Breast feeding is contraindicated in women who have neurological symptoms (suggesting tumour

growth) at the time of delivery, because they should be treated with a dopamine agonist.

Adrenal disorders in pregnancy

Addison disease in pregnancy

The fetus produces and regulates its own adrenal steroids. Therefore, pre-existing primary adrenal insufficiency in the mother is not associated with fetal morbidity.

The treatment of Addison disease in pregnant women is the same as that of non-pregnant patients. Hydrocortisone is the preferred glucocorticoid as it is metabolised by placental 11-beta-hydroxysteroid dehydrogenase, and thus fetal adrenal suppression is avoided. The glucocorticoid dose does not need to be increased during pregnancy. Patients should continue on their usual oral hydrocortisone and oral fludrocortisone as per their pre-pregnancy doses. Patients with severe hyperemesis gravidarum during the first trimester may require temporary parenteral hydrocortisone. Patients should be warned about this to avoid precipitation of a crisis.

At the time of delivery, high-dose intramuscular hydrocortisone should be given to cover the stress of labour. During uncomplicated labour, 100 mg of hydrocortisone is given intramuscularly 6-hourly for 24 hours, and is then reduced to maintenance dose over 72 hours. Patients should be kept well hydrated. Fludrocortisone may be discontinued while the patient is on high doses of hydrocortisone and restarted when the hydrocortisone doses are tapered.

Addison disease developing in early pregnancy may be missed, as vomiting, fatigue, hyperpigmentation, and hypotension may be wrongly attributed to pregnancy. However, clinicians should be alerted by persistent symptoms. Addison disease developing in pregnancy may present with an adrenal crisis, particularly at the time of delivery.

Congenital adrenal hyperplasia in pregnancy

Only the most common form of congenital adrenal hyperplasia (CAH) due to 21-hydroxylase deficiency is discussed here.

Reduced fertility in women with CAH may be due to inadequate vaginal introitus despite reconstructive surgery and/or anovulation caused by hyperandrogenaemia. However, with improvements in surgical, medical and psychological treatments, more women with classic CAH can successfully complete pregnancies. About 80% of women with the simple virilising form of CAH and 60% of those with the severe salt-wasting form are fertile. Women with CAH are more likely to require caesarean section due to cephalopelvic disproportion.

No major complications in pregnancy are known in women with CAH. Management is similar to that of non-pregnant women, and steroids are increased at the time of delivery as for Addison disease.

Serum androstenedione, testosterone, 17-hydroxyprogesterone, and electrolytes should be monitored every 6 weeks. The glucocorticoid dosage should be adjusted, if necessary, to maintain the concentrations of these hormones within the normal ranges for the stage of pregnancy.

The unaffected female offspring of women with classic CAH are not at risk of virilisation. This is because the placenta aromatises maternal androgens to oestrogens. However, the affected female offspring (i.e. those with 21-hydroxylase deficiency) are at risk of virilisation *in utero* due to excess androgen production by the fetal adrenals (see Chapter 9).

The male partner must be screened for CAH using basal and adrenocorticotrophic hormone (ACTH)-stimulated 17-hydroxyprogesterone (see Chapter 9). If 17-hydroxyprogesterone levels are elevated, genotyping must be done. If the male partner is heterozygote, the fetus is at risk of inheriting CAH and developing virilisation so prenatal treatment is recommended (see below). Prenatal treatment is also recommended in women who have had a previous child with CAH from the same partner.

The aim of prenatal treatment is to prevent virilisation of an affected female. *Dexamethasone* (20 µg/kg per day divided into three doses) is given to the mother as soon as the pregnancy is recognised. Because virilisation occurs within the first 12 weeks of gestation, one cannot wait until the sex and diagnosis of the fetus are known. Dexamethasone crosses the placenta, suppresses fetal ACTH secretion, and prevents overproduction of fetal adrenal androgens.

Dexamethasone treatment is discontinued if chorionic villus sampling (done at 8–12 weeks' gestation) or amniocentesis (done at 18–20 weeks' gestation) indicates that the fetus is male, or if genetic analysis indicates that the fetus is unaffected.

With treatment, 50% of affected female fetuses do not require reconstructive surgery. There are no known fetal congenital malformations associated with glucocorticoid treatment.

The prenatal treatment of women with non-classic CAH with dexamethasone is controversial. There have been no reports of women with non-classic CAH giving birth to a virilised female. However, infants should be screened in the neonatal period by measuring 17-hydroxyprogesterone levels.

Phaeochromocytomas in pregnancy

Phaeochromocytomas are rare in pregnancy but are potentially disastrous for both mother and fetus. The highest risk of hypertensive crisis and death is during labour (precipitated by anaesthesia or even normal delivery). Maternal mortality may be as high as 17% and fetal mortality may be up to 30% if not treated promptly.

The main sign of the disease is hypertension, but this is also common in pregnancy. However, phaeochromocytomas should be suspected in patients with hypertension (persistent or intermittent) with no proteinuria or oedema, and in women with paroxysmal headache, sweating, and palpitation.

Catecholamine metabolism is not altered in the pregnant state, and thus biochemical tests are the same as those in non-pregnant women, i.e. three 24-hour urine collections for measurement of catecholamines and fractionated metanephrines. Plasma metanephrine levels may also be used. Raised levels should be considered significant. It is important to note that antihypertensives commonly used in pregnancy (e.g. labetalol, methyldopa) can lead to false-positive results. MRI is used for localisation of tumours after confirmation of the diagnosis, as it avoids exposing the fetus to ionising radiation.

Prenatal screening should be performed in high-risk women, for example those with a history or family history of multiple endocrine neoplasia type 2 or von Hippel–Lindau syndrome.

Treatment

Phenoxybenzamine (an alpha-blocker) is safe in pregnancy. It is started at a dose of 10 mg twice a day and increased gradually to a maximum of 20 mg three times a day. Propranolol (a beta-blocker) should only be given after alpha-blockade (at a dose of 40 mg three times a day). Unopposed alpha-adrenergic activity may lead to vasoconstriction and a hypertensive crisis.

After 24 weeks of gestation, uterine size makes abdominal exploration and access to the tumour difficult, and surgery must be deferred until fetal maturity is reached. Removal of the tumour may then be combined with caesarean section. However, some surgeons perform the adrenalectomy 4–6 weeks after elective early caesarean section. Adequate adrenergic blockade must be ensured prior to surgery.

Diabetes mellitus in pregnancy

Pre-existing diabetes in pregnancy

Women with pre-existing diabetes are at greater risk of miscarriage, congenital malformations (particularly cardiac), pre-eclampsia, pregnancy-induced hypertension, large for gestational age babies (macrosomia) with associated maternal and fetal birth-related trauma, neonatal morbidity and hypoglycaemia, and stillbirth. Thus, they should receive preconception counselling and advice about the management and potential complications of diabetes before and during pregnancy. This involves targeting good glycaemic control (HbA1c 48 mmol/mol) and ensuring adequate folic acid supplementation (5 mg once daily) in the preconception period.

Diabetes diagnosed during pregnancy

Gestational diabetes mellitus (GDM) is defined as glucose intolerance with an onset or first recognition during pregnancy. During pregnancy, increased placental secretion of diabetogenic hormones such as growth hormone, corticotrophin-releasing hormone (which stimulates ACTH and cortisol release), human placental lactogen (also known as chorionic somatomammotrophin) and progesterone increases maternal insulin resistance. In addition, a postreceptor defect may contribute to the decline in insulin action. GDM occurs when a woman's endogenous insulin production cannot overcome both the insulin resistance created by these anti-insulin hormones and the increased fuel consumption necessary to provide for the growing mother and fetus.

Gestational diabetes affects about 16% of pregnant women in the UK, usually in the second or third trimester. Up to 60% of women with gestational

diabetes will develop diabetes within 10 years of their index pregnancy. The major risk associated with GDM is that of a large baby and risks of shoulder dystocia during normal vaginal delivery.

Screening for gestational diabetes and diagnosis

Pregnant women are screened for GDM according to local and national guidelines. In some areas, screening for GDM is offered to women with risk factors for GDM (Box 31.1); in other areas, all women are screened. Screening may be performed at 24–28 weeks of gestation or as early as the first prenatal visit if unrecognised pregestational diabetes is suspected. A 75 g 2-hour (or a 100 g 3-hour) oral glucose tolerance test is performed to make a diagnosis of GDM. The diagnostic criteria for GDM differ according to different organisations (Table 31.1).

Box 31.1 Risk factors for GDM

Body mass index more than 30 kg/m^2
Previous macrosomic baby weighing 4.5 kg or more
Previous gestational diabetes
Maternal age older than 35 years
Family history of diabetes (first-degree relative with diabetes)
Family origin with a high prevalence of diabetes

Table 31.1 GDM diagnosis from various organisations if one or more glucose values are equal to or exceeding the threshold values

	Plasma glucose concentration thresholds (mmol/L) after 75 g glucose load		
Organisation	**Fasting**	**1 h**	**2 h**
NICE	5.6		7.8
WHO	5.1–6.9[a]	10.0	8.5–11.0[a]
IADPSG	5.1	10.0	8.5
ADA[b]	5.1	10.0	8.5

ADA, American Diabetes Association; IADPSG, International Association of Diabetes and Pregnancy Groups; NICE, National Institute for Health and Care Excellence; OGTT, oral glucose tolerance test; WHO, World Health Organization.
[a] Values above these are considered diagnostic of pre-existing diabetes.
[b] The ADA also uses a two-step approach using an initial 50 g OGTT followed by a 100 g OGTT.

Management of diabetes during pregnancy

The care of all women with diabetes during pregnancy requires a multidisciplinary team approach, including regular joint endocrinology/obstetrics specialist clinics. Patients should be supported by dietitians and diabetes specialist nurses for further advice regarding diet, insulin therapy, exercise, and glucose monitoring.

Management of pre-existing diabetes in pregnancy

An early viability scan should be offered to all women. In addition to the routine formal dating scan at 12 weeks and anomaly scan at 20 weeks, growth scans should take place at 28, 32, and 36 weeks of gestation. Women with pre-existing diabetes should start folic acid 5 mg od immediately if not already taking it and continue until at least 12–16 weeks gestation.

Medications should be reviewed and all oral hypoglycaemic agents, apart from metformin, should be stopped. In addition, ACE inhibitors and statins should be stopped; antihypertensive management should follow local or national guidelines. Aspirin 150 mg od should be routinely offered between 12–36 weeks' gestation to help prevent pre-eclampsia. Retinal assessment should be undertaken every trimester (see below).

Women with pre-existing diabetes should check their capillary blood glucose at least four times per day. All women with type 1 diabetes should be offered continuous glucose monitoring during pregnancy to support blood glucose management at the earliest opportunity. Women should also be provided with ketone meters and educated about the potential for developing diabetic ketoacidosis if they are unwell or become hyperglycaemic (in both type 1 and type 2 diabetes). Insulin pumps can continue to be used during pregnancy.

Target blood glucose levels according to the National Institute for Health and Care Excellence are below 5.3 mmol/L fasting, below 7.8 mmol/L 1 hour after a meal, and below 6.4 mmol/L 2 hours after a meal, if achievable without causing problematic hypoglycaemia. Tightened glycaemic control and higher insulin resistance during pregnancy increase the risk of hypoglycaemia and impaired awareness of hypoglycaemia. This should be discussed, and women offered a glucagon pen and their partner shown how to use it.

All women with pre-existing diabetes are advised to deliver between 37 + 0 and 38 + 6 weeks' gestation by

either induction of labour or caesarean section. During labour and delivery, maternal blood glucose concentration should ideally be maintained between 4 and 8 mmol/L.

Exacerbation of retinopathy in pregnancy

Diabetic retinopathy may worsen during pregnancy. The Diabetes in Early Pregnancy study showed that the risk of progression of retinopathy is related to the severity of retinal involvement before pregnancy and the initial glycated haemoglobin values. Changes in hormones, growth factors, and systemic haemodynamics, and lower retinal blood flow, may contribute to the exacerbation of retinopathy in pregnancy.

The modest increase in risk of worsening of retinopathy during pregnancy necessitates more frequent retinal evaluations during this time and for one year post partum. Women should be screened during the first trimester and then every 3 months while pregnant.

Treatment recommendations are the same as for other patients. Laser therapy and vitreous surgery can be carried out safely during pregnancy if required. Women can be reassured that their long-term risk of retinopathy progression is not increased by pregnancy.

Management of gestational diabetes in pregnancy

A programme of medical nutritional therapy, self-monitoring of blood glucose, metformin and insulin therapy, when needed, has been shown to improve perinatal outcome. Target blood glucose levels according to the National Institute for Health and Care Excellence are below 5.3 mmol/L fasting, below 7.8 mmol/L 1 hour after a meal, and below 6.4 mmol/L 2 hours after a meal, if achievable without causing problematic hypoglycaemia.

The initial approach to managing blood glucose levels in GDM is through *lifestyle measures and diet control*, ideally supervised by a specialist diabetes dietitian.

Patients should check their blood glucose upon awakening and 1 hour after each meal to evaluate the effectiveness of the medical nutritional therapy. A programme of moderate exercise (for 30 minutes five times per week) is recommended for all pregnant women. In those with GDM, a brief period of exercise after eating (e.g. walking for 10 minutes) can increase glucose dispersal and thus lower blood glucose levels.

Metformin is safe in pregnancy and should be offered to women with GDM if blood glucose targets are not met using changes in diet and exercise within 1–2 weeks at 500 mg bd (see Box 31.2).

Box 31.2 Treatment algorithm for women with newly diagnosed GDM

>7.0 mmol/L	<7.0 mmol/L
Offer insulin and diet/exercise advice ± metformin	Offer diet/exercise advice (consider immediate insulin if fasting plasma glucose 6.0-6.9 mmol/L)
	If glucose target not met after 1–2 weeks, offer metformin
	If glucose target not met or unable to take metformin, offer insulin
	If unable to take insulin, offer glibenclamide

Insulin therapy must be initiated if fasting blood glucose is above 7.0 mmol/L or if adequate glycaemic control is not achieved with dietary therapy and exercise alone and metformin is contraindicated or unacceptable (i.e. when target blood glucose levels are not met on two or more occasions within a 2-week interval). Women should continue to monitor their blood glucose levels. The goal is a fasting blood glucose of less than 5.3 mmol/L and a 1-hour postprandial blood glucose of less than 7.8 mmol/L. Women starting insulin who drive must inform the DVLA.

Poorly controlled diabetes in the first trimester is associated with increased risks of miscarriage and congenital malformations. Fetal development is evaluated by obstetricians via sonographic examination and maternal serum multiple marker screening. In addition to routine antenatal scans, growth scans should take place at 28, 32, and 36 weeks gestation.

If there is good glycaemic control and there are no pregnancy or additional maternal complications, it is reasonable to wait for the spontaneous onset of labour. However, extending pregnancy beyond 40 weeks of gestation is not advised. Earlier delivery may be warranted in the presence of high-risk factors such as worsening retinopathy or nephropathy, poor control, pre-eclampsia, or restricted fetal growth.

Induction should be avoided because of suspected fetal macrosomia. If the expected fetal weight is more than 4.5 kg, caesarean delivery is recommended to avoid possible trauma from shoulder dystocia. During labour and delivery, maternal blood glucose concentration should be maintained between 4 and 8 mmol/L.

Women with gestational diabetes are at increased risk of developing diabetes after pregnancy and should have a 2-hour 75 g oral glucose tolerance test at least 2 weeks after delivery.

KEY POINTS

- Pregnant women have increased serum 'total' T_4 and T_3 (due to raised thyroid-binding globulin levels), and a slight increase in serum free T_4 and T_3 levels and suppressed TSH levels in the first trimester (due to raised hCG levels).
- Pregnant women with subclinical hypothyroidism must be treated with levothyroxine.
- Overt hyperthyroidism should be treated with antithyroid drugs. Radio-iodine treatment is absolutely contraindicated in pregnancy.
- Women with macroprolactinomas must be treated with dopamine agonists to shrink the tumour substantially before they can attempt to become pregnant.
- The male partner of a woman with classic CAH must be screened for CAH.
- Phaeochromocytomas should be suspected in pregnant women with hypertension and no proteinuria or oedema.
- An oral glucose tolerance test is performed to make a diagnosis of gestational diabetes.
- Metformin and/or insulin therapy must be initiated if adequate glycaemic control is not achieved with dietary therapy and exercise alone.

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Neuroendocrine tumours

Neuroendocrine cells contain neurotransmitters, neuromodulators or neuropeptide hormones within secretory granules, from which they are released by exocytosis in response to an external stimulus. Unlike neurones, these cells do not have axons and do not make synapses. Neuroendocrine cells make up the diffuse neuroendocrine system, dispersed throughout the body. The *gastroenteropancreatic neuroendocrine system* provides the richest source of regulatory peptides outside the brain.

It was originally thought that all neuroendocrine cells derived from neuroectoderm, but increasingly this has been found not to be the case for all neuroendocrine cells.

Neuroendocrine cells can be characterised by a number of molecular markers such as *chromogranin A* (a protein located alongside specific hormones in large dense-core vesicles) and the subtilase proprotein convertases 2 and 3.

Neuroendocrine tumours (NETs) originate from neuroendocrine cells within the gut (75%), pancreatic islet cells (5%), lung (15%), and other organs (e.g. parafollicular cells within the thyroid, giving rise to medullary thyroid carcinoma [MTC]). Historically, NETs were classified according to their embryological origin into:

- foregut tumours (bronchi, stomach, duodenum, pancreas, gallbladder)
- midgut tumours (jejunum, ileum, appendix, right colon)
- hindgut tumours (left colon and rectum).

Now, NETS are more typically classified according to their primary site and functionality as this better describes biologically similar tumours arising in different areas.

NETs may be functioning or non-functioning depending on whether a secreted hormone is detectable and associated symptoms are present.

The majority of NETs occur as non-familial (sporadic) isolated tumours. However, NETs may be part of familial syndromes such as multiple endocrine neoplasia type 1 (MEN 1), MEN 2, neurofibromatosis type 1 (NF 1), von Hippel–Lindau syndrome (see Chapter 8), and Carney complex (see Chapter 16).

The term *carcinoid* is used for NETs mostly derived from serotonin-producing enterochromaffin cells. In excess of 50% of NETs are of the 'carcinoid' type. About 70% of carcinoid tumours occur in the gut and 25% occur in the lung.

The classification of NETs into benign and malignant depends on tumour size, local spread, vascular invasion, metastases, and nuclear atypia.

Aetiology

The aetiology of neuroendocrine disorders is poorly understood. Most NETs are sporadic, but epidemiological studies show a small increased familial risk for small intestinal and colon NETs.

It has been proposed that NETs may result from a series of genetic mutations leading to the activation of oncogenes and/or inactivation of tumour suppressor genes and failure of apoptosis. A number of genes are known to be involved in the formation of NETs, including *MEN1*, *RET*, *VHL*, *TSC1*, and *TSC2*. Mutations in *MEN1* (a tumour suppressor gene) are the most common form of genetic predisposition to NETs. NETs overexpress somatostatin receptors (SSTR) on the cell surface which enables targeted imaging and treatment utilising somatostatin analogues.

Epidemiology

The incidence of NETs is about 3–4 per 100 000 per year. There is a slight predominance in women.

The annual incidence of pancreatic NETs is approximately 2–4 per million. However, postmortem data suggest a higher incidence. Insulinomas and gastrinomas are the most common among this rare

Endocrinology and Diabetes: Lecture Notes, Second Edition. Amir H. Sam, Karim Meeran and Neil Hill.
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group of tumours. The prevalence of NETs is relatively high because many NETs are slow growing and even malignant NETs are associated with prolonged survival.

The risk of a NET in an individual with one affected first-degree relative is about four times and with two affected first-degree relatives is over 12 times that in the general population.

MEN 1 has a prevalence of about two per 100 000 and MEN 2 has an estimated prevalence of 2.5 per 100 000 in the general population. The incidence of MEN 1 in gastroenteropancreatic NETs varies from virtually 0% in gut carcinoids to 5% in insulinomas and 25–30% in gastrinomas. Around 50% gastrinomas are malignant; often these occur at multiple sites. Insulinomas are usually benign (90%) and <2 cm diameter (90%); less than 10% are multiple at presentation.

Clinical presentations

Diagnosis of NETs is often delayed due to non-specific symptomatology; also, the majority do not secrete hormones in excess. Non-functioning NETs often present late with advanced disease and a worse prognosis.

Gastroenteropancreatic tumours can be asymptomatic or may present with obstructive symptoms due to tumour bulk (pain, nausea, vomiting), symptoms of metastases (liver) or syndromes of hormone hypersecretion.

Carcinoid syndrome is usually a result of metastases to the liver with the subsequent release of hormones (serotonin, tachykinins, and other vasoactive compounds) into the systemic circulation.

Carcinoid syndrome is characterised by flushing, diarrhoea and occasionally wheezing. Less commonly, patients may present with pellagra due to niacin deficiency (caused by diversion of dietary tryptophan for the synthesis of large amounts of serotonin). Pellagra is characterised by dermatitis (rough scaly skin), glossitis, diarrhoea, and dementia. Muscle wasting may occur as a result of poor protein synthesis. Some patients may experience rhinorrhoea, lacrimation, and episodic palpitations. About 70% of patients with carcinoid syndrome give a history of intermittent abdominal pain at the time of diagnosis. Patients with the 'atypical' carcinoid syndrome present with protracted purplish flushing, which affects the limbs and the upper trunk and frequently results in telangiectasia.

Carcinoid heart disease is seen if the syndrome has been present for some years. It is characterised by deposits of fibrous tissue on the endocardium of the valvular cusps and cardiac chambers. The right side of the heart is most often affected because the inactivation of humoral substances by the lung protects the left side of the heart.

Patients with bronchial carcinoid may present with evidence of bronchial obstruction, pneumonitis, pleuritic chest pain, dyspnoea, cough, and haemoptysis in addition to a variety of other symptoms, including weakness, nausea, weight loss, night sweats, neuralgia, and Cushing syndrome.

The *carcinoid crisis* is characterised by profound flushing, bronchospasm, tachycardia, and fluctuating blood pressure. It may be due to the release of mediators that lead to the production of high levels of serotonin and other vasoactive peptides. The carcinoid crisis may be precipitated by anaesthetic induction, intraoperative handling of the tumour, or invasive therapeutic procedures such as embolisation and radiofrequency ablation.

Presenting features of pancreatic NETs are summarised below:

- *Insulinoma*: symptoms and signs of hypoglycaemia: sweating, dizziness, tachycardia, weakness, confusion, unconsciousness. The symptoms are relieved by eating. Symptoms often occur in the morning and may be described as 'funny turns'.
- *Gastrinoma* (Zollinger–Ellison syndrome): severe peptic ulceration and diarrhoea.
- *Glucagonoma:* necrolytic migratory erythema (a rash affecting the lower abdomen, buttocks, perineum, and groin), weight loss, diabetes mellitus, diarrhoea, and stomatitis.
- *VIPoma* (Werner–Morrison syndrome): profuse watery diarrhoea with marked hypokalaemia.
- *Somatostatinoma*: cholelithiasis, weight loss, diarrhoea, steatorrhoea, and diabetes mellitus.

It is important to search thoroughly for MEN 1, MEN 2, and NF 1 in all patients with NETs by obtaining a detailed family history and clinical examination. A familial syndrome should be suspected in all cases where there is a family history of a NET or a second endocrine tumour. A diagnosis of MEN 1, MEN 2, or NF 1 has important implications for the patient and their relatives, who should be considered for genetic testing and screening for the associated tumours (see below).

Investigations

The diagnosis of gastroenteropancreatic NETs is based on clinical symptoms, hormone concentration, radiological and nuclear medicine imaging, and

histological confirmation. The gold standard in diagnosis is detailed histology, and this should be obtained whenever possible. If histology is available from a previous primary site, biopsy of the secondaries may not be necessary.

Biochemical tests

If a patient presents with symptoms suspicious of a gastroenteropancreatic NET, biochemical tests should include:

- plasma *chromogranin A* (note, this is elevated in other conditions and by proton pump inhibitors)
- 24-hour urinary *5-hydroxyindoleacetic acid* (5-HIAA)
- a *fasting gut hormone* profile including gastrin, insulin, glucagon, somatostatin, pancreatic polypeptide, vasoactive intestinal peptide and neurotensin. Blood should be taken in a 10 mL standard heparin bottle containing aprotinin (0.2 mL) and spun immediately before being frozen and sent to a reference laboratory. Multiple hormones may be secreted by some tumours.

All patients should be evaluated for second endocrine tumours and possibly for other gut cancers. Baseline tests that may be appropriate include calcium, parathyroid hormone (PTH), PTH-related protein (if PTH is low), thyroid function tests, calcitonin, prolactin, alpha-fetoprotein, carcinoembryonic antigen (CEA), and beta-human chorionic gonadotrophin.

Chromogranin A is a large protein that is produced by all cells deriving from the neural crest. The function of chromogranin A is not known, but it is produced in very significant quantities by NET cells regardless of their secretory status.

5-HIAA is the main metabolite of serotonin. The 24-hour urinary 5-HIAA is raised in 70% of patients with midgut carcinoid and some patients with foregut carcinoid. Urinary excretion of 5-HIAA may be affected by certain foods and drugs if they are taken just before collection of the urine sample (Box 32.1).

Box 32.1 Factors that affect urinary 5-hydroxyindoleacetic acid excretion

Factors that may cause false-positive results

Bananas, avocados, aubergines, pineapples, plums, walnuts, caffeine
Paracetamol, naproxen, fluorouracil, methysergide

Factors that may cause false-negative results

Aspirin, levodopa, methyldopa, phenothiazines

Tachykinins (neurokinin A and B) are raised in midgut carcinoids.

Specific endocrine tests should be requested depending on which syndrome is suspected.

Novel biomarkers

The relatively late diagnosis of many NETs has led to the search for improved diagnostic and prognostic markers. Recently, the term 'liquid biopsy' has been used to describe blood tests that look for circulating tumour cells and DNA and micro-RNAs that are released into the circulation during tumour growth. NETest is a recently developed multianalyte NET-specific gene transcript analysis that has shown high specificity and sensitivity for diagnosing gastrointestinal NETs. These novel biomarkers are not widely available and require further analysis but may enhance diagnosis and monitoring of NETs in the future.

Suspected insulinoma

In patients presenting with acute hypoglycaemia, serum should be taken quickly for blood glucose, *insulin*, and *C-peptide* levels *prior* to giving glucose. Low C-peptide and high insulin levels indicate exogenous insulin. High C-peptide and insulin levels indicate endogenous insulin, for example either stimulated by surreptitious sulfonylurea ingestion or released by an insulinoma.

Patients with a history suggestive of hypoglycaemic episodes should be investigated with a 72-hour fast, allowing unlimited non-caloric fluids. Elevated plasma insulin and C-peptide levels in the presence of hypoglycaemia (laboratory glucose <2.2 mmol/L) are diagnostic. A plasma glucose level of less than 2.2 mmol/L is achieved by 48 hours of fasting for over 95% of insulinomas. If no hypoglycaemia is achieved by the end of the fast, the sensitivity can be further increased by exercising the patient for 15 minutes. The fast is terminated after the exercise period, or prior to this if hypoglycaemia is achieved (but only after samples for insulin and C-peptide have been taken). A mixed meal test will identify 5–8% of people with insulinoma.

Patients with 'factitious hypoglycaemia' (due to exogenous insulin) do not have elevated C-peptide levels. All patients should also have simultaneous urine samples for *sulfonylurea analysis*, which must be shown to be negative for the diagnosis of insulinoma.

The differential diagnosis of fasting hypoglycaemia is summarised in Box 32.2.

Box 32.2 Differential diagnosis of hypoglycaemia

Diabetic patients: insulin, oral hypoglycaemic agents
Drugs: alcohol, salicylates, quinine, pentamidine
Adrenal insufficiency
Hypopituitarism
Renal failure
Liver failure
Tumours: insulinomas, hepatomas, sarcomas, big-insulin-like growth factor 2

A rare cause of fasting hypoglycaemia is the secretion of an incompletely processed form of insulin-like growth factor 2 ('big-IGF-2') by mesenchymal tumours. These patients have suppressed insulin levels, low IGF-1 and a raised ratio of IGF-2 to IGF-1.

Suspected gastrinomas

Investigations for suspected gastrinomas include fasting gastrin level (raised basal serum gastrin) and gastric secretion studies (high gastric acid secretion).

To measure gastrin in a patient with a suspected gastrinoma, the patient must not take proton pump inhibitors for at least 2 weeks and be off histamine-2 blockers for at least 3 days. However, caution is required if the clinical likelihood of a gastrinoma is high since there is a high risk of peptic ulcer perforation when medical therapy is stopped for the gastrin test. Even on proton pump inhibitors, very high gastrin levels (>250 pmol/L) are indicative of gastrinoma, and repeat testing off therapy should not be recommended.

Differential diagnoses, which include atrophic gastritis, hypercalcaemia and renal impairment, may be excluded by measuring basal acid output. Spontaneous basal acid outputs of 20–25 mmol per hour are almost diagnostic and over 10 mmol per hour is suggestive. If the test results are equivocal, the secretin test is helpful; a rise in gastrin of more than 100 pmol/L (instead of the normal fall) in response to intravenous secretin has a sensitivity of 80–85% for gastrinoma.

Imaging

The optimum imaging modality depends on whether it is to be used for detecting disease in a patient suspected of a NET or for assessing the extent of disease in a known case. As with much endocrinology, imaging should only take place with good biochemical evidence of disease and it is important to establish that any lesions detected are those responsible for causing symptoms.

For detecting the primary tumour, a multimodality approach is best. Computed tomography (CT) and magnetic resonance imaging (MRI) can localise and stage disease but do not indicate if the tumour is functionally active. The sensitivity of CT/MRI to detect NETs varies but may be as low as 50%. The sensitivity and specificity for detecting NETs can be enhanced by using functional imaging modalities such as positron emission tomography (PET) and single-photon emission computed tomography (SPECT) scans.

Combining PET and SPECT with scintigraphy using radiolabelled somatostatin analogues (also known as somatostatin receptor scintigraphy, SRS) such as octreotide has improved NET detection and enabled determination of treatment response. This takes advantage of the widespread expression of SSTR by NETs. Rapidly growing tumours (with more malignant potential) often have lower SSTR expression but may be detected by imaging radioactive glucose uptake (fluorine-18 fluorodeoxyglucose [FDG] PET). Gallium-68 combined with somatostatin analogues (^{68}Ga-DOTA-TATE) with PET scanning has greater sensitivity and specificity than octreotide scintigraphy.

Endoscopic ultrasound (with a mean 92% detection rate for pancreatic NETs) and visceral angiography (helpful for subcentimetre tumours, where a 'tumour blush' is seen) plus calcium stimulation (see below) are also used.

For assessing secondaries, SRS is the most sensitive modality. When a primary tumour has been resected, SRS may be indicated for follow-up. SRS has a sensitivity of up to 90% and a specificity of 80% (excluding insulinomas), and has a sensitivity of 10–50% for insulinomas.

For pancreatic tumours amenable to surgical excision, the surgeon requires as much information as possible regarding location. Selective angiography with secretagogue injection into the main pancreatic arteries allows angiographic and biochemical localization. In this procedure, the main pancreatic arteries (gastroduodenal, superior mesenteric, inferior pancreaticoduodenal, splenic) are cannulated separately and examined for a 'tumour blush'. Calcium (acting as a secretagogue) is injected into each of these arteries individually, and venous samples are collected from the hepatic vein for biochemical analysis of the suspected hypersecreted hormone (e.g. gastrin, insulin). In the presence of a tumour, the hormone levels double after 30 seconds, whereas the normal effect is a reduction in levels.

The hepatic artery is always cannulated at the end of the procedure. A rise in hormone levels detectable in the hepatic vein after calcium injection into the hepatic artery is diagnostic of liver metastases.

Treatment

All cases must be discussed and managed within a specialist multidisciplinary team. The choice of treatment depends on the symptoms, stage of disease, degree of uptake of radionuclide, and histological features of the tumour.

Surgery is the only curative treatment for NETs and should be offered to patients who are fit and have limited disease (i.e. primary tumour with or without positive regional lymph nodes; about 20% of cases).

For patients who cannot have surgery, the aim of treatment is to improve and maintain an optimal quality of life. Treatment choices for non-resectable disease include somatostatin analogues, chemotherapy, radionuclides, and ablation therapies. External beam radiotherapy may relieve bone pain from metastases.

Surgical treatment

Conduct of surgery is dependent on the method of presentation and stage of disease. Surgery should only be undertaken in specialist units. Patients presenting with suspected appendicitis, intestinal obstruction or other gastrointestinal emergencies are likely to require resections sufficient to correct the immediate problem. Once definitive histopathology has been obtained, a further, more radical resection may have to be considered.

Where abdominal surgery is undertaken and long-term treatment with somatostatin analogues is likely, cholecystectomy should be considered (see the side-effects of somatostatin analogues, below). Surgery also has a place in palliation when tumour bulk is too extensive for curative resection.

Endoscopic resection may be appropriate for some intraluminal pulmonary or gastrointestinal NETs.

Liver metastases

Gastroenteropancreatic NETs preferentially metastasise to the liver, which is the only site of distant metastasis in a proportion of patients. Surgery should be considered in those with liver metastases and potentially resectable disease. Debulking procedures (see below) are also used to manage liver metastases. Liver transplantation has been performed in selected patients with numerous liver metastases, with survival of about 50% after 1 year.

Preparation

A potential carcinoid crisis should be prevented by the intravenous infusion of octreotide at a dose of 50 µg per hour for 12 hours prior to and at least 48 hours after surgery. It is also important to avoid drugs that release histamine or activate the sympathetic nervous system. Other prophylactic measures for other NETs include glucose infusion for insulinomas, and proton pump inhibitors and intravenous octreotide for gastrinomas.

Non-surgical debulking

Transarterial embolisation is indicated for patients with non-resectable multiple and hormone-secreting metastases with the intention of reducing tumour size and hormone output. Arterial embolisation induces ischaemia of the tumour cells, thereby reducing their hormone output and causing liquefaction.

There are two types of embolisation: particle embolisation and chemoembolisation. Particles used include polyvinyl alcohol and gel foam powder. For chemoembolisation, agents such as doxorubicin and cisplatin are primarily used. Ischaemia of the tumour cells induced by embolisation increases their sensitivity to chemotherapeutic substances.

Postembolisation syndrome (nausea, fever, abdominal pain) is the most common side-effect. Hormone therapy should be used prior to all embolisations: 50–100 µg octreotide per hour intravenously for 12 hours before and 48 hours after the procedure. Some units use hydrocortisone 100 mg intravenously and prophylactic antibiotics prior to the procedure, and predosing with allopurinol to prevent a tumour lysis syndrome.

Selective internal radiation therapy (SIRT) using ^{90}yttrium-labelled microspheres may reduce the number of particles required and the severity of postembolisation syndrome but is yet to be fully evaluated in large clinical trials

Radiofrequency ablation involves placement of a probe within the tumour under radiological guidance, which then emits radiofrequency waves. These increase the temperature within the tumour and lead to necrosis. Other ablation techniques such as cryoablation and microwave ablation may also be used.

Medical treatment

Medical treatment has to be initiated for symptom control until curative surgical treatment is performed, or if surgery is not indicated. Box 32.3 summarises the medical treatments for the various hypersecretion syndromes.

Somatostatin analogues

The only proven hormonal management of NETs is the administration of somatostatin analogues. SSTRs are present in 70–95% of NETs overall and in about 50% of insulinomas and occur less often on poorly differentiated NETs and somatostatinomas. Somatostatin analogues inhibit the release of various peptide hormones in the gut and antagonise growth factor effects on tumour cells.

Patients may be stabilised with octreotide (short acting) for 10–28 days before converting them to long-acting somatostatin analogues. Octreotide is administered by subcutaneous injection starting at 50–100 µg twice or three times a day to a maximum daily dose of 1500 µg. Inhibition of hormone production (biochemical response) is seen in 30–70% of patients, with symptomatic control in the majority of patients. Tumour growth may stabilise, and rarely shrinkage of tumour may be seen.

Analogues with sustained release from depot injections may be given every 2–4 weeks. Lanreotide (fortnightly injections), lanreotide Autogel®, and Sandostatin® long-acting repeatable (LAR) (monthly injections) have been shown to significantly improve patients' quality of life. Lanreotide and octreotide bind preferentially to the subtype 2 SSTR and to a lesser extent to the subtype 5 SSTR.

The side-effects of somatostatin analogues include gall stones and gallbladder dysfunction, fat malabsorption, vitamin A and D malabsorption, headaches, diarrhoea, dizziness, and hyperglycaemia. Circulating and, where relevant, urinary hormone levels should be monitored during periods of treatment. Patients should also have regular relevant imaging.

In a recent phase III study, pasireotide LAR was not superior to octreotide LAR in achieving symptom control after 6 months in patients with metastatic neuroendocrine tumours and carcinoid symptoms refractory to first-generation somatostatin analogues.

Chemotherapy

Chemotherapy may be used for inoperable or faster growing metastatic pancreatic and bronchial tumours, and for poorly differentiated NETs. Various combinations of chemotherapy have been used, including streptozotocin and doxorubicin in well-differentiated

Box 32.3 Medical treatments for neuroendocrine tumour syndromes

Carcinoid
Somatostatin analogue for somatostatin receptor scintigraphy (SRS)-positive carcinoid
Alpha-interferon for SRS-negative carcinoid
Histamine antagonists (H_1 and H_2), ondansetron, cyproheptadine, nicotinamide

Insulinoma
Frequent slow-release complex carbohydrate intake
Diazoxide for controlling hypoglycaemic symptoms; side-effects include fluid retention and hirsutism
Intravenous glucose for periods of fasting or acute hypoglycaemia
Intramuscular glucagon for the treatment of acute hypoglycaemia
Somatostatin analogue if SRS positive (usually malignant); these have variable effects on blood glucose, possibly due to the suppression of counter-regulatory hormones such as glucagon

Gastrinoma
High-dose proton pump inhibitor (lifelong in patients with MEN 1, since there is a high recurrence rate with surgery)

Glucagonoma
Somatostatin analogue
Anticoagulation since associated with thrombophilia
Insulin for diabetes mellitus
Zinc therapy for skin lesions (necrolytic migratory erythema)

VIPoma
Somatostatin analogue (titrate the dose against vasoactive intestinal peptide levels, aiming for a normalisation of levels)
Aggressive intravenous rehydration in acute attacks of diarrhoea
Potassium and bicarbonate in acute attacks

Somatostatinoma
Pancreatic enzyme supplementation
Insulin for diabetes mellitus

Non-functioning tumours
A somatostatin analogue if the SRS scan is positive and there is progressive disease

pancreatic NETs, lomustine and 5-fluorouracil in advanced NETs, and etoposide and cisplatin in poorly differentiated and aggressive NETs. Toxicity rates are high and responses generally poor. Newer agents (temozolomide, capecitabine, gemcitabine) may also be used.

Novel targeted chemotherapy

Everolimus, an inhibitor of the mammalian target of rapamycin (mTOR) pathway regulating protein synthesis and cellular proliferation, has been used in combination with octreotide and alone. Clinical trials in patients with high-grade or advanced NETs have shown improved progression-free survival with everolimus plus octreotide compared to octreotide LAR alone. However, the octreotide group had a longer overall survival than the octreotide plus everolimus group so there is debate over whether the addition of everolimus to octreotide LAR confers survival advantages over octreotide LAR alone. Evidence for the beneficial effect of other agents (sunitinib and bevacizumab) is accumulating.

Alpha-interferon

This may be used in both secreting carcinoid tumours and other NETs on its own or added to long-acting somatostatin analogues, although results have been disappointing. Side-effects include flu-like symptoms, weight loss, fatigue, depression, hepatotoxicity, and autoimmune disorders.

Peptide receptor radionuclide therapy (PRRT)

This is a useful palliative option for symptomatic patients with inoperable or metastatic tumour. Beta-emitting radionuclides are combined with somatostatin analogues (^{90}Y-octreotide, ^{90}Y-lanreotide). Adverse effect of PRRT include hepatic, renal, and haematological toxicity, and therefore scintigraphy to establish that there is avid uptake of the corresponding gamma-emitting imaging radionuclide (^{123}I-MIBG, ^{111}In-octreotide) at all known tumour sites is performed. ^{177}Lu-octreotide emits beta particles and gamma rays and can thus be used for treatment, and has shown improved progression-free survival and quality of life compared to octreotide alone in people with advanced progressive midgut NETs.

Prognosis

Recent increases in the survival of individuals with NET have been documented. The overall 5-year survival of all NET cases is about 67% but the range of survival is very wide.

Survival depends on the histological type, degree of differentiation, mitotic rate, Ki-67 or MIB-1 index (indices of proliferative activity), tumour size (>3 cm), depth, location, presence of liver or lymph node metastases, and age over 50 years. Following complete resection of the primary tumour and liver metastases, if present, the overall 5-year survival is 83%. In cases where this is not possible, survival ranges from 30% to 95% depending on the factors above and the treatment employed.

Median overall survival (OS) ranges from 99 months in those with grade 3 well-differentiated NETs to 17 months for grade 3 poorly differentiated neoplasms. There is also a wide range in outcome in those with metastasised disease depending on the primary site, with worse outcomes for those with colon and lung NETs (median 14 and 24 months OS) compared to midgut NETs (median 98–103 months OS).

The best prognosis is in bronchial and appendicular carcinoids. The 5-year survival for typical lung carcinoids and carcinoid tumours of the appendix is 80–90%, whereas that for atypical lung tumours is 40–70%.

The overall 5-year survival for pancreatic NETs is 50–80%, with insulinomas and gastrinomas having up to 94% 5-year survival, although there is clearly a large variation depending on the stage at presentation and whether curative surgery is possible.

Multiple endocrine neoplasia

Multiple endocrine neoplasia is characterised by tumours involving two or more endocrine glands within a single patient. Although these syndromes are rare, recognition is important for both the treatment and evaluation of family members.

There are two major forms of MEN: type 1 (Wermer syndrome) and type 2 (Sipple syndrome). MEN syndromes are inherited as autosomal dominant disorders. Around 5–10% of cases of MEN 1 and MEN 2A may arise sporadically, rising to 75% in MEN 2B. However, it is sometimes difficult to distinguish sporadic and familial forms as the parent with the disease may have died before developing any manifestations.

MEN type 1

Multiple endocrine neoplasia type 1 is characterised by a predisposition to:

- parathyroid adenomas
- enteropancreatic endocrine adenomas
- pituitary adenomas.

A consensus statement from an international group of endocrinologists defines MEN 1 as the presence of two of the above tumours. Familial MEN 1 is defined as an index MEN 1 case with at least one relative who has one of the above tumours. The incidence of MEN 1 is about 1 in 30 000, and between 30–70% of people with MEN 1 will die of causes related to the disease.

- *Parathyroid adenomas* result in primary hyperparathyroidism and hypercalcaemia. This is the initial manifestation of the disorder in 90% of patients and is highly penetrant. Primary hyperparathyroidism occurs in about 75% of patients by 21 years of age and 95% by age 50 years. About 1–2% of all cases of primary hyperparathyroidism are due to MEN 1. Multigland hyperplasia is more common than single-gland disease.
- *Enteropancreatic endocrine adenomas* occur in 40% of individuals with MEN 1. The majority of patients with familial MEN 1 develop non-functioning pancreatic tumours; 30–40% develop gastrinomas and 10–30% develop insulinomas. Glucagonomas, VIPomas, and somatostatinomas are rare. Pancreatic polypeptidomas are more common but remain asymptomatic.
- *Pituitary adenomas* occur in 30% of MEN 1 patients. Most (60%) are prolactinomas, which tend to be aggressive. Growth hormone-secreting tumours account for 20% of the pituitary tumours. Other types of pituitary adenoma that may occur in MEN 1 include non-functioning adenomas and corticotroph adenomas.

As tumours arise in patients with MEN 1, patients present with symptoms of hormone secretion (e.g. PTH, gastrin, insulin, prolactin, growth hormone) and tumour bulk (e.g. pituitary tumours compressing the optic chiasm, non-functioning pancreatic tumours with liver metastases).

Other tumours that may be associated with MEN 1 include facial angiofibromas (88%), collagenomas (72%), carcinoid tumours (5–10%), adrenocortical tumours (5%), and lipomas (1%). There is a higher reported risk of breast cancer.

The possibility of phenocopy must be considered; that is, people having coincidental conditions that would make a diagnosis of MEN 1 but are in fact coincidental – for example, a person with acromegaly may subsequently develop primary hyperparathyroidism (which is relatively common) and may not be MEN 1. Thorough history and additional screening may help distinguish true MEN 1 and phenocopy.

In people with incidentally discovered pancreatic tumours, cystic lesions carry a 20% risk of MEN 1 (or von Hippel-Lindau), and solid lesions a 5% risk of MEN 1.

Aetiology

In MEN 1, germline inactivating mutations in the tumour suppressor gene *MEN1* (on chromosome 11) are found in 95% of patients. *MEN1* encodes a protein called menin, which suppresses gene transcription activated by *JunD* and controls cell proliferation.

Absence of detectable mutations in *MEN1* may reflect deficiencies of current technology or the fact that the inactivation process occurs via non-mutation mechanisms such as methylation of a region of the *MEN1* gene. Familial and somatic *MEN1* mutations differ in terms of the former usually presenting at an earlier age, with multiple organs affected and multiple tumours in one organ. A small number of families with disease suggestive of MEN 1 have mutations in the *CDKN1B* gene, referred to as MEN 4.

Screening

Screening for MEN 1 involves genetic testing, thorough clinical history and examination, and biochemical tests.

Genetic testing for mutations in the *MEN1* gene is performed in index cases with a clinical diagnosis of MEN 1, all first-degree relatives of an affected individual (including those who are asymptomatic), and individuals with an increased chance of disease. Relatives who do not have the mutation can be reassured and do not require regular screening. It is important to note that 5–10% of people with MEN 1 do not have a mutation in the MEN coding region.

Clinical and biochemical screening is commenced annually from 5 years of age in MEN 1-affected families. Patients with known MEN 1 should have 6-monthly screening for additional tumours.

Clinical history and examination should look for symptoms and signs of the endocrine tumours associated with MEN 1:

- parathyroid adenomas: hypercalcaemia and nephrolithiasis
- gastrinomas: peptic ulcer disease
- insulinomas: symptoms and signs of sympathetic overactivity and neuroglycopenia

- pituitary adenomas: hypopituitarism, galactorrhoea and amenorrhoea in women, acromegaly, Cushing disease, and visual field loss
- subcutaneous lipomas, facial angiofibromas, and collagenomas.

Biochemical tests should include serum calcium, PTH, fasting gastrin and glucose, gut hormones, prolactin, and IGF-1. Specific endocrine function tests are indicated in those with symptoms and signs of MEN 1-associated tumours.

Imaging should include annual MRI abdomen and endoscopic ultrasound for pancreatic NETs (and adrenocortical tumours), MRI or CT chest every 1–2 years for bronchial or thymic carcinoid.

Management

The management of affected families is complex, requiring careful co-ordination between the medical team (endocrinologist, geneticist, surgeon, general practitioner) and the family. The management of MEN type 1 includes:

- subtotal parathyroidectomy for hyperparathyroidism, and on occasion thymectomy
- cinacalcet may be effective for persistent hypercalcaemia
- surgical resection of pancreatic NETs where surgically feasible except for gastrinoma, for which recurrence is high after surgery in MEN 1 and for which some advocate non-surgical therapy
- the treatment of pituitary tumours in a similar way to sporadic cases.

MEN type 2

Multiple endocrine neoplasia 2 is the association of MTC with phaeochromocytoma. Three variants are recognised: MEN 2a, MEN 2b, and MTC only (Box 32.4).

Aetiology

Multiple endocrine neoplasia type 2 results from germline mutations in the *RET* proto-oncogene (on chromosome 10), which encodes a tyrosine kinase receptor which is expressed in neural crest cells (e.g. thyroid C cells and adrenal medullary cells). In all variants, there is a high (90%) penetrance of MTC. Around 98% of MEN 2 index cases have an identified *RET* mutation. *RET* mutations can be categorised as high, intermediate and low risk, referring to the potential risk for local and distant metastases at an early age. The likelihood of *RET* germline mutations in a patient with apparently sporadic MTC is 1–7%.

MTC determines mortality in people with MEN 2 (causing 4% of all thyroid cancer but 15% of thyroid cancer deaths). Familial cases account for 25% MTC diagnoses, the remainder being sporadic, usually occurring in the fifth or sixth decade of life.

Box 32.4 MEN 2 syndromes

MEN 2a (95% of all MEN 2)

Medullary thyroid carcinoma (MTC) (90%)
Phaeochromocytoma (50%)
Parathyroid adenomas (20–30%)
Cutaneous lichen amyloidosis: pruritic, scaly, papular, pigmented skin lesions in the interscapular region or on the extensor surfaces of the extremities (rare)

MEN 2b (now also referred to as MEN 3) (~5%)

Medullary thyroid carcinoma (100%)
Phaeochromocytoma (50%)
Mucosal neuromas (>90%)
Intestinal autonomic ganglion dysfunction leading to multiple diverticula and megacolon
Marfanoid habitus (90%)
Medullated corneal fibres

MTC only

MTC – this is a phenotypic variant of MEN 2a, with reduced penetrance of phaeochromocytoma and primary hyperparathyroidism; the MTC typically presents later than in 2a but is invasive early

Screening

Indications for screening for MEN 2 are:

- MTC, or two or more MEN 2-associated endocrine tumours
- one MEN 2-associated endocrine tumour and age less than 30 years
- mucosal neuromas or somatic features of MEN 2b
- any individual with a relative with MEN 2.

Screening involves genetic testing, thorough clinical history and examination, and biochemical tests.

Genetic testing for mutations in the *RET* gene is indicated in index cases and asymptomatic (usually first-degree) relatives to allow appropriate monitoring and treatment (e.g. prophylactic thyroidectomy). Further clinical and biochemical screening is restricted to family members who have inherited the mutation.

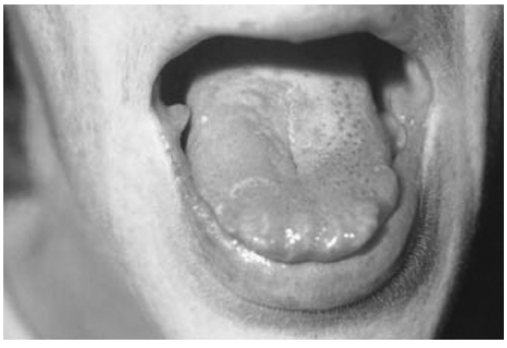

Figure 32.1 Mucosal neuromas on the tongue and lips in a patient with multiple endocrine neoplasia type 2b.

Clinical and biochemical screening is performed every 3–6 months in patients known to have MEN 2 to identify the development of additional tumours, and every 6–12 months in unaffected carriers. Screening for phaeochromocytoma and primary hyperparathyroidism is done in childhood and is guided by the mutation.

Clinical history and examination should look for symptoms and signs of endocrine tumours associated with MEN 2:

- MTC: lumps in the neck, dysphagia (16%) and diarrhoea (30%)
- phaeochromocytoma: headaches, palpitations, sweating and hypertension
- parathyroid adenomas: hypercalcaemia
- MEN 2b-related neuromas (Figure 32.1) and somatic features.

Biochemical tests include serum calcitonin (basal and post-pentagastrin stimulation), plasma metanephrines, 24-hour urinary catecholamines and/or metanephrines, and serum calcium and PTH.

Management

The management of affected families is complex, requiring careful co-ordination between the medical team (endocrinologist, geneticist, surgeon, general practitioner) and the family.

Total *thyroidectomy* should be performed for patients with MEN 2. Unfortunately, MTC tends not to be responsive to either chemotherapy or radiotherapy. There is a strong genotype-phenotype correlation between different *RET* mutations which determines the timing and the invasive nature of MTC and thus treatment (Box 32.5). Phaeochromocytomas, if present, should be removed before thyroidectomy. A number of strategies for adjuvant therapy after total thyroidectomy have been investigated, all with limited success.

Postoperatively, patients should be monitored with serum *calcitonin* measurements and neck ultrasound for evidence of recurrence. Calcitonin is measured at least yearly, and in intermediate- or high-risk patients every 6 months. The 'calcitonin doubling time' is used as a surrogate marker of tumour volume and may help estimate prognosis (>2 years appears to be associated with a better long-term prognosis then <6 months.).

Serum CEA levels are also monitored by some experts. These often take several months to normalise postoperatively because CEA is a large glycosylated molecule. Calcitonin is a more sensitive test, but at a

Box 32.5 Genotype risk categorisation for medullary thyroid cancer and timing of thyroidectomy in *RET* mutation carriers

Risk	*RET* codon mutation	Recommended age to begin annual screening for MTC (year)[a]	Recommended timing of prophylactic thyroidectomy[b]
Highest	918	Not applicable	In the first months to year of life
High	634, 883	3	At or before age 5 years
Moderate	533, 609, 611, 618, 620, 630, 666, 768, 790, 804, 891, 912	5	Childhood or young adulthood

Risk of MTC development in MEN2 depends on mutated *RET* codon.
MEN2, multiple endocrine neoplasia type 2; MTC, medullary thyroid cancer.
[a] Annual physical examination, neck ultrasound, measurement of serum calcitonin.
[b] Patients with MEN2 and a diagnosis of MTC (regardless of age) must have pheochromocytoma excluded prior to thyroidectomy.

Source: Wells SA Jr, Asa SL, Dralle H, et al. Revised American Thyroid Association guidelines for the management of medullary thyroid carcinoma. Thyroid 2015;25:567.

later stage of the disease, due to dedifferentiation, the ratio between calcitonin and CEA may change.

All *RET* mutation carriers should undergo prophylactic total thyroidectomy to prevent the almost certain development of MTC. Timing of thyroidectomy should be performed according to the *RET* mutation (see Box 32.5). MEN 2b has a more aggressive course than MEN 2a or familial MTC. If MTC is found in a hemithyroidectomy, in someone not known to have MEN or familial MTC, a further extensive neck dissection should follow.

The preferred therapy for unilateral adrenal phaeochromocytoma is laparoscopic resection, following adequate preoperative alpha- and beta-adrenergic blockade. Bilateral adrenal and extra-adrenal phaeochromocytomas require open resection.

Hyperparathyroidism is milder than in MEN 1, but often more than one parathyroid gland is enlarged. The exact parathyroid procedure performed (e.g. subtotal, only enlarged glands) should be the same as in other disorders with multiple parathyroid tumours.

KEY POINTS

- NETs originate from neuroendocrine cells within the gut, pancreatic islet cells, lung, and other organs (e.g. parafollicular cells within the thyroid, giving rise to MTC).
- Gastroenteropancreatic tumours can be asymptomatic or may present with obstructive symptoms due to tumour bulk (pain, nausea, vomiting), symptoms of metastases (liver), or syndromes of hormone hypersecretion.
- Carcinoid syndrome is characterised by flushing, diarrhoea, and occasionally wheezing.
- The initial investigation of gastroenteropancreatic NETs includes plasma chromogranin A, 24-hour urinary 5-HIAA, and a fasting gut hormone profile.
- Surgery is the only curative treatment for NETs.
- Medical treatment (e.g. somatostatin analogues) should be initiated for symptom control until curative surgical treatment is performed, or if surgery is not indicated.
- MEN type 1 is characterised by a predisposition to parathyroid adenomas, enteropancreatic endocrine adenomas, and pituitary adenomas. MEN 2 is the association of MTC with phaeochromocytoma.

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Obesity

Appetite regulation

Appetite regulation is primarily controlled by peripheral hormones and neural signals that interact with the central nervous system (CNS) appetite circuits. The CNS receives afferent signals from the periphery, including the gut, pancreas, and adipose tissue, about food intake and energy stores. This information is integrated, and appropriate cognitive and metabolic responses are initiated to control food intake and metabolism.

Afferent signals

Messages from the periphery reach the brain via:

- the circulation: for example, leptin, glucose and amino acids reach the brain by transport across the blood–brain barrier or directly in regions of the brain where this barrier is incomplete
- neural circuits, for example the *vagal afferents* from the gastrointestinal tract.

These signals are influenced by what is eaten.

Leptin is produced in adipocytes (fat cells) and signals to the brain about the quantity of stored fat. The primary role of leptin is to indicate whether fat stores are sufficient for survival and reproduction. Leptin inhibits orexigenic neurones and stimulates anorexigenic neurones in the arcuate nucleus of the hypothalamus (see below).

Gut peptides such as cholecystokinin, peptide YY (PYY) 3–36, and glucagon-like peptide (GLP-1) reduce food intake. *Ghrelin*, a peptide produced in the stomach, increases food intake and stimulates growth hormone (GH) secretion. Serum levels of ghrelin increase in anticipation of a meal and are suppressed by food ingestion. Serum ghrelin levels increase after diet-induced weight loss, suggesting that it plays a role in the compensatory changes in appetite and energy expenditure that make the maintenance of diet-induced weight loss difficult.

CNS stimulators of food intake include melanin-concentrating hormone, GH-releasing hormone, orexin A and orexin B (also called hypocretins).

Other satiety signals include *gastric distension* and *nutrients* (e.g. glucose and lipids). The taste and smell of food are recognised as key factors influencing eating behaviour, which may also be influenced by an individual's emotional state.

CNS areas involved in regulation of appetite

Several areas in the CNS are important in the regulation of appetite.

- The *nucleus of the tractus solitarius* receives and integrates vagal and other neural inputs.
- The *arcuate nucleus* (at the base of the hypothalamus) integrates leptin signals by changing the production and release of neuropeptide Y and agouti-related peptide, which increase food intake, and alpha-melanocyte-stimulating hormone (alpha-MSH), which decreases food intake. There are reciprocal connections between the brainstem and hypothalamus.
- The *paraventricular nucleus* receives neural inputs from the arcuate nucleus.
- Damage to the *ventromedial hypothalamus* leads to increased food intake and obesity.
- Damage to the *lateral hypothalamus* leads to reduced food intake and lower body weight.
- The *ventral tegmental area* is involved in hedonic reward circuits that amplify eating behaviours.

Noradrenaline, serotonin, and several neuropeptides are involved as neurotransmitters or neuromodulators of this control system.

Endocrinology and Diabetes: Lecture Notes, Second Edition. Amir H. Sam, Karim Meeran and Neil Hill.
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Efferent mediators

The sympathetic nervous system has a tonic role in maintaining energy expenditure.

Glucocorticoids increase food intake. The hyperphagic effect of glucocorticoids may be mediated via inhibition of the sympathetic nervous system.

Obesity

Obesity is associated with significant morbidity and mortality, and an excess risk of many disorders such as insulin resistance, type 2 diabetes mellitus, hypertension, dyslipidaemia, coronary heart disease, stroke, obstructive sleep apnoea, cancer, gallstones, hypogonadism and infertility, osteoarthritis, gout, non-alcoholic fatty liver disease, and idiopathic intracranial hypertension. Furthermore, obesity is associated with increased risk of depression and anxiety, and depression and anxiety are associated with increased risk of obesity.

The *body mass index* (BMI) is widely used to evaluate the degree of overweight. It is calculated from height and weight:

$$\text{BMI} = \text{body weight}\left(\text{in kg}\right) \div \text{the square of the height}\left(\text{in metres}\right)$$

The World Health Organization (WHO) has defined obesity as a BMI of 30 kg/m^2 or more. Individuals with a BMI between 25 and 29.9 are 'overweight'. Recently, some groups have assigned lower BMI cut-offs to define overweight and obesity in certain ethnic groups, e.g. people from the Indian subcontinent.

Waist circumference (and the waist-to-hip ratio) is a practical means of determining abdominal obesity (which reflects intrabdominal visceral fat) and correlates with diabetes and metabolic risk factors for cardiovascular disease.

Epidemiology

In most populations, the prevalence of overweight and obesity has steadily increased over the past 20 years. In the USA, the lifetime risks of becoming overweight or obese are about 50% and 25% respectively. In the United Kingdom, about 25% of adults are obese and an additional 50% are overweight.

Ethnicity influences the incidence of obesity. For example, black men tend to be less obese than white men. However, black women are more obese than white women. The prevalence of obesity in Hispanic men and women is higher than in white individuals. There are troubling socioeconomic aspects affecting people who are obese – they are frequently stigmatised, are less likely to marry and more likely to have lower incomes.

Aetiology

Many factors may contribute to the development of obesity (Box 33.1).

Lifestyle and social factors

Sedentary lifestyle

A sedentary lifestyle reduces energy expenditure and promotes weight gain. In an affluent society, energy-sparing devices also reduce energy expenditure.

Sleep deprivation

Observational data suggest a possible association between sleep deprivation and obesity. Sleep restriction may be associated with a decrease in serum leptin (an anorexigenic hormone) and an increase in serum ghrelin (an orexigenic hormone).

Cessation of smoking

Weight gain is very common when people stop smoking. This may be mediated by nicotine withdrawal.

Social networks

A report of a social network constructed from the Framingham Offspring Study illustrated that an individual's chance of becoming obese was increased if he or she had a friend, sibling or spouse who became obese.

Dietary factors

Energy intake and the composition of the diet play an important role in the pathogenesis of obesity. Overeating relative to energy expenditure causes obesity. Most obese subjects have lost control of their

Box 33.1 Causes of obesity

Lifestyle and social factors
Dietary factors
Genetic factors
Drugs
Neuroendocrine disorders
Prenatal factors
Psychological factors

eating (disinhibition). Epidemiological data suggest that a diet high in fat is associated with obesity.

The more important and frequent eating disorder associated with obesity is binge-eating disorder.

Infant feeding practices may also contribute to weight gain. Breast feeding, when compared with formula feeding, may be associated with a lower risk of overweight.

Genetic factors

Studies of twins, adoptees and families suggest the existence of genetic factors in obesity. Genetic factors influence obesity in two ways:

- genes that are primary factors in the development of obesity are very rare
- susceptibility genes on which environmental factors act to cause obesity. There are different susceptibilities within different ethnic groups.

Obesity is a feature of at least 24 genetic disorders such as Prader–Willi (caused by a deletion of paternal DNA on the long arm of chromosome 15) and Bardet–Biedl (an autosomal recessive disorder) syndromes.

A small proportion of obesity is due to monogenic causes. Heterozygous mutations in the gene encoding the *melanocortin-4 receptor* (MC4R) are the most common monogenic cause of obesity in childhood. MC4R is the receptor for alpha-MSH, which is a potent inhibitor of food intake. Childhood obesity due to leptin deficiency has been reported in some consanguineous families. Obesity resulting from leptin receptor deficiency has also been described. However, most obese subjects do not have any abnormalities in the leptin gene and have intact leptin receptors and high serum leptin levels because of central leptin resistance.

The genes that contribute to the more common forms of obesity have been difficult to identify. A variant in the *FTO* (fat mass and obesity associated) *gene* on chromosome 16 increases the risk of obesity in the general population. Mutations in the gene for peroxisome proliferator-activated receptor gamma 2 (a transcription factor involved in adipocyte differentiation) accelerate the differentiation of adipocytes and are associated with obesity in some subjects.

Drugs

A number of drugs can cause weight gain, including atypical antipsychotics (e.g. clozapine, olanzapine), tricyclic antidepressants, antiepileptic drugs (e.g. valproate, carbamazepine), insulin (possibly through the anabolic effect of insulin and insulin-driven hyperphagia), sulfonylureas, thiazolidinediones, and glucocorticoids.

Psychological factors

Depression, anxiety, and post-traumatic stress disorder are linked to weight gain. Furthermore, weight gain can be due to emotion-driven eating, poor self-care, sleep issues, and psychiatric medications.

Neuroendocrine disorders

Several neuroendocrine disorders may be associated with the development of obesity:

- *Hypothalamic obesity* is a rare syndrome in humans. Damage to certain hypothalamic nuclei, such as the ventromedial hypothalamus, by trauma, tumour, inflammatory disease, or surgery may result in hyperphagia and obesity.
- In patients with *Cushing syndrome*, a stimulation of food intake by excess glucocorticoids contributes to weight gain.
- In patients with *hypothyroidism*, the slowing of metabolic activity leads to weight gain.
- About half of patients with *polycystic ovary syndrome* are obese. The underlying aetiology is not fully understood.
- *GH deficiency* results in increased abdominal and visceral fat.

Prenatal factors

Maternal smoking and gestational/type 2 diabetes increase the risk of obesity in the offspring. Infants who are small, short, or have a small head circumference are at higher risk of abdominal adiposity and other comorbidities associated with obesity later in life.

Clinical evaluation

The clinical evaluation of overweight and obese individuals should include measurement of:

- height and weight, and calculation of BMI
- waist circumference in patients with a BMI less than 35 kg/m^2
- blood pressure
- fasting lipid profile (serum triglyceride, high-density and low-density lipoprotein cholesterol)
- fasting blood glucose and HbA1c (insulin and/or c-peptide levels may be measured in order to calculate insulin resistance)
- thyroid function tests

- liver function tests
- renal profile
- full blood count.

The medical history should include age at onset of weight gain, change in dietary patterns, history of exercise, and questions regarding the possible aetiology, including medications, history of smoking cessation and features of endocrine disorders such as hypothyroidism, polycystic ovary syndrome and Cushing syndrome. Screening questions should also probe for other co-morbidities, e.g. history of snoring (sleep apnoea), joint pain (osteoarthritis), change in bowel habit (bowel cancer), etc.

Treatment

Management of obesity is complex and requires an integrated multidisciplinary approach including physicians, psychologists, dietitians, surgeons and exercise therapists. The health gains of even moderate weight loss are significant (Box 33.2). Important areas to address include:

- addressing the cause of obesity
- assessing and managing the consequences of weight gain
- investigating the patient's perspective
- advising on appropriate action and measures to be taken
- evaluating the results of interventions.

Diet and lifestyle

Weight loss is most effectively achieved by restricting energy intake; maintenance of lower body weight can be sustained by increased physical activity. Obese patients should receive counselling on diet, lifestyle and exercise. Overweight patients who have an increased waist circumference (>102 cm in men or >88 cm in women) or co-morbidities deserve the same consideration for obesity intervention as obese patients. Readiness to change is an essential feature of those who are successful in losing weight.

Box 33.2 10 kg weight loss in a person with obesity can lead to the following health gains

>20% reduction in mortality
>30% reduction in diabetes-related mortality
>40% reduction in obesity-related cancer
Fall in systolic blood pressure of ~10 mmHg
Reduction in fasting blood glucose in people with diabetes
Significant improvement in lipid profile (30% reduction in triglycerides, 15% reduction in low-density lipoprotein)

Approximately 22 kcal per day is required to maintain 1 kg of body weight in a normal adult (i.e. 2200 kcal per day for an individual weighing 100 kg). Diets that have a 600 kcal/day deficit or that reduce calories by lowering the fat content in combination with expert support and intensive follow-up are recommended for sustainable weight loss.

Low-calorie diets (800–1600 kcal/d) can be considered but are less likely to be nutritionally complete. However, the success of intensive lifestyle interventions is largely disappointing, with mean weight loss of 2.3–5.0 kg and more than half of patients dropping out within 12 months. Pilot studies (e.g. I-SatPro) have shown that a multifaceted approach to weight loss for people with obesity, encompassing dietary advice, time-restricted eating, physical activity and coaching to support behaviour change, can lead to clinically meaningful weight loss and the potential for long-term health and well-being improvements.

Recently, the Diabetes Remission Clinical Trial (DiRECT) in overweight people with type 2 diabetes has shown that complete meal replacement very low calorie diets (~800 calories/day meal replacement for 3 months followed by gradual food reintroduction) can achieve remission of type 2 diabetes and significant weight loss in community settings. Over 12 months, mean weight loss was 10, and 7.6 kg at 24 months. It is important to note that only a proportion of participants (24%) were able to achieve the co-primary outcome of >15 kg weight loss at 12 months, and this had fallen to 11% at 24 months. Nevertheless, these findings are encouraging. In those who lost more than 10 kg weight, 64% were in remission from diabetes at 24 months.

As alluded to above, achieving and maintaining weight loss can be extremely challenging. Many headline studies and diets report only short-term effects. The biological drive to restore weight from a 'nutritionally deplete' state (possibly mediated by falling leptin levels with resultant lowering of metabolic rate and reduction in energy expenditure that is associated with weight loss) amplifies hunger signalling. Serum ghrelin levels increase following diet-induced weight loss. Ghrelin stimulates appetite and may also play a role in the difficulty with maintaining weight loss, which is a significant challenge in an obesogenic environment.

Pharmacological therapy

Pharmacological therapy should be considered for patients who have not achieved their weight loss goals through diet and exercise alone. It is important for patients to understand that current drug therapy does not cure obesity. Patients must be advised that when the maximal therapeutic effect is achieved, weight loss ceases. When drug therapy is discontinued, weight is frequently regained.

The goals for weight loss must be realistic, and a return to normal body weight is unrealistic. Success may be assessed by the degree of weight loss and improvement in associated co-morbidities. A weight loss of 10% from baseline can significantly reduce the risk factors for diabetes and cardiovascular disease in higher-risk patients (see Box 33.2).

Orlistat inhibits pancreatic lipases and prevents the hydrolysis of ingested fat to fatty acids and glycerol, resulting in increased faecal fat excretion. Orlistat (120 mg three times a day before meals) may be started as first-line pharmacological therapy in obese patients with elevated blood pressure, dyslipidaemia or cardiovascular disease. Orlistat has beneficial effects on lipid profile and an excellent cardiovascular safety profile.

The main side-effects of orlistat therapy are gastrointestinal, including intestinal cramps, flatus, faecal incontinence and oily spotting. The side-effects may occur at frequency rates of 15–30%. However, these subside as patients learn how to avoid high-fat diets and stick to the recommended intake of no more than 30% fat. The absorption of vitamins A and E and beta-carotene may be slightly reduced, and it may be advisable to give vitamin supplements to patients treated with this drug. Orlistat does not seem to affect the absorption of other drugs except for ciclosporin. In clinical practice, people find the unpleasant side-effects of orlistat (steatorrhoea) outweigh the modest weight loss achieved so it is neither widely prescribed nor adhered to.

The GLP-1 agonist liraglutide is licensed for weight loss in people with BMI 30 kg/m^2 or more (obese), or from 27 kg/m^2 to less than 30 kg/m^2 (overweight) in the presence of at least one weight-related co-morbidity. These drugs are also used to manage type 2 diabetes, utilising the endogenous incretin effect to augment glucose-dependent insulin secretion and inhibit glucagon release. In addition, GLP-1 analogues suppress appetite through central effects and slow the rate of gastric emptying. Combined, these lead to significant weight loss. To mitigate gastrointestinal side-effects of nausea, constipation and belching, the dose is uptitrated over time. Gallstones and pancreatitis are recognised side-effects of GLP-1 analogues. In people with type 2 diabetes, a wider array of GLP-1 analogues is available, including once-weekly preparations to aid compliance.

Improvements in risk factors such as blood pressure, lipid profile and hyperglycaemia after weight loss are important criteria in the determination of whether to continue therapy.

Tirzepatide, a novel GLP-1 and GIP (glucose-dependent insulinotropic polypeptide) receptor agonist (administered once-weekly subcutaneously) may be more effective than GLP-1 receptor agonists in achieving weight loss.

Bariatric surgery

Indication

In the UK, bariatric surgery is a treatment option for people with a BMI of 40 kg/m^2 (with or without obesity-related co-morbidities) or a BMI ≥35 kg/m^2 in the presence of obesity-related co-morbidities (e.g. hypertension, diabetes mellitus, dyslipidaemia, sleep apnoea). Growing emphasis is placed on the importance of offering bariatric surgery based on the presence of obesity-related co-morbidity as BMI alone is a poor indicator of the metabolic burden of disease in an individual patient. When considering patients for bariatric surgery, in addition to BMI, clinicians should focus on the presence of co-morbidity which may improve or resolve with surgery. Weight loss surgery should only be performed in the context of a multidisciplinary programme, with extensive expertise in bariatric surgery.

Contraindications

Contraindications to bariatric surgery include patients with active untreated mental illness, e.g. major depression or psychosis, the presence of an eating disorder, e.g. binge-eating disorder, misuse of drugs or alcohol, severe coagulopathy, severe cardiac disease with an excessive anaesthetic risk or inability to comply with lifelong postsurgical lifestyle changes, e.g. food portions, daily vitamin supplements. Bariatric surgery in those above 65 or under 18 is controversial.

Outcomes

All bariatric procedures are effective in achieving significant and sustained weight loss and improving obesity-related co-morbidities. The mean overall percentage of body weight loss from baseline is about 20%, varying according to the specific bariatric procedure performed. Weight loss is maximal after 1–2 years with regain in all surgical groups in subsequent years (Table 33.1). After 8–10 years, weight regain stabilises.

Diabetes remission has been reported to be as high as 85–90% of cases in the months after surgery but is

Table 33.1 Mean% weight changes (SD) from baseline observed in the Swedish Obese Subjects trial (control +/–3%)

	Maximum% weight loss (SD)		
	After 1–2yrs	After 10yrs	After 15yrs
Control	*n* = 2037	*n* = 1267	*n* = 556
Gastric bypass	32 (8) *n* = 265	25 (11) *n* = 180	27 (12) *n* = 37
Gastric banding	20 (10) *n* = 376	14 (14) *n* = 284	13 (14) *n* = 150
Vertebral banded gastroplasty	25 (9) *n* = 1369	16 (11) *n* = 1007	18 (11) *n* = 489

highly dependent on duration of diabetes, with those having diabetes for more than 10 years less likely to have postoperative remission. However, a high (50%) relapse rate in postbariatric surgical diabetes remission has also been noted after 10 years. Bariatric procedures have also been shown to improve hyperlipidaemia (in approximately 75%), hypertension (in around 75–80%) and obstructive sleep apnoea (in around 85%). The reduction in comorbidities appears to translate into a reduction in all-cause mortality. The Swedish Obese Subjects (SOS) trial showed that bariatric surgery for severe obesity is associated with long-term weight loss and decreased overall mortality.

Surgical procedures

Surgical therapies are based on two mechanisms: (i) *restrictive procedures* which result in a restriction of caloric intake via a small stomach reservoir and (ii) *malabsorptive procedures* which lead to a malabsorption of nutrients via a shortened functional small bowel length. Mixed restrictive and malabsorptive procedures also exist.

- Sleeve gastrectomy (SG) is now the most widely performed bariatric procedure worldwide (Figure 33.1). It reliably produces weight loss and diabetes remission rates which appear to be similar to that of Roux en Y gastric bypass (RYGB). Weight loss appears to be mediated through changes in incretin hormones, GLP-1 and PYY as well as ghrelin. Alterations in bile acid homeostasis may also play a role in long-term weight loss and glucose regulation following SG. There are concerns about its suitability for some patient groups, particularly those with gastro-oesophageal reflux, as it has been demonstrated to produce a worsening of symptoms or even *de novo* reflux in those not previously affected. This may have long-term implications with regard to the development of Barrett metaplasia, and routine surveillance endoscopy is advised at 1 year postoperatively and then every 2–3 years thereafter.
- RYGB is one of the most commonly performed bariatric procedures, with long-term data supporting its efficacy and safety (Figure 33.2). It is considered a more technically challenging procedure than SG due to the need to form two anastomoses but it may be more suitable in those who suffer from reflux. RYGB is also thought to act through changes in neurohormonal signalling, primarily through GLP-1 and PYY as well as altered bile acid metabolism. The most significant procedure-specific complication associated with RYGB is the possibility of internal herniation which may result in bowel ischaemia. Treatment of gallstone-related disease requiring endoscopic retrograde cholangiopancreatography (ERCP) may also be more challenging due to the alteration of anatomy and need to access the remnant stomach.
- One anastomosis gastric bypass (OAGB) is viewed as a modification of the RYGB as it also involves bypass of the proximal gut. Its popularity as a procedure has grown in recent years because it is technically less demanding than a RYGB while producing similar neurohormonal changes. Weight loss and remission of T2DM results are comparable

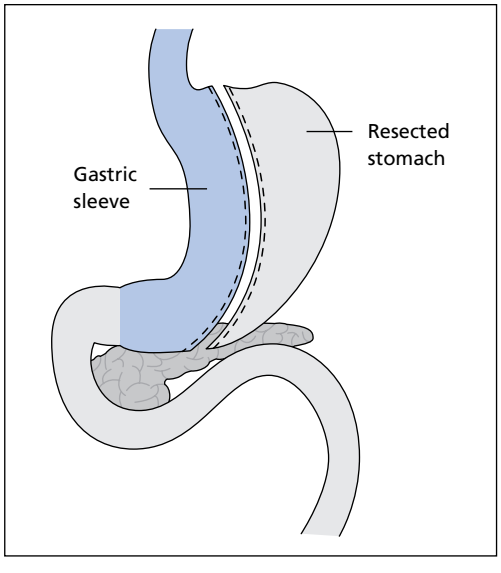

Figure 33.1 Vertical sleeve gastecrtomy.

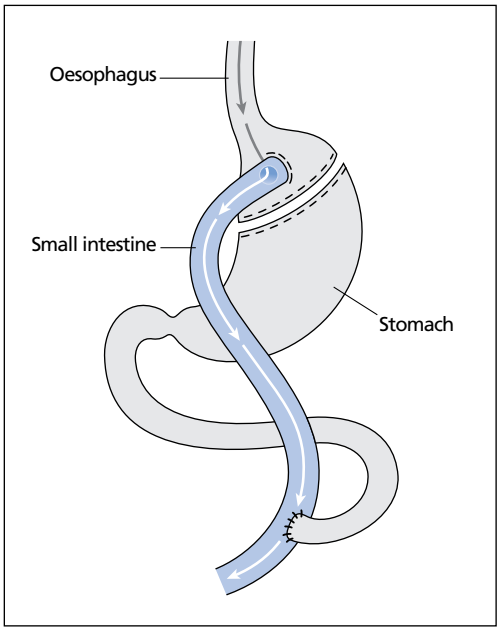

Figure 33.2 Roux-en-Y gastric bypass.

to RYGB but there are concerns about increased rates of postoperative nutritional deficiencies and complications such as steatorrhoea and diarrohea. As a result of the anatomical configuration of the anastomosis, studies have also indicated that a proportion of patients suffer from bile reflux and oesophagitis which may have implications for the development of dysplasia in the long term.

Biliopancreatic diversion and duodenal switch (BPD/DS) is infrequently performed despite resulting in up to 40% total weight loss and up to 95% remission of T2DM. It presents a considerable technical challenge and also significant postoperative risk. Although all patients following bariatric surgery are required to adhere to life-long nutritional supplementation, BPD/DS may result in severe vitamin deficiencies which in a small minority of cases are refractory to treatment, necessitating a reversal of the procedure to avoid significant complications such as Wernicke encephalopathy, peripheral neuropathy or night blindness.

Complications

The safety profile of bariatric surgery has dramatically improved with refinements of techniques and the near universal adoption of the laparoscopic approach, bringing it in line with procedures such as laparoscopic cholecystectomy and hysterectomy with regard to morbidity and mortality. Early complications are typically managed by the surgical team and include bleeding, staple line leak, bowel perforation and obstruction, and wound infections. The most common cause of mortality following bariatric surgery is venous thromboembolism. Other complications include myocardial infarction, pneumonia, and urinary tract infection. The overall 30-day postoperative mortality is 0.1% for restrictive procedures, 0.5% for gastric bypass and 1.1% for biliopancreatic diversion or duodenal switch.

After bariatric surgery, patients experience changes in medical co-morbidities and eating, and significant psychological changes.

Prolonged vomiting may be due to food intolerances, overeating, or the development of stomal stenosis, marginal ulcers in gastric bypass patients, overtightening of the band, internal hernias, or subacute bowel obstruction and requires urgent investigation. Dumping syndrome causing clinically recognised hypoglycaemia occurs in less than 10% of patients after RYGB and is characterised by symptoms of nausea, shaking, sweating, and diarrhoea immediately after eating foods containing high quantities of carbohydrate. Patients should be advised to avoid foods that provoke symptoms.

Female patients must be advised to avoid pregnancy for 12–18 months after surgical weight loss procedures.

Postoperative diet and vitamin/mineral supplements

Following bariatric surgery, all patients require dietary supplementation due to the risk of nutritional deficiencies although the specific needs will be in part determined by the procedure. Specific follow-up regimes are highly variable although most would recommend monitoring calcium, vitamins A, E, K, B12 and D, thiamine, selenium, zinc, copper and iron which are then replaced when identified. Generally, all patients will be advised to take a complete daily multivitamin which contains adequate levels of many of the above vitamins/minerals and specific supplementation can be guided by individual results.

Follow-up and monitoring

Patients should be reviewed regularly until rapid weight loss decreases (e.g. on postoperative day 10, and at 3, 6 and 12 months) followed by annual specialist clinical assessment for a minimum of 2 years; further follow-up may be assumed by their local GP.

More frequent monitoring may be needed if postoperative problems or complications develop.

At each visit in the first 6 months, the following should be undertaken.

- Review of protein and food intake and patterns of eating, and individuals should be assessed for the development of psychological or eating disorders.
- Blood pressure and weight measurement.
- Full blood count, urea, creatinine, and electrolytes, liver function tests, glucose, albumin, and serum measurement. Serum magnesium, phosphate, vitamin B12, and iron studies in patients who are losing more than 9 kg (20 lb) per month.
- Medications for hypertension and diabetes frequently need to be reduced or stopped, often as inpatients prior to discharge after surgery.
- Pregnancy testing in women of child-bearing potential with cessation of menses.
- Physical activity advice and support.
- Psychological support and access to professional or peer support groups.

Serum full blood count, electrolytes, albumin, calcium, iron studies, vitamin B12, folate, and 25-hydroxyvitamin D should be measured at each annual review.

KEY POINTS

- Peripheral signals such as gut peptides, nutrients, and leptin from adipose tissue signal to the hypothalamus and the brainstem via the circulation and vagal afferents. This information is integrated, and appropriate cognitive and metabolic responses are initiated to control food intake and metabolism.
- The WHO has defined obesity as a BMI of 30 kg/m^2 or more. Individuals with a BMI between 25 and 29.9 kg/m^2 are 'overweight'.
- Obesity is associated with significant morbidity and mortality.
- Many factors contribute to the development of obesity, including lifestyle and social factors, dietary habits, genetic factors, drugs, and rarely neuroendocrine disorders.
- The clinical evaluation of obese patients should include measurement of BMI, waist circumference, blood pressure, renal function, lipid profile, and fasting blood glucose and HbA1c.
- The treatment of obesity includes counselling on diet, lifestyle and exercise, pharmacological therapy, and bariatric surgery.

34

Diabetes mellitus: classification, pathogenesis, and diagnosis

Insulin

Insulin is a 51-amino acid peptide hormone synthesised and secreted by *beta* (β) *cells* in the pancreatic *islets of Langerhans*.

Proinsulin is the prohormone precursor to insulin. Cleavage of an internal fragment from proinsulin generates *C-peptide* and mature *insulin*, consisting of the A chain and B chain connected by disulfide bonds (Figure 34.1). Thus C-peptide and insulin are secreted in a 1:1 equimolar ratio; however, the half-life of insulin (~5 minutes) is much shorter than that of C-peptide (~30 minutes), making C-peptide a useful surrogate for insulin secretion.

In addition to beta cells, the pancreatic islets also contain alpha cells (located at the periphery of the islets) secreting glucagon, and delta cells secreting somatostatin.

Postprandially, a glucose load elicits a rise in insulin and a fall in glucagon.

Insulin release

The key regulator of insulin release is glucose. However, amino acids, gastrointestinal peptides (e.g. glucagon-like peptide 1), and neurotransmitters also influence insulin secretion. Glucose is transported into pancreatic beta cells by the GLUT2 transporter. Glucose is phosphorylated to glucose-6-phosphate by the enzyme *glucokinase*. Further metabolism of glucose-6-phosphate generates adenosine triphosphate (ATP), which inhibits the activity of an ATP-sensitive potassium channel. This results in depolarisation of the beta cell membrane, opening of voltage-gated calcium channels and insulin release.

Mechanism of action of insulin

Binding of insulin to its receptor on the cell membrane of the target cells results in autophosphorylation of the receptor via the receptor's intrinsic tyrosine kinase activity. The phosphorylated receptor in turn phosphorylates the insulin receptor substrates 1 and 2.

The activated insulin receptor substrates bind to a number of docking proteins via PI3K and Akt, which in turn bind to other cellular proteins to initiate a cascade of phosphorylation and dephosphorylation reactions resulting in the transcription of insulin-regulated genes.

Insulin receptor-mediated activation of the mitogen-activated protein kinase pathway has been implicated in insulin's effects on growth (see below).

Metabolic effects of insulin

Insulin lowers blood glucose levels by:

- *inhibition of gluconeogenesis* in the liver and kidney, directly and indirectly via a decreased availability of gluconeogenic precursors: free fatty acids and amino acids. Insulin inhibits the lipolysis of stored triglycerides by inhibiting hormone-sensitive lipase and increases triglyceride storage.

Endocrinology and Diabetes: Lecture Notes, Second Edition. Amir H. Sam, Karim Meeran and Neil Hill.
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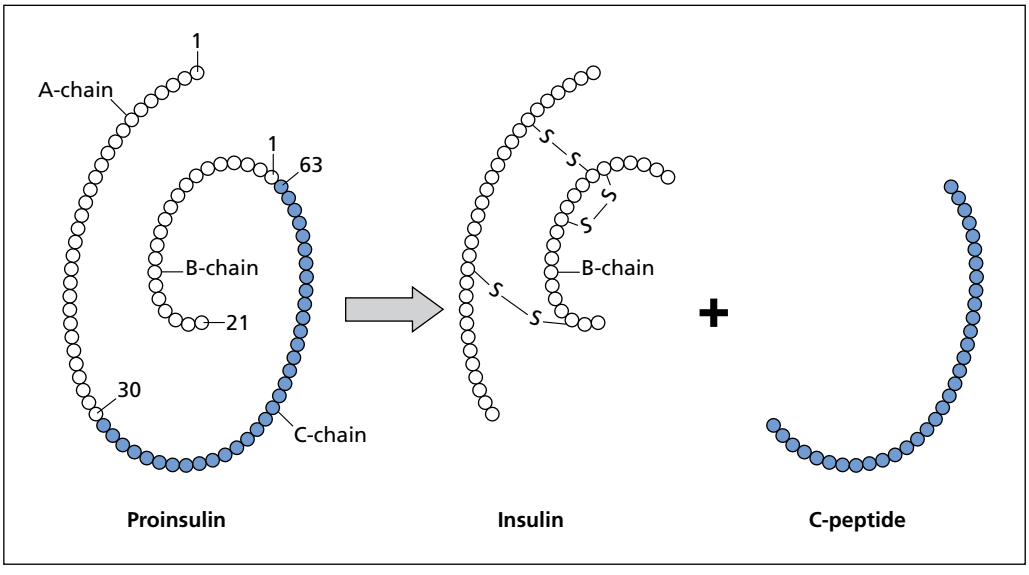

Figure 34.1 Proinsulin, insulin, and C-peptide.

Insulin also inhibits protein breakdown and increases protein synthesis

- *inhibition of glycogenolysis* via inhibition of glycogen phosphorylase and stimulation of glycogen synthase
- *increased glucose uptake* into adipocytes and skeletal muscle cells by activation of phosphoinositide 3 kinase and translocation of the glucose transporter GLUT4 from the cytoplasm to the cell membrane
- *increased glycolysis* (glucose breakdown) in adipocytes and skeletal muscle cells by increasing the activity of hexokinase and 6-phosphofructokinase.

Insulin also has paracrine effects on the neighbouring islet cells. Insulin reduces glucagon secretion by the alpha cells. This in turn increases the metabolic effects of insulin since glucagon normally stimulates glycogenolysis and gluconeogenesis by the liver and kidney.

Other actions of insulin

In addition to its metabolic effects, insulin can also affect steroidogenesis, vascular function, fibrinolysis, growth regulation, and cancer (e.g. colorectal, ovarian, breast cancer). The latter effect may be mediated through both anabolic effects on protein and lipid metabolism, and interactions with other mediators of growth, e.g. insulin-like growth factors 1 and 2 and their receptors. Insulin resistance and hyperinsulinaemia (e.g. in polycystic ovary syndrome) may increase ovarian androgen secretion by stimulating luteinising hormone release or increasing ovarian luteinising hormone receptors.

Diabetes mellitus

Diabetes mellitus comprises a group of common metabolic disorders that share the phenotype of *hyperglycaemia* (see 'Diagnosis of diabetes mellitus', below). Type 2 diabetes is a huge cause of morbidity and mortality. The number of cases worldwide quadrupled between 1980 and 2014 and it is anticipated that 472 million people will have type 2 diabetes by 2030. Diabetes reduces life expectancy by 5–10 years and is the most common cause of blindness in adults of working age.

Presentation

People with diabetes may present with:

- fatigue
- polyuria, polydipsia and nocturia
- recent weight loss (less frequently in type 2 than in type 1 diabetes)
- diabetic ketoacidosis or hyperosmolar hyperglycaemic state (see Chapter 36)

- microvascular complications (retinopathy, nephropathy, neuropathy)
- macrovascular complications (ischaemic heart disease, stroke, peripheral vascular disease)
- recurrent infections.

Many people with type 2 diabetes are asymptomatic at presentation and are identified by screening.

Classification and pathogenesis of diabetes mellitus

Type 1 diabetes

Type 1 diabetes mellitus is caused by destruction of the pancreatic insulin-producing beta cells, resulting in absolute insulin deficiency. The beta cell destruction is caused by an autoimmune process in 90% of people with type 1 diabetes. This process progresses over a latent period (many months or years) during which the individual is asymptomatic and euglycaemic. This reflects the large number of functioning beta cells that must be lost before hyperglycaemia occurs.

A number of pancreatic beta cell autoantigens may play a role in the initiation or progression of autoimmune islet injury. These include glutamic acid decarboxylase (GAD), islet cell antibodies (ICA), and insulin and insulinoma-associated protein (IA-2). The cation efflux zinc transporter (ZnT8) is another type 1 diabetes autoantigen. However, it is not clear which of these autoantigens is involved in the initiation of the injury, and which is released only after the injury. At presentation of type 1 diabetes, 80–85% people will be positive for one or more of the aforementioned autoantibodies.

Type 1 diabetes is likely to occur in genetically susceptible subjects and is probably triggered by environmental agents.

Polymorphisms of a number of genes may influence the risk of type 1 diabetes. These include the gene encoding preproinsulin and a number of genes related to immune system function, such as those for HLA-DQ alpha, HLA-DQ beta, and HLA-DR (encoding class II major histocompatibility complex molecules, which present antigens to T lymphocytes), PTPN22 (lymphoid protein tyrosine phosphatase, a suppressor of T-cell activation), and cytotoxic T lymphocyte antigen (CTLA-4).

Several environmental factors have been suggested to trigger the autoimmune process in type 1 diabetes. However, none has been conclusively linked to diabetes. Factors include pregnancy-related and perinatal influences, viruses (e.g. coxsackie, rubella), and dietary factors (e.g. bovine milk proteins, cereals, and omega-3 fatty acids).

Type 2 diabetes

Type 2 diabetes is characterised by increased *peripheral resistance to insulin* action, *impaired insulin secretion*, and increased hepatic glucose output. Both genetic and environmental factors contribute to the development of insulin resistance and relative insulin deficiency in type 2 diabetes. The major risk factor for type 2 diabetes is obesity; 80% people with type 2 diabetes are obese.

A genetic influence on the development of type 2 diabetes is supported by the following observations.

- Monozygotic twins have a 90% concordance rate.
- Forty percent of people with type 2 diabetes have at least one parent with type 2 diabetes.
- The lifetime risk for a first-degree relative of a patient with type 2 diabetes is 5–10 times higher than for those without a family history of diabetes.

Monogenic causes of type 2 diabetes represent a very small fraction of cases (Box 34.1). It is likely that multiple genetic anomalies at different loci confer varying degrees of predisposition to type 2 diabetes. Several inherited polymorphisms have been

Box 34.1 Causes of diabetes mellitus

Type 1 diabetes

Type 2 diabetes

Genetic defects of beta cell function

MODY 1: mutations in hepatocyte nuclear transcription factor 4-alpha
MODY 2: mutations in glucokinase
MODY 3: mutations in hepatocyte nuclear transcription factor 1-alpha
MODY 4: mutations in insulin promoter factor 1
MODY 5: mutations in hepatocyte nuclear transcription factor 1-beta
MODY 6: mutations in neurogenic differentiation 1 (NeuroD1)
Mutations in mitochondrial DNA (maternally transmitted) – maternally inherited diabetes and deafness (MIDD) and mitochondrial encephalomyopathy, lactic acidosis, stroke-like episodes (MELAS) are the most common

Genetic defects in insulin action resulting in insulin resistance

Type A insulin resistance: caused by insulin receptor mutations in some, but by an unknown signalling defect in most
Donohue syndrome (leprechaunism): caused by insulin receptor mutations; associated with intrauterine growth retardation and dysmorphic features, e.g. protuberant and low-set ears, flaring nostrils, and thick lips. Death occurs in childhood
Rabson–Mendenhall syndrome (caused by insulin receptor mutations; associated with coarse and senile-appearing facies, premature and abnormal dentition, abdominal distension, enlarged genitalia, and a hypertrophic pineal gland)
Lipodystrophic syndromes: congenital or acquired disorders characterised by a complete or partial lack of adipose tissue (lipoatrophy)

Pancreatic diseases

Chronic pancreatitis
Cystic fibrosis
Hereditary haemochromatosis
Pancreatic cancer
Fibrocalculous pancreatopathy
Surgical removal of the pancreas

Endocrinopathies (excess secretion of hormones that antagonise the metabolic effects of insulin)

Cushing' syndrome (excess cortisol)
Acromegaly (excess growth hormone)
Phaeochromocytoma (excess catecholamines)
Glucagonoma (excess glucagon)
Somatostatinoma (excess somatostatin)

Drug-induced diabetes

Glucocorticoids, atypical antipsychotic agents, protease inhibitors, beta-blockers, thiazide diuretics, ciclosporin, nicotinic acid

Infections

Congenital rubella, coxsackie virus, cytomegalovirus

Gestational diabetes

Uncommon forms of immune-mediated diabetes

Stiff man syndrome (associated with muscle stiffness and anti-GAD antibodies)
Insulin receptor autoantibodies

Genetic syndromes associated with diabetes

Down syndrome, Klinefelter syndrome, Turner syndrome, Wolfram syndrome, Prader–Willi syndrome, Lawrence–Moon–Biedl syndrome, Huntington chorea, Friedreich ataxia, myotonic dystrophy, porphyria

MODY, maturity-onset diabetes of the young

identified which individually contribute only small degrees of risk for diabetes (see below).

The gene for the protease calpain 10 may confer major susceptibility to type 2 diabetes in Mexican-American individuals.

Insulin resistance

Obesity causes resistance to insulin-mediated glucose uptake and may also decrease the sensitivity of the beta cells to glucose. Centripetal obesity (visceral adiposity) has a much greater association with insulin resistance than subcutaneous fat distribution. The mechanism by which obesity induces insulin resistance is poorly understood. The c-Jun amino-terminal kinase (JNK) pathway may be an important mediator of the relationship between obesity and insulin resistance as JNK activity is increased by fatty acids and inflammatory cytokines, interfering with insulin action through serine phosphorylation of the insulin receptor substrate.

Plasma *free fatty acid* concentrations are high in obese people. A high plasma free fatty acid concentration can also impair insulin-stimulated glucose uptake in skeletal muscle.

Insulin resistance may, at least in part, be related to *adipokines,* including leptin, adiponectin, tumour necrosis factor (TNF)-alpha and resistin, secreted by adipocytes. Leptin deficiency and leptin resistance are associated with obesity and insulin resistance. Adiponectin deficiency may contribute to the development of insulin resistance and subsequent type 2 diabetes. Increased release of TNF-alpha from adipocytes may also play a role in the impairment of insulin action.

Polymorphisms in the gene for peroxisome proliferator-activated receptor (PPAR) gamma-2, a transcription factor that has a key role in adipocyte differentiation, may contribute to the variability in insulin sensitivity in the general population.

Impaired insulin secretion

The reasons for the decline in insulin secretory capacity in type 2 diabetes are not clear. Chronic hyperglycaemia can have a toxic effect on beta cells

(*glucotoxicity*). An elevation of free fatty acid levels may also worsen pancreatic beta cell function (*lipotoxicity*).

Animal models have suggested that GLUT2 (a beta cell glucose transporter) and Abca1 (ATP-binding cassette transporter, a cellular cholesterol transporter) may play a role in impaired insulin secretion and the development of type 2 diabetes. There is evidence that processing of proinsulin to insulin in the beta cells may be impaired in type 2 diabetes, potentially mediated by proinflammatory cytokines (e.g. interleukin [IL]-1).

Islet amyloid polypeptide (amylin) is stored in insulin secretory granules in the pancreatic beta cells. Many people with type 2 diabetes have increased amounts of amylin in their pancreas. However, it is not clear whether this has a causative role or is a consequence of the defect in insulin secretion.

Single nucleotide polymorphisms in the gene for TCF7L2 (transcription factor 7-like 2) significantly increase the risk of type 2 diabetes. This variant genotype is associated with decreased insulin secretion from beta cells in response to glucose. Other genes purported to be related to the development of type 2 diabetes include SLC30A8, zinc transporter in islets; HHEX, transcriptional repressor involved in pancreas development; CDKAL1, cyclin-dependent kinase inhibitor involved in insulin secretion; KCNJ11, potassium channel in beta cells.

Monogenic diabetes

Monogenic diabetes, also known as maturity-onset diabetes of the young (MODY), is a rare cause of type 2 diabetes resulting from mutations transmitted in an autosomal dominant manner. These mutations occur in 1–4% people with diabetes. Typically, monogenic diabetes is diagnosed in people aged 10–45 years; there is usually no autoimmune history (frequently seen in type 1 diabetes) or clinical evidence of insulin resistance (obesity, acanthosis nigricans). Monogenic diabetes is due to one of *GCK*, *HNF1A*, *HNF4A* or *HNF4B* genes in 80–90% of cases. MODY type 1, MODY type 2 and MODY 5 are due to mutations in the genes encoding hepatocyte nuclear transcription factors 4-alpha, 1-alpha, and 1-beta, respectively. The mechanism by which these mutations result in diabetes is not well understood. In addition to liver, these transcription factors are also expressed in other tissues such as kidney. As a result, people may also have renal cysts and renal absorption abnormalities.

We now present a summary of MODY types.

MODY type 1

Due to *HNF4A* mutations. *HNF4A* is a transcription factor 'master regulator of genes' expressed in the liver, kidney, intestine, and islets.

- Uncommon (5–10% in UK).
- Inherited from mother or father.
- Fifty percent of babies with *HNF4A* are macrosomic and may have neonatal hyperinsulinaemic hypoglycaemia.
- Presents from childhood onwards and is progressive so lifestyle important.
- Sensitive to sulfonylureas (e.g. glibenclamide) but may also need insulin.

MODY type 2

Due to glucokinase gene mutations. Glucokinase phosphorylates glucose to glucose-6-phosphate and acts as the glucose sensor within the pancreatic beta cells. As a result, higher glucose levels are required to elicit insulin secretory responses in people with MODY 2.

- Most common MODY in children (30% total).
- There is a higher set point for blood glucose.
- Onset is at birth.
- Stable over time.
- Oral glucose tolerance test – fasting glucose high (5.5–8.0 mmol/L); 2-hour glucose normal.
- Complications are rare.
- HbA_{1c} is rarely >53–59 mmol/mol.
- No pharmacological treatment is needed as these do not improve HbA_{1c}.
- May need insulin in pregnancy if there is fetal macrosomia on scanning.

MODY type 3

Due to *HNF1A* mutations.

- Most common MODY (~50% in UK adults).
- Onset young child/teens.
- Progressive hyperglycaemia.
- Complications resulting from hyperglycaemia may occur (as with types 1 and 2 diabetes).
- Oral glucose tolerance test – high fasting and 2-hour plasma glucose.
- Highly sensitive to sulfonylureas (may get hypoglycaemia on standard doses).
- It may be possible to withdraw insulin even after years (under expert supervision) and maintain good control on sulfonylureas for many years.
- There is a lower renal threshold for glucose reabsorption (reduced SGLT2 expression in the proximal convoluted tubule), so glycosuria is used as a marker of unaffected mutation carriers in childhood.

MODY 4

Caused by mutations in the insulin promoter factor 1, a transcription factor that regulates pancreatic development and insulin gene transcription.

MODY 5, or renal cysts and diabetes (RCAD)

Due to *HNF1B* mutations. May result in minimal or end-stage renal disease; associated with exocrine pancreatic deficiency and genitourinary abnormalities. Limited penetrance so family history is not always positive. Early insulin is often required soon after diagnosis of diabetes.

MODY 6

Caused by mutations of the gene encoding the protein NeuroD1. NeuroD1 is a transcription factor that promotes transcription of the insulin gene as well as some genes involved in formation of beta cells and parts of the nervous system.

Maternally inherited diabetes and deafness (MIDD)

Causes sensorineural hearing loss and is associated with short stature, pigmentary retinopathy, myopathy, cardiac disease (heart failure and arrhythmia), and renal disease (FSGS). MIDD is due to a mitochondrial mutation (m.3243A>G) with 100% penetrance.

Treatment is initially with sulfonylureas but most need insulin within 2 years due to progressive loss of insulin secretion. Metformin is contraindicated due to the superimposed risk of lactic acidosis. MIDD affects muscle, liver and pancreas and thus may lead to a mixed type 1 or type 2 diabetes picture.

It may be associated with other mitochondrial syndromes, e.g. MELAS.

Other causes of diabetes

Other rare causes of diabetes mellitus are listed in Box 34.1. Gestational diabetes is discussed in Chapter 31.

Syndromes of insulin resistance

Several rare syndromes of severe insulin resistance have been identified, many of which are associated with mutations of the insulin receptor gene (Box 34.1). These syndromes are characterised by hyperinsulinaemia and sometimes other abnormalities, such as acanthosis nigricans and signs of hyperandrogenism (hirsutism, acne, and oligomenorrhoea in women). Impaired glucose tolerance or overt diabetes occurs if compensatory increases in insulin secretion are inadequate.

Epidemiology of diabetes mellitus

Type 2 diabetes accounts for over 80% of cases of diabetes in Europe and North America. Type 1 diabetes is responsible for another 5–10%, with the remainder being due to other causes (Box 34.1). The prevalence of both type 1 and type 2 diabetes is increasing worldwide.

Type 1 diabetes mellitus

Type 1 diabetes is one of the most common chronic diseases in childhood, with a prevalence of 0.25% in the UK. There is considerable geographical variation in the incidence of type 1 diabetes. For example, the incidence in Scandinavia (35 per 100 000 per year in Finland) is much higher than that in the Pacific Rim (2 per 100 000 per year in Japan and China). The United States and northern Europe have an intermediate incidence (8–17 per 100 000 per year).

Type 2 diabetes mellitus

The prevalence of type 2 diabetes in the UK is 5–10%. The prevalence of type 2 diabetes varies remarkably between ethnic groups living in the same environment. People of Asian, African and Hispanic descent are at greater risk of developing type 2 diabetes. The incidence has increased dramatically over the last 20 years. The rise in type 2 diabetes has occurred in parallel with an increasing prevalence of obesity worldwide.

Diagnosis of diabetes mellitus

A person is diagnosed with diabetes mellitus if he or she has one or more of the following criteria:

- symptoms of diabetes and a random plasma glucose ≥11.1 mmol/L
- fasting plasma glucose ≥7.0 mmol/L (after an overnight fast of at least 8 hours)
- 2-hour plasma glucose levels ≥11.1 mmol/L after a 75 g oral glucose tolerance test

- an HbA_{1c} ≥48 mmol/mol[1] (a value of less than 48 mmol/mol does not exclude diabetes diagnosed using glucose tests).

In the absence of unequivocal hyperglycaemia and acute metabolic decompensation, these criteria should be confirmed by repeat testing on another day.

Prediabetes

Prediabetes can be diagnosed based upon a fasting blood glucose test or an oral glucose tolerance test.

- *Impaired fasting glucose* is defined as a fasting plasma glucose between 6.1 and 6.9 mmol/L.
- *Impaired glucose tolerance* is defined as a plasma glucose level of 7.8–11.0 mmol/L measured 2 hours after a 75 g oral glucose tolerance test.

Individuals with impaired fasting glucose or impaired glucose tolerance are at considerable risk for developing type 2 diabetes (40% risk over the next 5 years). Impaired glucose tolerance is very common and affects about 11% of people between the ages of 20 and 74 years.

Distinguishing type 1 and 2 diabetes mellitus

The need for insulin treatment does not distinguish between type 1 and type 2 diabetes as many people with type 2 diabetes also require insulin for glucose control. People with type 1 diabetes are more likely to have the following features:

- people at high risk who are acutely ill (e.g. those requiring hospital admission)
- people taking medication that may cause rapid glucose rise, e.g. steroids, antipsychotics
- people with acute pancreatic damage, including pancreatic surgery
- in pregnancy
- in the presence of genetic, haematological and illness-related factors that influence HbA_{1c} and its measurement.
- age of onset ≤30 years
- body mass index <25 kg/m^2
- acute symptoms
- a personal or family history of autoimmune disease.

However, none of these criteria is absolute and specific for type 1 diabetes. Autoimmune-mediated destruction of the beta cells can occur at any age. It is estimated that 5–10% of those who develop diabetes after age 30 have type 1 diabetes, known as *latent autoimmune diabetes in adults* (LADA; see below). Furthermore, type 2 diabetes may occur in overweight children and adolescents.

Although an acute presentation with diabetic ketoacidosis is a typical feature of type 1 diabetes, it can also occur in type 2 diabetes in certain circumstances, such as severe infection or other illnesses. People with *ketosis-prone type 2 diabetes* present with diabetic ketoacidosis as their first manifestation of type 2 diabetes. These people are usually obese and typically of African, Hispanic, or Caribbean descent. The mean age for diagnosis is 40 years. The cause of the ketoacidosis in these cases is unknown but may relate to toxic effects of hyperglycaemia on pancreatic insulin secretion. These people are initially treated with insulin. However, 50–70% achieve diabetic remission 3 months after presentation. Hyperglycaemia often relapses by 2 years.

When it is difficult to distinguish between type 1 and type 2 diabetes, testing for *ICA* and *anti-GAD* antibodies may be helpful in establishing the diagnosis of autoimmune type 1 diabetes. Genetic tests to exclude the diagnosis of MODY are also useful if the diagnosis is in doubt.

If type 1 diabetes is suspected on clinical grounds or if islet cell or GAD antibodies are positive, the patient should be presumed to have type 1 diabetes and treated with lifelong insulin replacement therapy. Insulin should also be started in any patient who is catabolic (i.e. presents with *weight loss* or *dehydration* in the setting of hyperglycaemia) or who has *increased ketogenesis* (ketonuria or ketoacidosis).

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[1] HbA_{1c} is not appropriate for diagnosis of diabetes in the following situations:

- all children and young people
- people of any age suspected of having type 1 diabetes
- people with symptoms of diabetes for less than 2 months.

People at high risk who are acutely ill (e.g. those requiring hospital admission)

People taking medication that may cause rapid glucose rise, e.g. steroids, antipsychotics

People with acute pancreatic damage, including pancreatic surgery

In pregnancy

In the presence of genetic, haematological and illness-related factors that influence HbA_{1c} and its measurement.

LADA is defined as adult-onset diabetes with circulating islet antibodies but not requiring insulin therapy initially. People with LADA have a high risk of progression to insulin dependency; some argue that LADA is a form of gradual-onset ('slow burning') type 1 diabetes.

KEY POINTS

- Insulin is a peptide hormone synthesised and secreted by the beta cells in the pancreatic islets of Langerhans.
- Insulin release is stimulated by a rise in plasma glucose. Insulin lowers postprandial blood glucose by an inhibition of gluconeogenesis and glycogenolysis, increased glucose uptake into adipocytes and skeletal muscle cells, and increased glycolysis.
- People with diabetes may present with fatigue, polyuria, polydipsia, weight loss, diabetic ketoacidosis, a hyperosmolar hyperglycaemic state, recurrent infections, and microvascular or macrovascular complications.
- Type 1 diabetes mellitus results from destruction of the pancreatic insulin-producing beta cells, usually due to an autoimmune process.
- Type 2 diabetes results from peripheral insulin resistance and impaired insulin secretion.
- Type 2 diabetes accounts for over 80% of cases of diabetes in Europe and North America. Type 1 diabetes is responsible for another 5–10%, with the remainder being due to other causes such as genetic mutations affecting beta cell function, pancreatic diseases, endocrinopathies, and drugs such as glucocorticoids.
- Diabetes mellitus can be diagnosed based on one or more of the following criteria:
  - symptoms of diabetes and a random plasma glucose ≥11.1 mmol/L
  - fasting plasma glucose ≥7.0 mmol/L (after an overnight fast of at least 8 hours)
  - 2-hour plasma glucose ≥11.1 mmol/L after a 75 g oral glucose tolerance test.

35

Treatment of diabetes mellitus

The treatment of a person with diabetes mellitus has four main components:

- education
- glycaemic control
- screening for and treatment of complications
- screening for and treatment of cardiovascular risk factors.

Education

Being diagnosed with diabetes can be an overwhelming experience, and people commonly have questions about why it has developed.

A good general approach is first to explore the person's understanding of diabetes. All newly diagnosed people should receive verbal and written information about their diagnosis, possible complications, the need for regular follow-up, treatment options and lifestyle adjustments. Women of reproductive age should be made aware of the importance of tight glycaemic control before and during pregnancy.

People with diabetes should be provided with resources for medical as well as psychological support, such as group classes, meetings with a *diabetes educator* and dietitian and other educational resources such as books, charities (e.g. Diabetes UK), websites, or magazines.

It must be emphasised that people who have diabetes can lead active lives and enjoy the foods and activities that they previously enjoyed.

Glycaemic control in type 1 diabetes

All people with type 1 diabetes must be treated with *insulin*. *Diet* and *exercise* are important components of non-pharmacological therapy in people with type 1 diabetes.

The Diabetes Control and Complications Trial (DCCT) showed that intensive insulin therapy to achieve lower levels of glycaemia reduces the risk of microvascular complications (retinopathy, nephropathy, neuropathy). Intensive insulin therapy also decreased fatal and non-fatal cardiovascular events in the Epidemiology of Diabetes Interventions and Complications (EDIC) follow-up study to the DCCT.

Glycated haemoglobin and the goal of glycaemic control

Glycated haemoglobin (HbA_{1c}) is formed in a non-enzymatic pathway by irreversible attachment of glucose to haemoglobin. HbA_{1c} correlates with mean blood glucose over the previous 8–12 weeks (Box 35.1).

HbA_{1c} values are influenced by red cell survival. The values may be falsely high when red cell turnover is low (e.g. in iron, vitamin B12 or folate deficiency). On the other hand, values may be falsely low when red cell turnover is rapid (e.g. in sickle cell disease, haemolytic anaemia or acute blood loss). Fructosamine (glycated albumin) may

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Box 35.1 HbA_{1c} values

HbA_{1c} (mmol/mol)	HbA_{1c} (%)	Estimated average blood glucose (mmol/L)
42	6.0	7.0
48	6.5	7.7
53	7.0	8.5
64	8.0	10.1
75	9.0	11.7
86	10.0	13.3
97	11.0	14.9

be used to estimate glycaemic control in these circumstances, although it is not always widely available in clinical practice. The turnover of serum albumin is about 28 days, and therefore serum fructosamine values reflect mean blood glucose values over the previous 1–2 weeks. Fructosamine values may be falsely low when albumin turnover is rapid (e.g. in protein-losing enteropathy or nephrotic syndrome).

The goal of glycaemic control is to achieve normal or near-normal glycaemia with an HbA_{1c} under 48 mmol/mol (6.5%). However, the benefits of intensive insulin therapy have to be weighed against the risk of severe hypoglycaemia associated with intensive therapy for each person. Less stringent, individualised goals may be appropriate for older or frail people and those with a history of severe hypoglycaemia, limited life expectancies or co-morbid conditions.

HbA_{1c} should be obtained at least twice yearly in people who are meeting glycaemic goals, and every 2 months in people who are not meeting glycaemic goals and in those whose treatment has changed.

Insulin types

The first successful insulin preparations came from cow and pig pancreata (bovine and porcine insulin). These were effective but could cause allergic reactions in some people. This problem has been minimised with the advent of synthetic human insulin manufactured using recombinant DNA technology. Bovine insulin is no longer available in the UK although porcine insulin can still be obtained.

Soluble (regular) insulin is a short-acting form of insulin and should be injected 30 minutes before meals.

In *rapid-acting insulin analogues* (*lispro*, *aspart*, *glulisine*), the normal amino acid sequence has been altered to reduce the tendency of the insulin to form hexamers by self-association. This keeps the insulin in dimeric and monomeric forms, which results in faster absorption, more rapid onset, and a shorter duration of action. Rapid-acting insulin analogues can be injected shortly before a meal. Hypoglycaemia occurs less frequently with rapid-acting insulin analogues than with soluble insulin. An ultra fast-acting insulin aspart, Fiasp®, has recently been introduced.

Isophane insulin is an *intermediate-acting* insulin formed by the addition of protamine to soluble insulin. It is also known as neutral protamine Hagedorn (NPH), as Hans Christian Hagedorn discovered that the effects of insulin could be prolonged by the addition of protamine (Table 35.1).

Of the *long-acting insulin analogues*, glargine is kept in hexamer form for a longer period due to alterations in its amino acid sequence. This results in a slower onset and longer duration of action. *Detemir* has a fatty acyl side chain that binds to albumin subcutaneously and in plasma. This delays dissociation and the release of the insulin into the circulation. Insulin degludec is an ultra long-acting basal insulin analogue. Degludec is conjugated to hexadecanedioic acid and may decrease the frequency of nocturnal and severe hypoglycaemia compared to glargine. Degludec is available in standard concentrations (100 units/mL) and concentrated (200 units/mL) which may be beneficial for people requiring large doses of insulin. A concentrated form of glargine, Toujeo® (300 units/mL), is also available.

Table 35.1 summarises the pharmacokinetics of most commonly used insulin preparations.

Insulin regimens

Intensive therapy involves the administration of a *basal* level of long-acting insulin (isophane, glargine,

Table 35.1 Types of insulin

	Onset of action	Time to peak effect	Duration of action
Lispro, aspart, glulisine	5–15 min	45–75 min	2–4 h
Soluble	~30 min	2–4 h	5–8 h
Isophane	~2 h	6–10 h	18–28 h
Glargine	~2 h	No peak	20 to >24 h
Detemir	~2 h	No peak	18–24 h

detemir) and premeal *boluses* of a rapid-acting insulin preparation (lispro, aspart, glulisine). The administration of a basal long-acting insulin and boluses of rapid acting insulin with meals is intended to mimic the normal insulin secretion profile of the pancreas. The basal insulin suppresses lipolysis (and thus ketogenesis) and hepatic glucose production. The boluses of insulin minimise the postprandial rise in blood glucose.

For intensive insulin regimens, people must be committed and be supported by an experienced diabetes team. The DAFNE (Dose Adjustment for Normal Eating) course teaches people with diabetes to calculate their carbohydrate intake and adjust their insulin doses accordingly.

The use of premixed insulins (see 'Insulin treatment in type 2 diabetes') is not recommended for people with type 1 diabetes. This is because intensive therapy in people with type 1 diabetes requires frequent adjustments of the premeal bolus of the rapid-acting insulin.

Basal insulin is delivered by daily or twice-daily injections of a long-acting insulin preparation, or by continuous subcutaneous infusion of a rapid-acting insulin preparation via a pump ('continuous subcutaneous insulin infusion'). Insulin detemir given twice daily is the preferred basal insulin for type 1 diabetes management as it is associated with lower HbA_{1c} with fewer episodes of hypoglycaemia. Glargine (once or twice daily) is also often used and detemir may be given once daily.

Insulin injection devices, technique and sites

Insulin is injected subcutaneously using single-use *syringes* with needles, *insulin pens* with needles, or an *insulin pump* (Figure 35.1).

Insulin pumps may be offered if attempts to achieve target HbA_{1c} levels with multiple daily injections (MDIs) result in the person experiencing disabling hypoglycaemia or HbA_{1c} levels remain high (≥69 mmol/mol) on MDI therapy despite a high level of care.

Insulin pens may be *prefilled* (disposable) or *reusable*. Prefilled pens are discarded when the insulin cartridge is spent. Reusable pens contain a replaceable insulin cartridge that is loaded into and removed from the pen by the patient.

Injection technique is the same with insulin syringes and with pens. People should learn the proper insulin injection technique from a diabetes specialist. An area of the body in which about 2.5 cm of subcutaneous fat can be pinched between two fingers should be used. The needle is inserted perpendicular to the pinched skin up to the hilt; 4 mm needles are standard. The needle is held in place for several seconds after insulin injection to avoid insulin leakage after withdrawal of the needle. People should be advised on the safe disposal of syringes and needles.

Potential sites for insulin injection are the upper arms, abdominal wall, upper legs and buttocks (Figure 35.2). The rate of insulin absorption varies according to injection site, individual characteristics and physical activity.

The long-acting insulin preparations are best injected into the leg or buttock (from which absorption is slow). The rapid-acting insulin preparations are best injected into the abdominal wall (from which insulin is absorbed more rapidly). The arm may not always be a suitable injection for people with less body fat as there is a greater chance of injecting into a muscle which could lead to hypoglycemia.

The injection sites must be rotated to avoid the risk of *lipohypertrophy* (Figure 35.3).

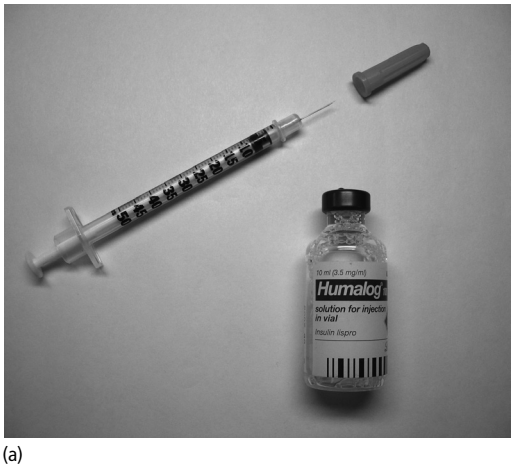
Insulin dose

Insulin requirement depends on a large number of variables including (but not limited to) body weight, age, pubertal stage, physical activity, phase of menstrual cycle in females, alcohol, ambient temperature, intercurrent illness and stress. Newly diagnosed children usually require an initial total daily insulin dose of 0.5–1.0 U/kg. Prepubertal children often require lower doses, and pubertal children may need higher doses. People in ketoacidosis and those receiving glucocorticoids also require higher doses. The basal insulin dose usually comprises about 50% of the total daily dose. The remaining 50% of insulin is given as rapid-acting insulin divided into three doses, administered before each meal. The boluses should be adjusted according to the carbohydrate content of the meals and the current blood glucose level.

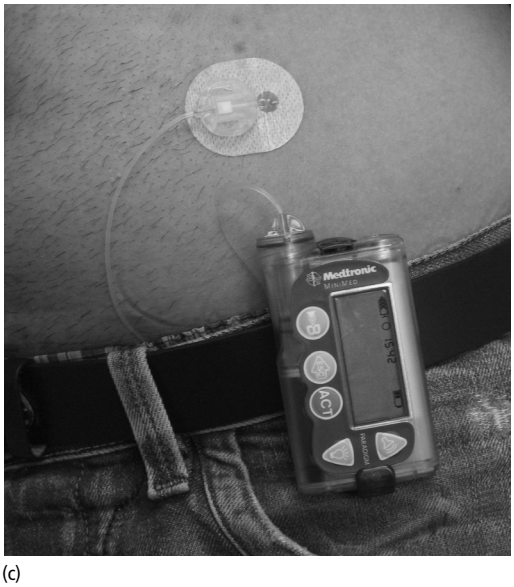
A period of decreasing insulin requirement may be seen a few weeks after the diagnosis and initiation of insulin. This 'honeymoon phase' is due to secretion of some endogenous insulin from the remaining functional beta cells and may last several months or occasionally years. Blood glucose must be closely monitored during this period. Hypoglycaemic episodes may occur if the insulin dose is not adjusted appropriately.

Side-effects

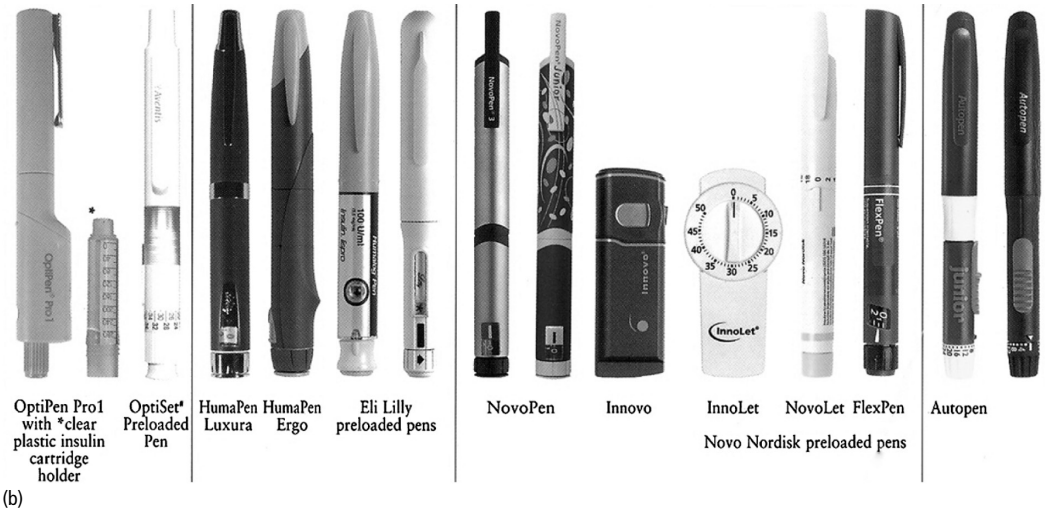
The main side-effects of intensive insulin therapy are *hypoglycaemia* and increased appetite, which may lead to weight gain and can affect compliance. People



(a)



(c)



(b)

Figure 35.1 (a) Insulin vial and syringe. (b) Insulin pens. (c) Insulin pump.

with diabetes and their families should be educated to prevent hypoglycaemic episodes and also to recognise and treat them. The treatment of hypoglycaemia is discussed in Chapter 36.

Monitoring of blood glucose and ketone levels

People should be encouraged to monitor their blood glucose using a *glucometer* 4–7 times daily (before meals, mid-morning, mid-afternoon, before bedtime and occasionally at 3 a.m., and also if they feel unwell or hypoglycaemic). HbA_{1c} should be checked regularly to establish long-term glucose control (see above). People should be reviewed every 3–6 months, and must have access to as-needed telephone or email consultations for insulin regimen adjustments.

Continuous glucose monitors measure interstitial fluid through a subcutaneous sensor, wirelessly transmitted to a receiver or mobile phone, allowing real-time estimation of blood glucose levels without the need for fingerprick blood glucose testing. Sensors are worn for up to 2 weeks, and may be programmed to alert at thresholds of hyper- and hypoglycaemia, as well as if hypoglycaemia is predicted. Flash glucose

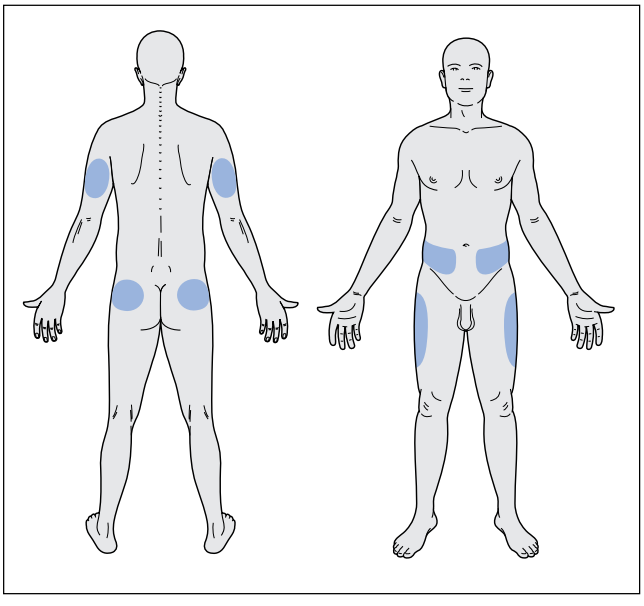


Figure 35.2 Insulin may be injected subcutaneously into the shaded areas. Injection sites should be rotated.

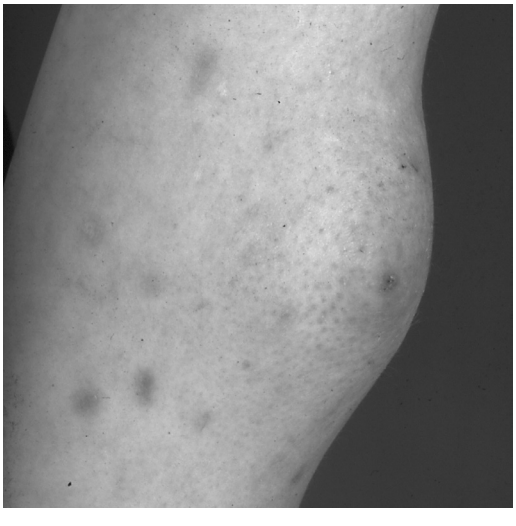


Figure 35.3 Lipohypertrophy caused by repeated insulin injections into the same site.

monitoring works similarly but requires the user to move the receiver close to the sensor, revealing current and historic blood glucose levels.

People with type 1 diabetes should be provided with a blood ketone monitor and instructed in its use. Ketones should be tested when unwell or if two consecutive blood glucose readings are >14 mmol/L. Sick-day rules should be followed if ketones are more than 0.6 mmol/L.

Sensor augmented insulin pump therapy

Sensor augmented insulin pump therapy is the simultaneous use of real-time continuous glucose monitoring with an insulin pump, usually with the continuous glucose sensor data wirelessly transmitted to the pump display. In basic sensor augmented pump systems, glucose sensor data are not utilised by the pump to adapt insulin delivery, even during hypo- or hyperglycaemia. Sensor augmented insulin pump therapy has been associated with less hypoglycaemia and lower HbA_{1c} levels. In more advanced systems the insulin infusion is paused in response to hypoglycaemia or in advance of impending hypoglycaemia predicted by the glucose falling.

A commercially available 'hybrid closed loop' system is available in some countries (sometimes referred to as an artificial pancreas). In this, the insulin pump's basal insulin infusion rate is adjusted according to the blood glucose levels sensed by a continuous glucose monitoring device. Individuals using the device still have to manually program the pump to deliver additional insulin boluses when consuming food.

Glycaemic control in type 2 diabetes

The *United Kingdom Prospective Diabetes Study* (UKPDS) showed that intensive therapy to achieve lower levels of glycaemia in newly diagnosed people

with type 2 diabetes reduces the risk of microvascular complications (retinopathy, nephropathy, neuropathy). The 10-year post-trial monitoring data from the UKPDS show that early intensive glucose control reduces the risk of myocardial infarction and all-cause mortality as well as continuing to reduce the risk of microvascular complications.

The aim is to achieve normal or near-normal glycaemia with an HbA_{1c} goal of below 53 mmol/mol. However, less stringent goals may be appropriate for older people and those with a history of severe hypoglycaemia, limited life expectancy, or co-morbid conditions.

In both the *Action to Control Cardiovascular Risk in Diabetes* (ACCORD) and the *Action in Diabetes and Vascular Disease: Preterax and Diamicron MR Controlled Evaluation* (ADVANCE) trials, intensive glycaemic control to achieve HbA_{1c} levels below 48 mmol/mol in people with long-standing diabetes did not reduce cardiovascular events over the time period studied (3.5–5 years). Data from the ACCORD study suggested that, in people with a long history of diabetes and at high risk of cardiovascular disease, reducing HbA_{1c} to near-normal may be unsafe (associated with a higher number of total and cardiovascular deaths, and a more common occurrence of severe hypoglycaemia). Therefore, a target HbA_{1c} of 53–64 mmol/mol may be safer for these people.

HbA_{1c} should be obtained at least twice yearly in people who are meeting glycaemic goals, and every 3 months in people who are not meeting glycaemic goals and in those whose treatment has changed.

Dietary modification and exercise

Lifestyle factors are the major components of non-pharmacological therapy in prediabetes and type 2 diabetes. For people willing and able to adopt these changes, a 3-month trial with appropriate dietetic support and education should be offered. Changes in diet and increased physical activity can slow the progression of impaired glucose tolerance to overt diabetes and can return HbA_{1c} to the non-diabetic range. Adherence to a low-calorie diet can lead to remission of type 2 diabetes.

People should exercise regularly (at least three times per week) and preferably at the same time in relation to meals (and insulin injections). The American Diabetes Association recommends at least 150 minutes of moderate-intensity aerobic activity distributed over at least 3 days each week. No screening is required for asymptomatic individuals who are planning low-moderate intensity exercise. People with proliferative retinopathy should avoid weight-lifting due to the increased risk of intraocular haemorrhage. People with neuropathy should take care with long-distance running or prolonged downhill skiing as these activities may precipitate stress fractures and pressure ulcers in the feet.

Metformin

Historically, metformin was the first-line oral hypoglycaemic agent recommended for treatment of type 2 diabetes. The advent of newer medications (eg SGLT2 inhibitors) and their increasing evidence base has meant that in some guidelines these may be preferred as the initial treatment. Metformin is usually started at the time of diagnosis in people with type 2 diabetes where HbA_{1c} remains above target in spite of lifestyle measures (or where lifestyle changes are not deemed likely by clinician and individual to achieve target HbA_{1c}). If there are no specific contraindications, metformin should be started at 500 mg once daily with meals. It is slowly titrated up over 1–2 months to the maximally effective dose (1000 mg twice a day) as tolerated. This is to prevent unpleasant gastrointestinal side-effects which frequently occur if maximum dose metformin is started immediately. A longer-acting formulation is available in some countries and can be given once per day. It should be emphasised that lifestyle modification remains an important component of type 2 diabetes management, even for those treated with medications.

Mechanism of action and efficacy

Metformin decreases hepatic glucose output, inhibits lipolysis (reduces serum free fatty acid levels and hence substrate availability for gluconeogenesis) and increases insulin-mediated glucose utilisation in the peripheral tissues (muscle and liver). It lowers serum lipid and blood glucose, possibly by working through LKB1 (a protein-threonine kinase), which phosphorylates and activates the enzyme adenosine monophosphate-activated protein kinase.

Metformin is not associated with weight gain and typically reduces HbA_{1c} levels by about 15 mmol/mol. It is less likely to cause hypoglycaemia than sulfonylureas and insulin. It can cause a decrease in serum triglyceride (triacylglycerol) levels, a small decrease in serum low-density lipoprotein (LDL) cholesterol, and a very modest increase in serum high-density lipoprotein (HDL) cholesterol. In overweight and obese individuals with diabetes, metformin may reduce all-cause mortality and rate of myocardial

infarction. Metformin has been suggested to reduce the risk of macrovascular complications, independently of its effects on glycaemic control.

Side-effects

Gastrointestinal side-effects (e.g. nausea, anorexia, abdominal discomfort, diarrhoea, a metallic taste in the mouth) are common with metformin, but usually settle after 1–2 weeks if started at a low dose and titrated slowly. People should be warned about this and encouraged to continue taking metformin if they experience these early gastrointestinal side-effects.

Although a frequent concern, a Cochrane review has stated that there is no evidence that metformin is associated with an increased risk of lactic acidosis, or with increased levels of lactate, compared to other antihyperglycaemic treatments. Nevertheless, common clinical practice is that metformin should not be administered in conditions predisposing to lactic acidosis – for example, reduced tissue perfusion, infection, cardiac failure, renal impairment (creatinine >125 µmol/L in women, >135 µmol/L in men), liver disease, or alcohol abuse. The use of serum creatinine alone to assess renal function may not be accurate in elderly people or others with reduced muscle mass. An estimated glomerular filtration rate of less than 60 mL per minute would be the equivalent of the above serum creatinine cut-off levels in these people.

In those who are about to receive intravenous iodinated contrast material with normal renal function, there is no need to stop metformin. People with reduced renal function (estimated glomerular filtration rate [eGFR] <60 mL/min/1.73 m^2) may need to stop taking metformin immediately prior to and for 48 hours after the procedure.

Metformin can cause low levels of vitamin B12 so levels should be checked periodically and if symptoms of neuropathy develop.

If lifestyle modification and metformin do not achieve or sustain the glycaemic goals (i.e. HbA_{1c} <53 mmol/mol) within 2–3 months, an additional oral agent should be started (if not contraindicated).

Sulfonylureas

Sulfonylureas are indicated in:

- people who are not candidates for metformin or who cannot tolerate metformin
- those in whom metformin therapy alone is not controlling the glycaemia.

The choice of sulfonylurea primarily depends on cost and availability. The dose is gradually increased if adequate glycaemic control is not attained (initially after 2–4 weeks). Shorter-acting sulfonylureas (e.g. glipizide, gliclazide) are preferred in elderly people.

Mechanism of action

Sulfonylureas bind to and inhibit the ATP-dependent potassium channel in the pancreatic beta cells, resulting in depolarisation of the beta cell membrane, calcium influx and stimulation of insulin secretion. Sulfonylureas are useful only in people with some beta cell function.

Side-effects

The most common side-effect of sulfonylureas is *hypoglycaemia*. This is more common with long-acting sulfonylureas (e.g. glyburide, chlorpropamide). People should be advised about the situations in which hypoglycaemia is most likely to occur. These include after exercise or a missed meal, with a high drug dose, in malnourishment or alcohol abuse, and with impaired renal or cardiac function, gastrointestinal disease, concurrent treatment with salicylates, sulfonamides, fibrates or warfarin, and after being in hospital.

Other less common side-effects that can occur with all sulfonylureas include nausea, skin reactions (including photosensitivity), and abnormal liver function tests. Some studies suggest that sulfonylureas may be associated with poorer outcomes after a myocardial infarction.

SGLT2 inhibitors

Sodium/glucose cotransporter (SGLT)2 inhibitors (e.g. empagliflozin, dapagliflozin, canagliflozin) can be added to metformin as a second agent or used in combination with metformin and one of either pioglitazone or a sulfonylurea as triple oral therapy. Some guidelines now recommend SGLT2 inhibitors as first line agents for the treatment of type 2 diabetes.

Mechanism of action

Glucose is freely filtered at the glomerulus and fully reabsorbed by SGLT2 at the proximal convoluted tubule (and to a lesser extent by SGLT1 in the distal tubule) until their maximum capacity is exceeded, after which some glucose will be lost in the urine. SGLT2 inhibitors prevent glucose reabsorption, thus lowering the renal threshold. This results in increased

urinary glucose excretion, thereby reducing glucose levels in the circulation.

Outcome data

A large randomised control study, *Empagliflozin, Cardiovascular Outcomes, and Mortality in Type 2 Diabetes* (EMPA-REG Outcome), in people with type 2 diabetes at high risk of cardiovascular events has shown significant reductions in cardiovascular mortality, death from any cause and hospitalisations for heart failure with empagliflozin. In people with albuminuria and reduced renal function (eGFR 30–90 mL/min/1.73 m^2), canagliflozin has been shown to reduce the risk of a composite endpoint of end-stage kidney disease, doubling of serum creatinine from baseline, and death from renal or cardiovascular disease when compared to placebo (*Canagliflozin and Renal Outcomes in Diabetic Nephropathy Clinical Evaluation*, CREDENCE). In people with heart failure with reduced ejection fraction (NYHA II–IV, left ventricular ejection fraction [LVEF] ≤40%) with or without type 2 diabetes, dapagliflozin decreased rates of cardiovascular death or worsening heart failure as well as all-cause mortality (*Dapagliflozin in Patients with Heart Failure and Reduced Ejection Fraction*, DAPA-HF).

Side-effects

Glycosuria increases the likelihood of urinary tract infections and genitourinary fungal infections (candidiasis). Beneficial effects of glycosuria include weight loss (excreting 60–80 g glucose per day) and lowering of blood pressure (a result of mild osmotic diuresis). SGLT2 inhibitors do not cause hypoglycaemia but are associated with a significantly increased risk of DKA, especially in people with type 1 diabetes or those who are insulin deficient.

DPP-IV inhibitors and GLP-1 analogues

Oral glucose has a greater stimulatory effect on insulin secretion than intravenous glucose. This 'incretin' effect is mediated by several gastrointestinal peptides, particularly *glucagon-like peptide-1* (GLP-1). GLP-1 is produced from the proglucagon gene in the L cells of the small intestine and is secreted in response to nutrients. GLP-1 stimulates glucose-dependent insulin release, inhibits glucagon release, slows gastric emptying and reduces food intake. GLP-1 has a short half-life due to N-terminal degradation by the enzyme *dipeptidyl peptidase IV* (DPP-IV).

DPP-IV inhibitors

DPP-IV inhibitors (e.g. sitagliptin, linagliptin, vildagliptin) inhibit the breakdown of endogenous GLP-1 and can be considered as monotherapy in people who have contraindications or an intolerance to metformin (e.g. those with chronic kidney disease). DPP-IV inhibitors may also be used as add-on drug therapy for people who do not achieve adequate glycaemic control on metformin or used in combination with metformin and a sulfonylurea as triple oral therapy. Used alone or with metformin, DPP-IV inhibitors have little or no risk of hypoglycaemia and therefore routine blood glucose monitoring is not required. They are generally well tolerated, but long-term safety data are lacking (because they are relatively new).

The biggest drawback, apart from expense, of DPP-IV inhibitor use is the lack of data supporting a beneficial impact on cardiovascular disease outcomes. Linagliptin can be used in chronic kidney disease without dose adjustment. Initially, there was concern that incretin-based treatments for diabetes were associated with an increased risk of pancreatitis and pancreatic cancer, but subsequent meta-analyses and systematic reviews have disproved this.

GLP-1 analogues

GLP-1 analogues (e.g. exenatide, liraglutide, semaglutide) are given by weekly or daily subcutaneous injection or orally (semaglutide) and can be considered for obese people with type 2 diabetes who are inadequately controlled on maximal doses of three oral agents and have a BMI >35kg/m^2. They confer a low risk of hypoglycaemia and are associated with weight loss. The main side-effect is nausea. GLP-1 analogues may be considered for people in whom hypoglycaemia is particularly undesirable, such as those holding hazardous jobs.

Both semaglutide (*Semaglutide and Cardiovascular Outcomes in Patients with Type 2 Diabetes*, the SUSTAIN-6 trial) and liraglutide (*Liraglutide and Cardiovascular Outcomes in Type 2 Diabetes*, the LEADER trial) have shown a lower rate of cardiovascular death, non-fatal myocardial infarction, or non-fatal stroke in high-risk people with type 2 diabetes. These effects appear to be independent of reductions in blood glucose and/or blood pressure and may relate to lower body mass (and thus insulin resistance), lower triglyceride levels, and a direct anti-inflammatory effect. GLP-1 analogues may also limit ischaemic myocardial damage.

Thiazolidinediones

Pioglitazone may be considered when hypoglycaemia is particularly undesirable, such as in those holding hazardous jobs or who drive professionally. Thiazolidinediones may reduce HbA_{1c} levels by about 15 mmol/mol when used as monotherapy. Pioglitazone can be added to metformin as a second agent or used in combination with metformin and one of either an SGLT2 inhibitor or sulfonylurea as triple oral therapy. Pioglitazone should be considered only for individuals without risk factors for heart failure or fracture (see 'Side-effects', next column).

Mechanism of action

Thiazolidinediones act mainly by increasing insulin sensitivity and the peripheral uptake and utilisation of glucose in muscle and fat. They bind to and activate peroxisome proliferator-activated receptors (PPARs), which regulate gene expression. Pioglitazone has PPAR-gamma with some PPAR-alpha agonist activity. Thiazolidinediones may improve insulin responsiveness by facilitating glucose transport in skeletal muscle and regulation of expression of adipose tissue adipokines. They may also decrease hepatic glucose production and improve pancreatic beta cell dysfunction.

Side-effects

Thiazolidinediones may cause weight gain and fluid retention, and increase the risk of heart failure. An increased incidence of bone fractures (in the upper arm, hand, and foot) has been observed in females. Therefore, the risk of fracture should be considered prior to initiation and during use.

Meglitinides

The meglitinides (repaglinide, nateglinide) are short-acting drugs that act by regulating ATP-dependent potassium channels in pancreatic beta cells, thereby increasing insulin secretion. They are rarely used in current clinical practice. The clinical efficacy of meglitinide monotherapy is similar to that of the sulfonylureas. Meglitinides can be used alone or in combination with metformin. They are taken before each meal, and the dose should be skipped if the meal is missed. Hypoglycaemia is the most common adverse effect. Repaglinide is principally metabolised by the liver, and less than 10% is renally excreted. Therefore, dose adjustments may not be necessary in people with renal insufficiency.

Insulin treatment in type 2 diabetes

In most people with type 2 diabetes, blood glucose levels and HbA_{1c} rise over time due to worsening beta cell dysfunction, decreased insulin release, and more severe insulin resistance. Insulin should be started in people who do not achieve optimal diabetes control despite maximal tolerated doses of oral antidiabetic treatment.

Insulin may be administered as first-line therapy to people presenting with HbA_{1c} of over 86 mmol/mol weight loss or ketonuria despite adequate calorie intake. Insulin is also initiated in people in whom it is difficult to distinguish type 1 from type 2 diabetes.

Insulin therapy may be started with a once-daily injection of an intermediate-acting insulin (e.g. isophane) or bedtime or morning long-acting insulin (e.g. detemir, glargine). Insulin can be initiated at a dose of 10 U or 0.2 U/kg.

People should check their *fasting blood glucose* levels usually daily, and increase their insulin dose, typically by 2 U every 3 days, until fasting blood glucose levels are consistently in the target range (4–7 mmol/L). If fasting blood glucose is more than 10 mmol/L, the dose can be increased in larger increments (e.g. by 4 U every 3 days). If HbA_{1c} is 53 mmol/mol (7%) or more after 2–3 months, and fasting blood glucose is in the target range, additional *premeal boluses* of rapid-acting insulin are required to control postprandial hyperglycaemia:

- If pre-lunch blood glucose is out of range: add rapid-acting insulin at breakfast.
- If pre-dinner blood glucose is out of range: add rapid-acting insulin at lunch.
- If pre-bed blood glucose is out of range: add rapid-acting insulin at dinner.

A rapid-acting insulin preparation can usually be started at a dose of about 4 U and is adjusted by 2 U every 3 days until blood glucose is in range. Individuals should check their blood glucose before their next meal or before bed (usually after about 4 hours) and adjust the preceding insulin boluses accordingly.

If hypoglycaemia occurs or fasting blood glucose is less than 3.9 mmol/L, the bedtime insulin dose should be reduced by 4 U or 10% (whichever is greater).

Some people with type 2 diabetes who require premeal insulin in addition to basal insulin prefer *premixed insulins* for convenience. Premixed (biphasic) insulins contain a mixture of short-acting insulin (e.g. 30% regular insulin or insulin analogues) and intermediate-acting insulin (e.g. 70% isophane insulin). These are given twice daily. Although fewer injections are given,

premixed insulins may be more difficult to titrate to achieve target blood glucose levels.

People with type 2 diabetes often need large daily doses of insulin (>65 U per day, and usually much more) to achieve acceptable glycaemic control.

Details of the different types of insulin, side-effects, insulin regimens, devices, injection technique, and sites were discussed earlier in this chapter (see 'Glycaemic control in type 1 diabetes').

Insulin and exercise

The effect of exercise on blood glucose depends on whether the person is hypoinsulinaemic or hyperinsulinaemic at the time of exercise.

In individuals without diabetes, the exercising muscles take up glucose from the circulation. As the blood glucose concentration starts to fall, insulin secretion decreases, levels of counter-regulatory hormones (glucagon, catecholamines, growth hormone, cortisol) rise and hepatic glucose output increases. Exercise may cause hypoglycaemia in people with diabetes with adequate serum insulin levels. This is because exogenous subcutaneous insulin cannot be shut off on commencement of exercise, meaning that insulin-driven muscle glucose uptake continues and hepatic glucose output is inhibited. In addition, the increased temperature and blood flow associated with exercise may enhance insulin absorption from subcutaneous depots.

Blood glucose must be measured and documented before, during, and after exercise. People may need to reduce the insulin dose that affects that time of the day, and the injection may be given 60–90 minutes before exercise. Insulin should be injected in a site not close to the exercised muscles to prevent increased insulin absorption (e.g. the arm is a suitable site if the patient is cycling).

People may need to take extra food (15–30 g of quickly absorbed carbohydrate, e.g. hard candies or juice) 15–30 minutes before exercise and approximately every 30 minutes during exercise. Late hypoglycaemia due to replenishment of depleted glycogen stores can usually be avoided by eating slowly absorbed carbohydrates (e.g. dried fruit) immediately after exercise.

In contrast, exercise can cause paradoxical hyperglycaemia; if the blood glucose concentration is over 15 mmol/L before exercise, blood ketone levels should be checked and if more than 1.5 mmol/L, exercise is contraindicated and glucose management should be initiated rapidly. The lack of insulin impairs glucose uptake by the muscles and cannot prevent the increase in hepatic glucose output caused by the counter-regulatory hormones secreted during exercise. If blood glucose levels are above 15 mmol/L and blood ketones levels between 0.6 and 1.4 mmol/L, exercise should be restricted to a light intensity for less than 30 minutes; a small corrective insulin dose might be needed before starting exercise. If ketones are low (<0.6 mmol/L), mild-to-moderate aerobic exercise can be started.

Blood glucose concentrations should be monitored during exercise to help detect whether they increase further. Intense exercise should be initiated only with caution as it could promote further hyperglycaemia.

In people with type 2 diabetes on oral hypoglycaemic drugs, exercise tends to lower blood glucose levels. This effect may depend on the timing of the patient's last meal. Exercise may result in hypoglycaemia if it is carried out after eating.

Treatment of obesity

Pharmacotherapy for weight loss may be used in obese people with type 2 diabetes. However, the weight loss may not be effectively sustained due to side-effects of the drugs. *Bariatric surgery* results in the largest degree of sustained weight loss and improvements in blood glucose control (see Chapter 33).

Screening for and treatment of complications

Retinopathy

People with diabetes should have regular eye examinations, ideally with *digital retinal photography*. The incidence of diabetic retinopathy increases over time in people with both type 1 and type 2 diabetes. The progression of retinopathy can be slowed by *laser photocoagulation* therapy.

Nephropathy

The progression of nephropathy can be slowed by the administration of an angiotensin-converting enzyme (ACE) inhibitor or angiotensin II receptor blocker (ARB) and management of high blood pressure.

Microalbuminuria is the earliest clinical finding in diabetic nephropathy. It is defined as a urinary albumin excretion rate of between 30 and 300 mg per day

(20–200 µg per minute). Microalbuminuria may be diagnosed by measuring the *albumin-to-creatinine ratio* in a spot urine sample. Abnormal results (urinary albumin-to-creatinine ratio >2.5 mg/mmol in men, >3.5 mg/mmol in women) should be repeated at least two or three times over a 3–6-month period to exclude false-positive results (e.g. transient microalbuminuria due to exercise, fever, heart failure or poor glycaemic control).

All people with type 2 diabetes should be screened for microalbuminuria from the time of diagnosis as they may have had diabetes for several years before diagnosis. Screening can be deferred for 5 years after the onset of disease in type 1 diabetes since microalbuminuria is uncommon before this time.

ACE inhibitors both lower urinary protein excretion and slow the rate of disease progression. People with microalbuminuria or overt nephropathy should receive an ACE inhibitor or an ARB even if they are normotensive. The maintenance of strict glycaemic control is also essential. Dietary protein restriction may be beneficial in people with established nephropathy.

Diabetic foot problems

Foot problems due to ischaemia and/or neuropathy are a common and important source of morbidity in people with diabetes. People should have regular (at least annual) screening examinations by their doctor for neuropathic and vascular involvement of the lower extremities. They must also be advised to inspect their feet regularly at home.

Examination of the feet in the diabetes clinic should include:

- *inspection* for integrity of the skin (especially between the toes and under the metatarsal heads), and the presence of erythema, warmth and callus
- checking for neuropathy (vibration sensation, *10 g monofilament testing*)
- screening for peripheral arterial disease by *palpation of the pedal pulses* and asking about a history of claudication. An ankle–brachial pressure index should be obtained if peripheral arterial disease is suspected.

People with any foot abnormality should be referred to clinicians with expertise in diabetic foot care. All people with diabetes should be advised to:

- Wash and check their feet daily (people must test the water temperature before stepping into a bath).
- Avoid going barefoot at home.
- Trim their toenails to shape of the toe, remove sharp edges with a nail file, and avoid cutting the cuticles.
- Avoid tight shoes.
- Change their socks daily.

Screening for and treatment of cardiovascular risk factors

People with diabetes are at increased risk of developing cardiovascular disease and of dying when cardiovascular disease is present. At the time of diagnosis of type 2 diabetes, many people already have risk factors for macrovascular disease (e.g. hypertension, obesity, dyslipidaemia, smoking) and many have evidence of atherosclerosis (e.g. peripheral vascular disease, history of ischaemic heart disease, ischaemic changes on ECG).

Cardiovascular risk factor modification in people with diabetes should include:

- blood pressure control
- screening for and treatment of dyslipidaemia
- smoking cessation.

The Steno-2 study showed that an intensified intervention aimed at multiple risk factors in people with type 2 diabetes and microalbuminuria reduces the risk of cardiovascular and microvascular events by about 50%. The intensive therapy regimen in this trial included smoking cessation, tight glycaemic control, blood pressure control, exercise, reduced dietary fat, and lipid-lowering therapy.

Blood pressure control

Extracellular fluid volume expansion (due to reabsorption of the excess filtered glucose in the proximal tubules along with sodium), hyperinsulinaemia (in type 2 diabetes), increased arterial stiffness, and diabetic nephropathy may contribute to the development of hypertension in diabetes.

Early and effective treatment of high blood pressure prevents cardiovascular disease and minimises the rate of progression of diabetic nephropathy and retinopathy. Blood pressure must be measured at every routine diabetes visit. The recommended goal blood pressure for most people with diabetes is less than 130/80 mmHg, but even lower values may be beneficial in people with diabetic nephropathy.

Non-pharmacological treatments should include advice regarding weight reduction, increased consumption of fresh fruits and vegetables, a low-fat intake, exercise, sodium restriction, and avoidance of smoking and excess alcohol intake.

Most diabetologists usually initiate therapy with an *ACE inhibitor* or an *ARB* as these protect against the development of progressive nephropathy. Other antihypertensive agents – for example, thiazide diuretics – may be added if the goal blood pressure is not achieved with the maximally tolerated dose of an ACE inhibitor or ARB.

Although there are concerns about the masking of hypoglycaemic symptoms and possible exacerbation of peripheral vascular disease, beta-blockers are commonly used to treat hypertension in people with diabetes. Some beta-blockers may cause a modest worsening of glycaemic control.

Screening for and treatment of dyslipidaemia

Hypercholesterolaemia increases the risk of cardiovascular disease. Screening for dyslipidaemia should be done at least annually, and more often if needed to achieve goals.

Both the *Cholesterol and Recurrent Events* (CARE) trial and the *Heart Protection Study* showed significant improvement in outcomes with statin therapy even at LDL-cholesterol values below 3.0 mmol/L. The *Collaborative Atorvastatin Diabetes Study* (CARDS) found similar benefits of statin therapy in people with an LDL-cholesterol above or below 3.1 mmol/L. People should be treated with a statin to reduce the LDL-cholesterol levels to below 2 mmol/L (and total cholesterol <4 mmol/L). If target levels cannot be achieved with statins alone, it is uncertain whether the addition of other agents such as ezetimibe (which inhibits cholesterol absorption) provides additional clinical benefit.

Triglyceride levels below 1.7 mmol/L and HDL levels above 1.0 mmol/L are preferable. When triglycerides are moderately elevated, treatment should include weight reduction strategies, increased physical activity, and a statin. When triglycerides are very high (>10 mmol/L), an omega-3 fatty acid compound or a fibrate may be given to prevent pancreatitis. Combination of a statin and a fibrate increases the risk of myositis, particularly in people with renal impairment or hypothyroidism. Combination therapy should therefore be used with caution, with monitoring of liver function tests and serum creatinine kinase.

Smoking cessation

A meta-analysis of several of the cardiovascular risk reduction trials showed that *smoking cessation* had a much greater benefit for survival than most other interventions. Pharmacological therapy (e.g. bupropion, nicotine replacement therapy) should be combined with behavioural interventions (e.g. brief clinician counselling in the office).

Pancreatic islet cell transplantation

Pancreatic islet transplantation is used for people with *problematic hypoglycaemia unawareness*. Pancreatic islets isolated from cadaver pancreases may be infused into the portal vein or liver via a percutaneous catheter. Both alpha and beta cells are transplanted. Even a small residual islet function can markedly decrease hypoglycaemic events for unexplained reasons. Insulin independence is not the aim of an islet cell transplant. In the UK, the rates of 1- and 5-year graft survival for people receiving a first routine islet transplant are 85% and 51%, respectively. The median rate of severe hypoglycaemia is significantly reduced after islet cell transplant and HbA_{1c} is also reduced 1 year post transplant.

The main complications include those related to the procedure (e.g. haemorrhage, portal vein thrombosis) and those caused by immunosuppression (e.g. mouth ulcers, diarrhoea, anaemia).

Pancreatic transplantation

It is possible to transplant a pancreas alone, or in combination with a kidney transplant. People with insulin-treated diabetes and chronic kidney disease may be considered for simultaneous pancreas and kidney (SPK) transplantation where their predicted survival, or survival free from progression of serious diabetic complications of diabetes, would be improved by SPK relative to available alternative therapies. In the UK, graft survival rates at 1 and 5 years for first SPK transplant from deceased donors are 90% and 81%, respectively. Pancreas alone transplants may occur after a renal transplant (pancreas-after-kidney) or in isolation. Solitary pancreas transplants are performed in people with insulin-treated diabetes and recurrent severe hypoglycaemia.

KEY POINTS

- The four main components of treatment of a patient with diabetes mellitus are patient education, glycaemic control, screening for and treatment of complications, and screening for and treatment of cardiovascular risk factors.
- Diet and exercise are important components of non-pharmacological therapy in people with diabetes.
- Intensive insulin therapy to achieve lower levels of glycaemia reduces the risk of microvascular complications (retinopathy, nephropathy, neuropathy) in both type 1 and type 2 diabetes.
- All people with type 1 diabetes must be treated with insulin.
- All people with type 2 diabetes should receive metformin (if not contraindicated) and advice regarding lifestyle modification at diagnosis.
- The goal of glycaemic control is to achieve normal or near-normal glycaemia with an HbA_{1c} under 7%. However, less stringent goals may be appropriate for older people and people with a history of severe hypoglycaemia, limited life expectancies, or co-morbid conditions.
- The main side-effects of intensive insulin therapy are hypoglycaemia and weight gain.
- Cardiovascular risk factor modification in people with diabetes should include blood pressure control, screening for and treatment of dyslipidaemia, and smoking cessation.

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Diabetic emergencies

Diabetic ketoacidosis

The triad of diabetic ketoacidosis (DKA) consists of *hyperglycaemia*, *high anion gap metabolic acidosis*, and *ketonaemia*. DKA is characteristically associated with type 1 diabetes. However, it has become increasingly common in people with type 2 diabetes.

Aetiology and pathogenesis

The precipitating factors for DKA are summarised in Box 36.1. DKA may be the first presentation of type 1 diabetes. It may occasionally be the first presentation of type 2 diabetes, especially in Afro-Caribbean individuals ('ketosis-prone type 2 diabetes').

In people with known diabetes, inadequate insulin treatment or non-compliance is a common precipitating factor for DKA. DKA may also be precipitated by stresses that increase the secretion of the counter-regulatory hormones glucagon, catecholamines, cortisol and growth hormone. Infection, such as pneumonia, gastroenteritis and urinary tract infection, can be found in about 30–40% of people with DKA.

Insulin deficiency causes impaired glucose utilisation, as well as increased gluconeogenesis and glycogenolysis, resulting in *hyperglycaemia*. The elevated plasma glucose increases the filtered load of glucose in the renal tubules. As the maximal renal tubular reabsorptive capacity is exceeded, glucose is excreted in the urine (*glycosuria*). The osmotic force exerted by unreabsorbed glucose holds water in the tubules, thereby preventing its reabsorption and increasing urine output (*osmotic diuresis*). This leads to dehydration and loss of electrolytes.

Insulin deficiency and increased catecholamines and growth hormone increase lipolysis, thereby increasing free fatty acid delivery to the liver. Normally, free fatty acids are converted to triglycerides in the liver. However, in DKA, hyperglucagonaemia alters hepatic metabolism to favour ketogenesis. Glucagon excess decreases the production of malonyl coenzyme A, thereby increasing the activity of the mitochondrial enzyme carnitine palmitoyltransferase I, which mediates the transport of free fatty acyl coenzyme A into the mitochondria, where conversion to ketones occurs.

Three ketone bodies are produced in DKA: two ketoacids (beta-hydroxybutyric acid and acetoacetic acid) and one neutral ketone (acetone). Acetoacetic acid is the initial ketone formed. It may then be reduced to beta-hydroxybutyric acid or non-enzymatically decarboxylated to acetone. Ketones provide an alternative source of energy when glucose utilisation is impaired.

Hyperglycaemic crises are proinflammatory states that lead to the generation of reactive oxygen species, which are indicators of oxidative stress.

Clinical presentations

People with DKA may present with:

- polyuria and polydipsia, resulting in dehydration
- abdominal pain and vomiting (which exacerbates the dehydration). Abdominal pain requires further evaluation if it does not resolve with treatment of the acidosis
- fatigue, weakness, and weight loss
- confusion; coma (10% of people).

Clinical examination includes assessment of cardiorespiratory status, volume status, and mental status to look for:

Endocrinology and Diabetes: Lecture Notes, Second Edition. Amir H. Sam, Karim Meeran and Neil Hill.
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Box 36.1 Precipitating factors for diabetic ketoacidosis

Infection (30–40%)
New-onset diabetes (25%)
Inadequate insulin treatment or non-compliance (20%)
Myocardial infarction
Stroke
Acute pancreatitis
Trauma

Drugs: clozapine/olanzapine, cocaine, lithium, terbutaline.

Box 36.2 Investigations in diabetic ketoacidosis

Blood ketones (urinary ketones if blood ketone testing unavailable)
Blood glucose
Venous blood gas analysis: pH, PCO_2, bicarbonate, chloride, lactate
Urea, creatinine and electrolytes: sodium, potassium, phosphate, magnesium
Full blood count
Septic screen: C-reactive protein, blood culture, chest radiograph, urinalysis and urine culture
ECG
Pregnancy test in women of childbearing age

- evidence of dehydration: tachycardia, postural hypotension, reduced tissue turgor, and confusion
- Kussmaul respiration (deep sighing respiration secondary to acidosis) and ketotic breath.

A medical history and clinical examination may identify a precipitating event such as infection (e.g. pneumonia, urinary tract infection) or discontinuation of or inadequate insulin therapy in known diabetics.

Investigations

The investigations in a person presenting with DKA are summarised in Box 36.2. The diagnosis of DKA requires:

- plasma glucose >11 mmol/L (and usually <44 mmol/L) or known diabetes
- ketonaemia >3.0 mmol/L or significant ketonuria (more than 2+ on standard urine sticks)
- acidosis (pH ≤7.30 and/or bicarbonate <15 mmol/L). The acidosis in DKA is a *metabolic acidosis* (associated with low bicarbonate levels and a reduction of partial pressure of carbon dioxide [PCO_2] due to compensatory hyperventilation) with a *high anion gap* (>12 mmol/L).

The plasma anion gap is calculated from the difference between the primary measured cations and the primary measured anions, i.e. serum [$Na^+ + K^+$] – serum [$Cl^- + HCO_3^-$].

In normal subjects, the anion gap is primarily determined by the negative charges on the plasma proteins, particularly albumin. The anion gap is elevated in those forms of metabolic acidosis in which there is buffering of the excess acid by bicarbonate (resulting in a reduction of bicarbonate) and replacement of the bicarbonate by an unmeasured anion (e.g. ketoacid anions in DKA).

Blood glucose levels as low as 10 mmol/L and severe acidaemia may be seen in people who have recently taken insulin or are using an SGLT2 inhibitor or following a low-carbohydrate diet, as this alone is insufficient to correct the acidosis in the presence of dehydration.

Capillary ketone meters measure the level of beta-hydroxybutyric acid, which is the principal ketone produced in DKA. *Urine ketone* detection systems generally detect acetoacetic acid and acetone, but not beta-hydroxybutyric acid. Sulfhydryl drugs, such as captopril, penicillamine and mesna, interact with the nitroprusside reagent and can cause a false-positive ketone test. In people treated with these drugs, direct measurement of beta-hydroxybutyric acid is recommended.

A septic screen should be performed to look for an underlying infection. An electrocardiogram (ECG) should be done to exclude acute coronary syndrome as a precipitating factor.

The white cell count may be elevated due to an underlying infection. However, an elevated white cell count (usually less than 25×10^9/L) is also commonly seen in the absence of infection. This may occur as a result of hypercortisolaemia and increased catecholamine secretion.

Serum amylase and lipase levels are elevated in 15–25% of people with DKA and, in most cases, do not reflect acute pancreatitis. However, acute pancreatitis may occur in about 10% of people with DKA (often in association with hypertriglyceridaemia). The diagnosis of pancreatitis in people with DKA should be based upon the clinical findings and a computed tomography (CT) scan.

Differential diagnosis

Ketoacidosis may also be caused by alcohol abuse or fasting. Other causes of a high anion gap metabolic acidosis include lactic acidosis (due to tissue hypoperfusion

caused by hypovolaemia, cardiac failure or sepsis), renal failure, and drugs such as aspirin, methanol, and ethylene glycol.

Treatment

A person with DKA should ideally be managed and closely monitored in a high-dependency or intensive therapy unit. Treatment of DKA includes:

- resuscitation (airway, breathing, circulation)
- insulin
- fluids
- potassium.

Broad-spectrum antibiotics are given if infection is suspected.

In people with impaired conscious level, a nasogastric tube is inserted to prevent vomiting and aspiration.

Two intravenous cannulae should be sited, one in each arm: one for 0.9% saline and one for insulin and later 10% dextrose. A urinary catheter is inserted in those with oliguria or elevated serum creatinine. A central line may be inserted in those with a history of cardiac disease or autonomic neuropathy and in those who are elderly.

All people should have thromboprophylaxis with low molecular weight heparin.

Fluid replacement

The average fluid loss in DKA is 100 mL/kg; *0.9% saline* is used to replace the fluid deficit.

If the patient is hypotensive (systolic blood pressure <90 mmHg), 500 mL of intravenous 0.9% saline is given over 15–20 minutes. This may be repeated, aiming for a systolic blood pressure over 100 mmHg. If this is not achieved, consider involving the critical care team. Once systolic blood pressure is over 100 mmHg, fluid is administered as follows:

- 1 L of 0.9% saline over 1 hour
- 1 L of 0.9% saline two-hourly × 2 (plus potassium replacement; see below)
- 1 L of 0.9% saline four-hourly × 2 (plus potassium replacement; see below)
- 1 L of 0.9% saline six-hourly × 1 (plus potassium replacement; see below).

Exercise caution in the following groups of people.

- Young people aged 18–25 years
- Elderly
- Pregnant
- Heart or kidney failure
- Those with other serious co-morbidities

In these situations, admission to a level 2/HDU facility should be considered. Fluids should be replaced cautiously following regular clinical review.

Insulin replacement

Insulin should be given only after fluid therapy has been commenced. Fifty units of soluble insulin are added to 50 mL 0.9% saline. Insulin infusion is started at a *fixed* rate of 0.1 U per kg body mass per hour (e.g. 7 units/h if weight is 70 kg). If body mass is not available, it should be estimated. The response to insulin infusion is reviewed after 1 hour with the aim of clearing the blood of ketones and suppressing ketogenesis. Aim for a reduction of capillary ketones by at least 0.5 mmol/h (or, in the absence of ketone measurements, a rise in bicarbonate by 3.0 mmol/L/h and fall in blood glucose by 3.0 mmol/L/h). If the ketone levels are not falling appropriately, consider increasing the insulin infusion rate by 1 unit per hour.

The fixed-rate insulin is continued until the DKA has resolved, defined as capillary ketones below 0.6 mmol/L and venous pH above 7.3. Do not rely on bicarbonate alone to assess the resolution of DKA at this point due to the possible hyperchloraemic acidosis secondary to high volumes of 0.9% sodium chloride solution which will lower the bicarbonate and thus lead to difficulty in assessing whether the ketoacidosis has resolved. At this point, if the patient is eating and drinking regularly, a subcutaneous insulin regimen is started, and the intravenous insulin pump is discontinued 30–60 minutes afterwards. If the patient is not eating and drinking, an intravenous sliding scale is used (Table 36.1).

Ketonuria may persist for more than 36 hours due to the slower removal of acetone, in part via the lungs.

Table 36.1 Example of a variable rate insulin infusion

Blood glucose (mmol/L)	Insulin infusion (U/h)
0–4.0	0.5
4.1–7.0	1
7.1–11.0	2
11.1–15.0	3
15.1–20	4
>20.0	6

50 U of soluble insulin is added to 50 mL 0.9% saline in a syringe and the intravenous infusion is administered via a pump. The rate of insulin infusion is adjusted according to the hourly capillary blood glucose measurements.

However, as acetone is biochemically neutral, these people do not have persistent ketoacidosis.

Individuals who normally take long-acting insulin (e.g. glargine or detemir) should continue their usual dose from the day of admission.

Potassium replacement

In people with DKA, both renal and gastrointestinal losses contribute to the potassium depletion. The increase in renal potassium excretion is primarily related to the glycosuria-induced osmotic diuresis and to hypovolaemia-induced hyperaldosteronism. However, despite this deficit, the serum potassium concentration is often high at presentation as insulin deficiency leads to potassium movement out of the cells and into the extracellular fluid.

Treatment with insulin lowers the potassium concentration and may cause severe hypokalaemia as potassium shifts into the cells under the action of insulin. Therefore, careful monitoring and administration of potassium are essential.

Hypokalaemia and hyperkalaemia are life-threatening conditions and are common in DKA. Potassium chloride is not given in the first litre of intravenous fluid or if the serum potassium is over 5.5 mmol/L. All subsequent fluids for the next 24 hours should contain potassium chloride, unless urine output is below 30 mL/h or serum potassium is over 5.5 mmol/L. The amount of potassium added to the fluids is adjusted according to plasma potassium levels (Table 36.2).

Bicarbonate

The use of bicarbonate is not indicated and there is no evidence that it improves outcome in DKA. There are three potential concerns with alkali therapy:

- a reduced acidaemic stimulus to hyperventilation, which leads to a rise in PCO_2. The carbon dioxide can rapidly cross the blood–brain barrier, resulting in a paradoxical fall in cerebral pH
- a reduced rate of recovery of the ketosis
- post-treatment metabolic alkalosis, since the metabolism of ketoacid anions with insulin results in the generation of bicarbonate and spontaneous correction of most of the metabolic acidosis.

Table 36.2 Potassium replacement

Potassium level	Replacement per liter fluid
>5.5 mmol/L	Nil
3.5–5.5 mmol/L	40 mmol/L
<3.5 mmol/L	May need faster rate of intravenous fluids or concentrated potassium to be given in an HDU/ITU setting

Phosphate and magnesium

Randomised trials of phosphate replacement in DKA in adults have failed to show any clinical benefit. Phosphate administration may induce hypocalcaemia and hypomagnesaemia. The main indication for phosphate therapy is a serum phosphate concentration less than 0.30 mmol/L. Intravenous phosphate (monobasic potassium phosphate) is infused at a maximum rate of 9 mmol every 12 hours. When phosphate is given, serum calcium and magnesium levels should be monitored.

Serum magnesium may fall during insulin therapy. If magnesium levels fall below 0.5 mmol/L, 4–8 mmol (2 mL of 50%) magnesium sulfate is administered over 15–30 minutes in 50 mL 0.9% saline.

Monitoring

Close monitoring of the following is critical.

For the *first 6 hours*

- Hourly clinical review.
- Blood glucose, capillary ketones, and urine output are monitored hourly and response to treatment assessed.
- Venous blood gas for pH, bicarbonate, and potassium is monitored at 60 minutes, 2, 4, and 6 hours.

6–12 hours

- Venous blood gas for pH, bicarbonate and potassium; if DKA has not resolved, continue 2-hourly venous blood gas measurements.
- Capillary ketones and blood glucose are monitored every hour until resolution.
- Plasma phosphate and magnesium are monitored daily.

12–24 hours

- Venous blood gas for pH, bicarbonate, and potassium; if DKA has not resolved, continue 2-hourly venous blood gas.
- Capillary ketones and blood glucose are monitored every hour.

It is unusual for DKA not to have resolved with 24 hours of treatment; this should prompt further consideration.

An arterial line is inserted in the intensive care unit to monitor pH, bicarbonate, and potassium levels. If an arterial line is not inserted, venous samples should be used for measurement of pH and bicarbonate rather than repeated arterial blood gases, which are uncomfortable.

Continuous cardiac monitoring should be initiated in those with severe DKA. Almost all people with DKA (except those with advanced renal failure) develop a normal anion gap acidosis during treatment. Insulin converts ketoacid anions back into bicarbonate. However, as some of the ketoacid anions (i.e. bicarbonate precursors) are excreted in the urine with sodium or potassium, the anion gap is reduced but the acidosis persists.

Cerebral oedema

Cerebral oedema causing symptoms is relatively uncommon in adults with DKA but occurs in 0.3–1% of children with DKA and has a high mortality rate of 20–25%. Younger children and those with newly diagnosed DKA, elevated serum urea, more profound acidosis or neurological symptoms are at greatest risk for cerebral oedema. Cerebral oedema generally develops during treatment for DKA due to sudden shifts in plasma osmolality. However, up to 20% of cases of cerebral oedema occur before the initiation of treatment.

All children should be carefully monitored for early signs of cerebral oedema throughout the course of treatment for DKA. Specific signs of increased intracranial pressure and radiological changes detected by head CT often occur too late for effective intervention. Cerebral oedema should be suspected in people with headache, recurrent vomiting, age-inappropriate incontinence, irritability, lethargy, and altered level of consciousness.

If cerebral oedema is suspected, treatment should be started promptly by reducing the rate of fluid administration and administering intravenous mannitol (0.25–1.0 g/kg) or hypertonic 3% saline.

Hyperosmolar hyperglycaemic state

Hyperosmolar hyperglycaemic state (HHS) and DKA are part of a spectrum representing the metabolic consequences of insulin deficiency, glucagon excess, and counter-regulatory hormonal responses to stressful triggers in people with diabetes. It is important to note that a mixed picture of HHS and DKA may occur.

In HHS, there is little or no ketoacid accumulation, the serum glucose concentration often exceeds 50 mmol/L, the plasma osmolality may reach 380 mosmol/kg, and neurological abnormalities are frequently present.

Insulin levels in HHS are insufficient to allow appropriate glucose utilisation but are adequate to prevent lipolysis and subsequent ketogenesis. HHS was previously known as hyperosmolar non-ketotic acidosis (HONK). Lower levels of counter-regulatory hormones and free fatty acids have been found in HHS than in DKA.

HHS usually occurs in elderly people with type 2 diabetes. It has a substantially higher mortality than DKA (up to 15% in some clinical series).

Clinical presentations

People with HHS present with:

- an insidious onset of polyuria and polydipsia (those with DKA generally excrete glucose more effectively than older people with HHS)
- severe dehydration
- neurological symptoms when the effective serum osmolality is over 320 mosmol/kg. Coma is usually associated with an osmolality of above 440 mosmol/kg (25–50% of cases).

The history and clinical examination may reveal symptoms and signs of the underlying precipitating factors (Box 36.3).

Diagnosis

A precise definition of HHS does not exist, but characteristic features that help to differentiate it from other hyperglycaemic states such as DKA include:

Box 36.3 Precipitating factors for a hyperosmolar hyperglycaemic state

Poor compliance with treatment
Previously undiagnosed diabetes
Infection (e.g. urinary tract, pneumonia)
Myocardial infarction
Stroke, subdural haematoma
Pulmonary embolism
Acute pancreatitis, intestinal obstruction
Hypothermia
Drugs: diuretics, beta-blockers, antihistamines, steroids
Total parenteral nutrition
Trauma

- hypovolaemia
- marked hyperglycaemia (≥30 mmol/L) without significant hyperketonaemia (<3 mmol/L) or acidosis (pH >7.3, bicarbonate >15 mmol/L)
- osmolality usually ≥320 mosmol/kg.

Investigations

Investigations in people with HHS are similar to those with DKA (see Box 36.2).

The *serum glucose* concentration often exceeds 50 mmol/L.

The *serum sodium* level reflects the balance between the dilution of sodium due to osmotic water movement out of the cells, and the concentration of sodium due to glycosuria-induced osmotic diuresis resulting in loss of water in excess of sodium. Reversing the hyperglycaemia with insulin will cause water to move from the extracellular fluid into the cells and increases the serum sodium concentration. Therefore, a patient with a normal initial serum sodium concentration will probably become hypernatraemic during therapy.

The *effective plasma osmolality* can be estimated from either of the following equations:

$$2 \times \left(Na^{+} + K^{+}\right) + \text{glucose}\left(\text{all in mmol/L}\right), \textit{ or}$$

$$\text{Measured plasma osmolality} - \text{urea}\left(\text{in mmol/L}\right)$$

The multiple 2 in the first equation accounts for the osmotic contribution of the anions (i.e. chloride and bicarbonate) accompanying sodium and potassium. Note that in the calculation of effective plasma osmolality, the urea concentration is not taken into account because urea is freely permeable and its accumulation does not induce major changes in the osmotic gradient across the cell membrane.

The presence of stupor or coma in people with diabetes and an effective serum osmolality below 320 mosmol/kg warrant prompt investigation with head CT and lumbar puncture for causes other than HHS. An underlying precipitant should be actively sought.

Treatment

People with HHS are severely dehydrated and may require 8–10 L of fluid in the first 48 hours. *Rehydration* is started with 1 L of 0.9% saline over the first hour, with the aim of giving 3–6 L within the first 12 hours. The remaining fluid deficit should be corrected in the next 12 hours until the person is rehydrated; 0.45% sodium chloride should only be used if the osmolality is not declining despite adequate positive fluid balance. An initial rise in sodium is expected and is not itself an indication for hypotonic fluids. The rate of fall of plasma sodium should not exceed 10 mmol/L in 24 hours to reduce the risk of central pontine myelinosis.

Potassium 40 mmol is given in each liter of intravenous fluid to keep the serum potassium concentration between 3.5 and 5.5 mmol/L.

Intravenous insulin should only be given once the blood glucose level is no longer falling with IV fluids alone, unless there is significant ketonaemia (>1 mmol/L). People with HHS tend to be more sensitive to the effects of insulin. Intravenous *insulin* is usually given at a reduced rate (compared to DKA) of 0.05 units/kg/h and should not exceed 4 U/h. Blood glucose should not fall by more than 5 mmol/L/h.

The underlying cause must be treated (e.g. antibiotics for suspected infection). People with HHS are at increased risk of venous and arterial thromboses, and *thromboprophylaxis* with low molecular weight heparin (e.g. enoxaparin or dalteparin) is essential. Fluid balance, urea and electrolytes, plasma glucose, and osmolality must be carefully monitored.

When the blood glucose reaches 15 mmol/L and the patient is able to eat:

- intravenous insulin can be tapered/stopped
- 0.9% saline is switched to 5% dextrose
- subcutaneous insulin or oral hypoglycaemic agents are started
- blood glucose monitoring is continued.

Reducing the serum glucose acutely below 14 mmol/L may promote the development of cerebral oedema. Once the intravenous insulin infusion has been stopped, blood glucose levels may start to rise if the individual has an underlying infection (which may have precipitated the HHS). Variable-rate insulin infusion may need to be started as for any poorly controlled diabetic patient with sepsis. Most people will be started on subcutaneous insulin regimens.

Foot protection to prevent development or worsening of pressure ulcers is mandatory. Feet should be examined daily.

Hypoglycaemia

Hypoglycaemia (lower than normal serum glucose concentration) is a common complication of treatment with insulin or oral hypoglycaemic agents (particularly long-acting sulfonylureas, e.g. glibenclamide). Hypoglycaemia is more common in people with type 1 diabetes mellitus and remains a significant

barrier to people achieving target blood glucose levels. Hypoglycaemia remains an important cause of morbidity and mortality in people with diabetes.

The responses to hypoglycaemia in people without diabetes include the ability to suppress insulin release and an increased release of counter-regulatory hormones (glucagon and adrenaline), which raise plasma glucose concentrations by stimulating gluconeogenesis and antagonising the insulin-induced increase in glucose utilisation.

In people with diabetes, the protective responses to hypoglycaemia are impaired: insulin is supplied exogenously and its release cannot be turned off. In addition, the glucagon and adrenaline response to hypoglycaemia becomes impaired later in the course of diabetes.

Recurrent hypoglycaemia itself also may contribute to the impaired counter-regulatory response. The compensatory increase in cortisol production during the first hypoglycaemic episode may play a role in minimising the protective hormonal responses during subsequent episodes.

People who have diabetes following a total pancreatectomy or pancreatitis have more frequent and severe episodes of hypoglycaemia because they lack glucagon-producing (alpha) cells as well as beta cells.

'Severe' hypoglycaemia is when a person with a hypoglycaemic episode requires assistance from a third party to manage it.

Clinical presentations

Hypoglycaemia causes symptoms of sympathetic overactivity (when the plasma glucose is <3.6 mmol/L) and symptoms of neuroglycopenia if the serum glucose concentration falls further (<2.6 mmol/L).

- The symptoms and signs of *sympathetic overactivity* include sweating, anxiety, tremor, tachycardia, palpitations, pallor, nausea, and hunger.
- The symptoms and signs of *neuroglycopenia* include dizziness, headache, visual disturbances, focal neurological defect (stroke-like syndromes), difficulty speaking, inability to concentrate, abnormal behaviour, confusion, drowsiness and ultimately loss of consciousness or seizures (blood glucose <1.5 mmol/L).

People whose diabetes is well controlled may have few warning symptoms when their plasma glucose concentration falls. These people may develop neuroglycopenia before sympathetic activation and complain of blunting, reduction or complete loss of the warning symptoms of hypoglycaemia (*impaired awareness of hypoglycaemia*, IAH). Hypoglycaemic episodes may lead to an upregulation of glucose transporters in the brain, resulting in the maintenance of glucose uptake and therefore the prevention of warning symptoms of hypoglycaemia.

Another factor that may contribute to IAH is diabetic autonomic neuropathy. Beta-blockers can also blunt the warning symptoms of sympathetic activation.

People with poorly controlled diabetes may develop sympathetic signs of hypoglycaemia when their blood glucose values fall to about 5 or 6 mmol/L. One mechanism by which this might occur is downregulation of glucose transporters in the brain in chronically hyperglycaemic people.

Investigations

Glucometers are often inaccurate at low blood glucose levels, and capillary blood glucose measurement must be confirmed by laboratory glucose measurements.

Urea and electrolytes must be measured as recurrent hypoglycaemia may be due to diabetic nephropathy. Diabetic nephropathy decreases insulin requirements as insulin is partly degraded by the kidney. Sulfonylureas are renally excreted. Recurrent unexplained hypoglycaemia should prompt consideration of endocrinopathies which result in loss of counter-regulatory hormones (e.g. Addison disease, growth hormone deficiency, hypothyroidism, and hypopituitarism).

Treatment

For people with diabetes who are hospital inpatients, any blood glucose less than 4.0 mmol/L should be treated.

If the patient is conscious and co-operative, he or she should receive 15–20 g of quick-acting carbohydrate (e.g. 5–7 Dextrosol® tablets or 4–5 Glucotabs®, 150–200 mL pure fruit juice, 3–4 heaped teaspoons of sugar dissolved in water, or 4–5 jelly babies). Capillary blood glucose should be checked again in 10–15 minutes, and if it is still below 4.0 mmol/L, more fast-acting glucose should be given.

If the individual has a reduced level of consciousness but is able to swallow, give either two tubes 40% glucose gel (e.g. Glucogel®) squeezed into the mouth between the teeth and gums or (if this is ineffective) glucagon 1 mg intramuscularly (this may be less effective in people prescribed sulfonylurea therapy or under the influence of alcohol).

If blood glucose remains less than 4.0 mmol/L after 30–45 minutes or 2–3 cycles of quick-acting carbohydrate, consider 1 mg glucagon (only one single dose)

or 150–200 mL of intravenous 10% glucose over 15 minutes. Once blood glucose is above 4.0 mmol/L and the patient has recovered, a long-acting carbohydrate should be given (e.g. two biscuits, one slice of bread/toast, 200–300 mL glass of milk [not soya or other forms of 'alternative' milk, e.g. almond or coconut], a normal meal if due which must contain carbohydrate).

In adults who are unconscious, having seizures and/or are very aggressive, after basic life support and any insulin infusions are stopped, give 75–100 mL of 20% glucose or 150–200 mL of 10% glucose intravenously over 15 minutes. Repeat capillary blood glucose measurement after 10 minutes and, if still less than 4.0 mmol/L, repeat. If no IV access is available, give glucagon.

People with hypoglycaemia should regain consciousness or become coherent within 10 minutes, although complete cognitive and neurological recovery may lag by 30–45 minutes. Subsequent regular doses of insulin should not be omitted but may need to be reduced. Bedtime snacks are the traditional strategy for preventing nocturnal hypoglycaemia. Individuals should not drive for 45 minutes after a 'hypo' and people who have more than one severe hypo in 12 months while awake should not drive and should inform the DVLA.

If hypoglycaemia is secondary to a sulfonylurea or long-acting insulin, people are at increased risk of further hypoglycaemia for 24–36 hours and may need to be admitted for intravenous infusion of 10% dextrose and blood glucose monitoring.

In those with hypoglycaemic unawareness, avoidance of hypoglycaemia for about 6 months can improve autonomic symptoms and restore hypoglycaemic awareness, even though counter-regulatory responses do not normalise.

All hospital wards and outpatient areas should have access to a 'hypo box' containing equipment and medications to treat hypoglycaemia.

KEY POINTS

- The triad of DKA consists of hyperglycaemia, high anion gap metabolic acidosis, and ketonaemia.
- Precipitating factors for DKA and HHS include infection, new-onset diabetes, inadequate insulin treatment or non-compliance, myocardial infarction, and stroke.
- Investigations in DKA include plasma or urinary ketones, blood glucose, venous gas analysis (pH, PCO_2, bicarbonate, chloride, lactate), urea and electrolytes, full blood count, a septic screen, and ECG.
- Close monitoring of blood glucose, capillary ketones, urine output, urea and electrolytes, and venous blood gas is critical.
- In HHS, there is little or no ketoacid accumulation, plasma glucose often exceeds 50 mmol/L, and plasma osmolality may reach 380 mosmol/kg.
- Treatment of DKA and HHS includes insulin, fluids and potassium replacement, treatment of the underlying condition, and thromboprophylaxis with low molecular weight heparins.
- Hypoglycaemia in a patient with a reduced level of consciousness should be treated with 75–100 mL of 20% glucose intravenously or 1 mg of intramuscular glucagon if there is no intravenous access.

37

Diabetic retinopathy

Diabetic retinopathy is a progressive ophthalmic microvascular complication of diabetes. Diabetic retinopathy is a major cause of morbidity in people with diabetes mellitus.

Epidemiology

Diabetic retinopathy (DR) is the leading cause of blindness in the UK's working-age population. The Wisconsin Epidemiologic Study of Diabetic Retinopathy showed that the prevalence of retinopathy increases progressively with increasing duration of disease in both type 1 and type 2 diabetes mellitus.

- In *type 1* diabetes, retinopathy starts to occur about 3–5 years after diagnosis. Retinopathy is present in almost all patients at 20 years after diagnosis.
- In *type 2* diabetes, some people have retinopathy at the time of diagnosis, reflecting the insidious onset of hyperglycaemia in type 2 diabetes. Retinopathy is present in 50–80% of people at 20 years.

Aetiology

The primary cause of DR is thought to be chronic hyperglycaemia. The Diabetes Control and Complications Trial (DCCT) and the United Kingdom Prospective Diabetes Study (UKPDS) found that glycaemic control reduces the incidence of retinopathy in type 1 and type 2 diabetes, respectively. There appears to be an, as yet poorly understood, genetic component to retinopathy. Within the DCCT, a threefold increase in severe retinopathy was seen in relatives of people with retinopathy compared to those without. Furthermore, some studies suggest increased risk in certain ethnic groups. Interestingly, although background retinopathy is a near-universal phenomenon after sufficient duration of diabetes, a significant minority of people with long-standing diabetes, without historically 'tight' glycaemic control, do not progress to proliferative retinopathy. This has generated considerable research interest in the protective factors that limit progression of DR.

The main hypotheses for the pathogenesis of DR include:

- impaired autoregulation of retinal blood flow
- inflammation
- retinal neurodegeneration.

Impaired autoregulation of retinal blood flow

Retinal blood flow autoregulation (i.e. maintenance of a constant blood flow despite an increase in the mean arterial pressure of less than 40% above baseline) is impaired in the presence of hyperglycaemia. The ensuing increase in retinal blood flow in people with diabetes may cause increased shear stress through apoptosis of pericytes on the retinal blood vessels, resulting in vascular leakage and production of vasoactive substances. The loss of pericytes and endothelial cells leads to capillary occlusion and ischaemia which activates hypoxia-inducible factor 1 and, in turn, upregulation of growth factors.

Inflammation

Inflammation and leucostasis are key components in the development of DR. Increased levels of inflammatory cytokines, chemokines, endothelial adhesion molecules and selectins are present. Plasma levels of E-selectin and vascular cell adhesion molecule (VCAM)-1 correlate with severity of DR. Glucose is metabolised to sorbitol within the retinal cells by the enzyme aldose reductase. The role of sorbitol in the

Endocrinology and Diabetes: Lecture Notes, Second Edition. Amir H. Sam, Karim Meeran and Neil Hill.
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pathogenesis of diabetic retinopathy is uncertain. During sorbitol production, consumption of nicotinamide adenine dinucleotide phosphate (NADPH) can result in oxidative stress. Sorbitol accumulation can lead to alterations in the activity of protein kinase C, which may mediate the activity of vascular endothelial growth factor (VEGF) and regulate vascular permeability.

Non-enzymatic combination between some of the excess glucose and amino acids in proteins results in the formation of advanced glycation endproducts (AGEs). AGEs may cross-link with collagen and initiate microvascular complications. In addition, the interaction between AGEs and their receptor (RAGE) may generate new reactive oxygen species and cause further vascular inflammation.

Retinal neurodegeneration

Apoptosis of retinal neurons has been observed in animal models of diabetes and appears to be an early event in the pathogenesis of DR, possibly driven by proapoptotic factors (e.g. caspases) and/or mitochondrial dysfunction. It may be independent of inflammatory and microvascular changes.

Other factors

Growth factors such as insulin-like growth factor-1 (IGF-1) and VEGF, and erythropoietin, may increase vascular permeability and promote the growth of new blood vessels. Basic fibroblast growth factor may also contribute to the progression of the retinal disease. Carbonic anhydrase appears to play a role in retinal vascular permeability in people with proliferative retinopathy. Genetic factors may affect the severity of retinopathy.

Clinical presentations

The majority of people who develop DR have no symptoms until the late stages, when it may be too late for effective treatment.

Rarely, people may present with sudden loss of vision due to retinal detachment or a vitreous haemorrhage, decreased visual acuity due to macular oedema, floaters during the resolution of vitreous bleeds or odd colours in the peripheral vision due to cataracts.

The various identifiable stages of DR are described as:

- *background* retinopathy
- *preproliferative* retinopathy (collectively, background and preproliferative retinopathy are referred to as non-proliferative diabetic retinopathy)
- *proliferative* retinopathy.

Emergency review by an ophthalmologist should be arranged for:

- sudden loss of vision
- rubeosis iridis
- preretinal or vitreous haemorrhage
- retinal detachment.

The UK National Screening Committee (NSC) has produced grading criteria describing various levels of disease (Box 37.1).

Box 37.1 National Screening Committee grading criteria for diabetic retinopathy

R0 – none

R1 – background

Microaneurysms

Retinal haemorrhages

Hard exudates

R2 – preproliferative

Cotton wool spots

Venous beading, loops, reduplication, intraretinal microvascular abnormalities (IRMAs)

Multiple deep, round, or blot haemorrhages

R3 – proliferative

New vessels on disc (NVD)

New vessels elsewhere (NVE)

Preretinal or vitreous haemorrhage

Preretinal fibrosis +/– retinal detachment

M0 – no maculopathy

M1 – maculopathy

Exudates within one disc diameter of the centre of the fovea

Microaneurysms or haemorrhage within one disc diameter of the centre of the fovea associated with visual acuity ≤6/12

Retinal thickening within one disc diameter of the centre of the fovea (if stereo available)

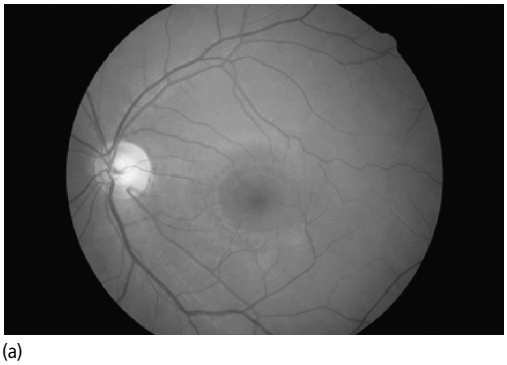
P – evidence of previous photocoagulation

Background retinopathy (R1)

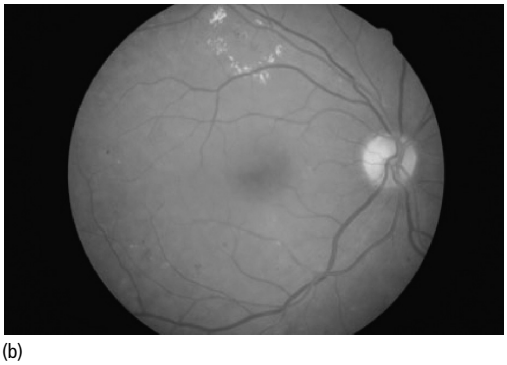
The early changes in diabetic retinopathy include death of the retinal pericytes, thickening of the retinal basement membrane, and impairment of its function. Pericytes are mesenchymal-like cells that support the walls of small blood vessels.

These changes are associated with the formation of retinal capillary *microaneurysms* (outpouchings of retinal capillaries with weakened walls partly due to pericyte loss) and increased vascular permeability, resulting in the leakage of lipid and proteinaceous material (*hard exudates*) (Figure 37.1). Capillary leakage often spreads in a circinate pattern.

The initial stage of cell death may be followed by cycles of renewal and further cell death. The intraluminal proliferation of cells, as well as changes in platelet function, erythrocyte aggregation and high plasma fibrinogen levels, can cause vascular occlusion and rupture. This can result in small flame-shaped and blot haemorrhages proximal to the occlusion.



(a)



(b)

Figure 37.1 (a) Normal retina with no retinopathy (NSC grade R0). (b) Background retinopathy with microaneurysms, haemorrhages, and hard exudates (NSC grade R1).

Preproliferative retinopathy (R2)

Intraretinal infarcts (*cotton wool spots* or *soft exudates*) may occur distal to microvascular occlusions (Figure 37.2). Proliferation of the endothelial cells of retinal veins results in venous calibre abnormalities, such as venous beading, loops, and dilation. IRMAs are dilated capillaries that occur in response to retinal ischaemia.

Proliferative retinopathy (R3)

Progressive microvascular occlusion and retinal ischaemia result in an increased release of vasoproliferative substances such as IGF-1 and VEGF, which promote the formation of new vessels (*neovascularisation*). New vessels (Figure 37.3) can arise from arteries or veins. The new vessels form a lace-like pattern with a fine mesh of fibrous tissue connecting them.

There are two main risks associated with new vessel formation:

- *Preretinal or vitreous haemorrhage:* the new vessels are fragile and therefore prone to rupture.
- *Retinal detachment:* as new vessels mature, the fibrous component becomes more prominent, resulting in contraction.

New vessel proliferation can also occur on the surface of the iris and in the anterior chamber. The latter change can cause glaucoma by blocking the outflow of the aqueous humour.

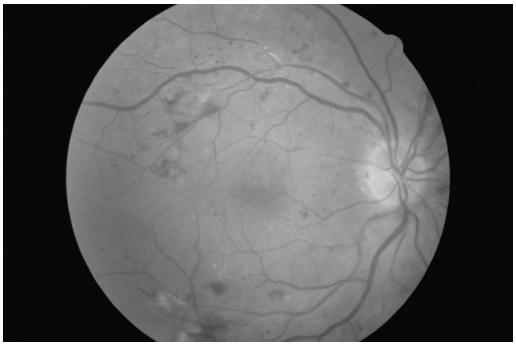
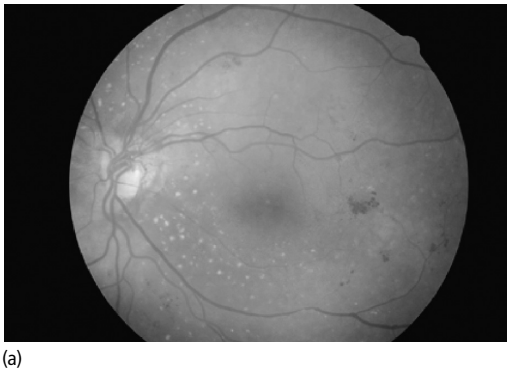


Figure 37.2 Preproliferative retinopathy (NSC grade R2) with cotton wool spots, intraretinal microvascular abnormalities, and multiple blot haemorrhages.



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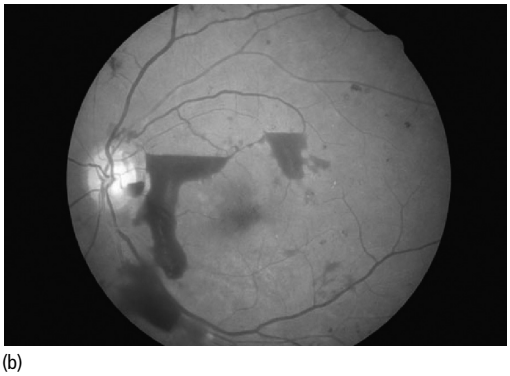

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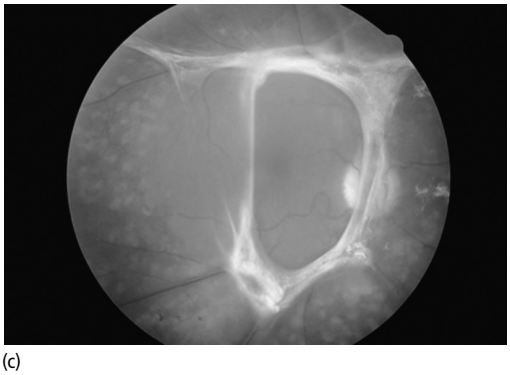

(c)

Figure 37.3 (a) Proliferative retinopathy (NSC grade R3) with new vessels at the optic disc. (b) Proliferative retinopathy with preretinal and vitreous haemorrhages (NSC grade R3). (c) Proliferative retinopathy with fibrous proliferation (NSC grade R3).

Maculopathy (M1)

Maculopathy is characterised by exudates or retinal thickening within one disc diameter of the centre of the fovea, or microaneurysms or haemorrhage within one disc diameter of the centre of the fovea associated with a best visual acuity of 6/12 or less (Figure 37.4).

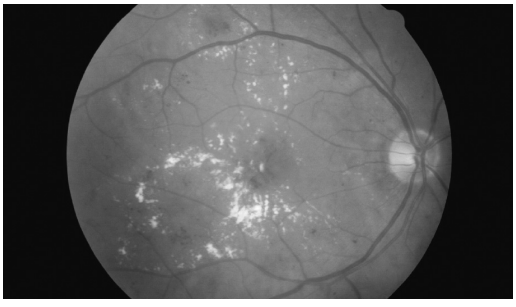

Figure 37.4 Diabetic maculopathy with haemorrhages and circinate exudates (NSC grade R2 M1).

Macular oedema

Macular oedema is characterised by retinal thickening due to leaky blood vessels and can develop at any stage of retinopathy. It typically presents with a gradual-onset blurring of near and distant vision. Macular oedema is difficult to detect on routine examination. People with suspected macular oedema should be referred to an ophthalmologist for a slit lamp examination (to detect thickening) and fluorescein angiography (to detect local leakage associated with oedema).

Exacerbation of retinopathy in pregnancy

Diabetic retinopathy may worsen during pregnancy. The Diabetes in Early Pregnancy (DIEP) study showed that the risk of progression of retinopathy is related to the severity of retinal involvement before pregnancy and the initial glycated haemoglobin (HbA_{1c}) values. Changes in hormones, growth factors and systemic haemodynamics, and lower retinal blood flow may contribute to the exacerbation of retinopathy in pregnancy.

Transient exacerbation of retinopathy with intensive insulin therapy

Data from the DCCT and other trials suggest that intensive insulin therapy may be associated with a transient worsening of retinopathy during the first year. This may result from closure of the small retinal blood vessels due to reduced plasma volume caused by the correction of hyperglycaemia. Increased IGF-1 levels may also contribute to the exacerbation of retinopathy.

Screening

It is important to screen people with diabetes regularly with digital retinal photography for the development of retinopathy. People with NSC grades R0 and R1 need annual screening. Those with NSC grade R3 should be seen by hospital eye service/specialists immediately. Those with NSC grade R2 or M1 should be seen by hospital eye service/specialists urgently (within 4 weeks).

Treatment

Treatment of diabetic retinopathy is directed both at reducing the risk and progression of retinopathy, and at the treatment of established disease.

Reducing risk and progression of retinopathy

Glycaemic control

Strict *glycaemic control* is effective in primary prevention in people without retinopathy, and in slowing the rate of progression of retinopathy in people with mild-to-moderate non-proliferative retinopathy. However, it is of little or no benefit in people with advanced retinopathy. Despite the general efficacy of glycaemic control, there is often transient worsening of the retinopathy during the first year of intensive glycaemic management (see above).

The DCCT found that intensive insulin therapy reduced the incidence of new cases of retinopathy in type 1 diabetics by 76% compared with conventional therapy. Progressive retinopathy was uncommon in people with an HbA_{1c} below 53 mmol/mol. The UKPDS showed that each 11 mmol/mol point reduction in HbA_{1c} in people with type 2 diabetes was associated with a 37% reduction in the development of retinopathy.

Blood pressure control

Control of hypertension slows the rate of progression of diabetic retinopathy. The UKPDS showed that people with lower blood pressures had a reduced deterioration in retinopathy and visual acuity.

Lisinopril (an angiotensin-converting enzyme inhibitor) has been reported to reduce the progression of retinopathy in normotensive people with type 1 diabetes. The mechanism by which angiotensin-converting enzyme inhibitors might inhibit the progression of retinopathy is unclear.

Multifactorial risk reduction

The Steno-2 trial showed that intensive risk factor reduction in people with type 2 diabetes and microalbuminuria (using behavioural therapy, advice regarding diet, exercise and smoking cessation, and the administration of multiple medications to achieve several aggressive therapeutic goals) reduced the development or progression of retinopathy.

Antiplatelet agents

The Early Treatment of Diabetic Retinopathy Study reported that aspirin has no beneficial effect on the development or progression of proliferative retinopathy, vitreous bleeding or visual loss. However, there were no ocular contraindications to its use in persons with diabetes who required aspirin for the treatment of cardiovascular disease or for other medical indications.

Fibrates

Data from two large randomised controlled trials showed a reduction in progression of diabetic retinopathy in those with established retinopathy at baseline. However, further clinical and experimental studies are needed before fenofibrate can be launched as a new tool in the management of diabetic retinopathy.

Treatment of established retinopathy

Photocoagulation

Laser photocoagulation (Figure 37.5) is the primary treatment for advanced retinopathy and reduces the risk of developing visual loss. Early photocoagulation is not usually recommended except for focal laser therapy used to treat macular oedema. This therapy reduces the risk of visual loss. With aggressive monitoring and treatment, good visual acuity can be maintained.

Intravitreal steroids

Intravitreal triamcinolone injection may be used for refractory macular oedema and in cases that do not respond to anti-VEGF therapy, and may improve visual acuity.

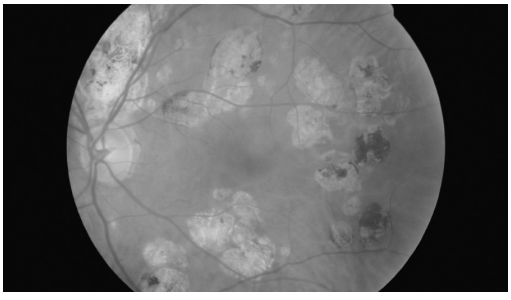

Figure 37.5 Evidence of previous laser photocoagulation (NSC grade P).

The treatment response in diabetic macular oedema may be transient, and repeated injections are often necessary. However, intravitreal steroid implants may reduce the need for multiple injections.

Vitrectomy

Vitrectomy can also be used to preserve useful vision in advanced cases. Removal of the opaque vitreous humour followed by photocoagulation to the retina can restore some functional vision. The timing of such interventions is critical.

Growth factor inhibitors

As mentioned above, VEGF increases retinal vascular permeability. The effects of VEGF are mediated, in part, by protein kinase C.

A number of VEGF inhibitors have been approved for use in the treatment of diabetic retinopathy, including pegaptanib, ranibizumab, bevacizumab, and aflibercept, and have demonstrated improvements in visual acuity and other visual outcomes. Non-specific antiangiogenic agents are also undergoing clinical trials.

Pregnancy

The modest increase in risk of worsening of retinopathy during pregnancy necessitates more frequent retinal evaluations during this time and for 1 year post partum. Women should be screened during the first trimester and then every 3 months while pregnant. Treatment recommendations are the same as for other people. Laser therapy and vitreous surgery can be carried out safely during pregnancy if required. Women can be reassured that their long-term risk of retinopathy progression is not increased by pregnancy.

KEY POINTS

- Diabetic retinopathy is a progressive ophthalmic microvascular complication of diabetes.
- Glycaemic control reduces the incidence of retinopathy in both type 1 and type 2 diabetes.
- Control of hypertension slows the rate of progression of diabetic retinopathy.
- The majority of people who develop diabetic retinopathy have no symptoms until the late stages. Therefore, it is important to screen people with diabetes regularly for the development of retinopathy.
- The various identifiable stages of diabetic retinopathy are described as background retinopathy, preproliferative retinopathy, and proliferative retinopathy.
- People with proliferative retinopathy should be seen by hospital eye service/specialists immediately. People with preproliferative retinopathy and those with maculopathy should be seen urgently by hospital eye service/specialists.
- Laser photocoagulation is the primary treatment for advanced retinopathy and reduces the risk of developing visual loss.

38

Diabetic nephropathy

Diabetic nephropathy (kidney disease) occurs in both type 1 and type 2 diabetes mellitus.

The natural history of diabetic nephropathy is characterised by a fairly predictable sequence of events (Figure 38.1). Glomerular hyperperfusion, increased glomerular filtration, and increased kidney size (renal hypertrophy) occur in the first years after the onset of diabetes.

The earliest clinical finding of diabetic nephropathy is *microalbuminuria*. Microalbuminuria is defined as the persistent excretion of small amounts of albumin (30–300 mg per day) into the urine. Microalbuminuria is an important predictor of progression to *proteinuria* (>300 mg per day). Once proteinuria appears, there is a steady decline in the glomerular filtration rate (GFR). People with microalbuminuria or reduced GFR are at increased risk of *end-stage renal disease* and premature cardiovascular morbidity and mortality.

The major histological changes in the glomeruli in diabetic nephropathy include:

- *expansion of the mesangium* (glomerular supporting tissues)
- *glomerular basement membrane thickening*
- *glomerular sclerosis*.

Diabetic glomerular sclerosis may be diffuse or nodular. The latter is known as the *Kimmelstiel–Wilson lesion*. Nodular glomerular sclerosis is usually associated with hyaline deposits in the glomerular arterioles, reflecting the insinuation of plasma proteins such as albumin, fibrin, immunoglobulins, and complement into the vascular wall.

People with type 1 diabetes and nephropathy almost always have retinopathy. However, the converse is not true. Most people with advanced retinopathy have little or no renal disease as assessed by renal biopsy and protein excretion. The relationship between diabetic nephropathy and retinopathy is less predictable in type 2 diabetes.

Type IV renal tubular acidosis (hyporeninaemic hypoaldosteronism) also occurs in diabetes mellitus. People develop a propensity to hyperkalaemia.

People with diabetes are predisposed to radiocontrast-induced nephrotoxicity. People with diabetes undergoing radiological investigations with contrast dye should be well hydrated before and after the procedure, and the serum creatinine should be monitored for several days after imaging. Consider temporarily stopping metformin, angiotensin-converting enzyme (ACE) inhibitors, angiotensin II receptor blockers (ARB)s, and other nephrotoxic agents in people having iodinated contrast agents if they have chronic kidney disease with an eGFR <40 mL/min/1.73 m^2 for at least 48 hours.

Pathogenesis

Figure 38.2 shows a simplified model for the pathogenesis of diabetic nephropathy. The mechanisms by which diabetes leads to nephropathy involve advanced glycation endproducts (AGEs), cytokines, growth factors, angiotensin II, and haemodynamic factors.

Hyperglycaemia results in increased *reactive oxygen species* (by increased activation of mitochondrial electron transport) and *AGEs* (generated by non-enzymatic combination of the excess glucose with amino acids in proteins). These in turn activate a number of signalling pathways involving *protein kinase C*, *mitogen-activated protein kinase* (MAPK) and *transforming growth factor* (TGF)-*beta*, resulting in the accumulation of extracellular matrix proteins (e.g. collagen type IV and fibronectin) in the mesangial space, and 'glomerulosclerosis' (fibrosis in the renal glomeruli). Diabetes is associated with a reduced expression of renal bone morphogenic protein-7 (BMP-7), which appears to counter the profibrogenic actions of TGF-beta.

Endocrinology and Diabetes: Lecture Notes, Second Edition. Amir H. Sam, Karim Meeran and Neil Hill.
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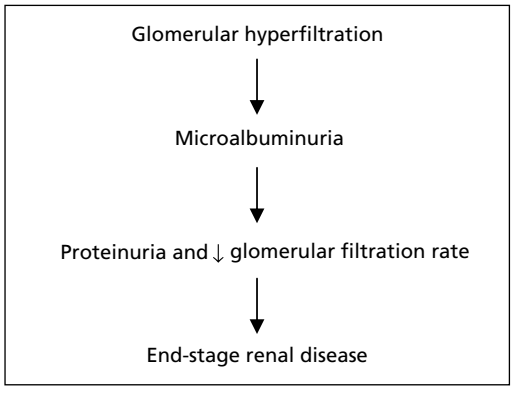


Figure 38.1 Sequence of events in diabetic nephropathy.

Haemodynamic factors including systemic hypertension and *glomerular hypertension* contribute to the pathogenesis of diabetic nephropathy. Diabetes is associated with impaired renal autoregulation. As a result, increased systemic blood pressure does not produce the expected afferent arteriolar vasoconstriction and leads to intraglomerular hypertension. Glomerular hypertension, the resultant mesangial cell stretch and *angiotensin II* also stimulate glomerulosclerosis.

Other factors that may play a role in the development of diabetic nephropathy include increased plasma *prorenin* activity (which activates MAPK), increased expression of *heparanase* (causing a loss of negatively charged heparan sulfates and increased glomerular basement membrane permeability to albumin) and a reduced expression of renal *nephrin* (a transmembrane protein expressed by podocytes).

In addition to mesangial cells, glomerular endothelial cells, podocytes, and tubular epithelial cells are also targets of hyperglycaemic injury. There is substantial cross-talk between endothelial cells, podocytes and mesangial cells. *Endothelial dysfunction* and *podocyte damage* may result in diabetic glomerulosclerosis.

The likelihood of developing diabetic nephropathy is markedly increased in people with a sibling or parent who has diabetic nephropathy. A number of factors, such as increasing age, race, obesity, smoking, and oral contraceptive use, may increase the risk of developing diabetic nephropathy.

Epidemiology

Diabetic nephropathy is the most common cause of end-stage renal disease in the UK and the USA.

Type 1 diabetes

After 10 years of type 1 diabetes, 20–30% of people will have microalbuminuria. Less than 50% of people with microalbuminuria will progress to proteinuria over an average period of 5–10 years. In total, 50% of people with proteinuria reach end-stage renal disease after 10 years. Those people who have no proteinuria after 20–25 years have a risk of developing overt renal disease of only about 1% per year.

Microalbuminuria may regress or remain stable with improved glycaemic and blood pressure control and the use of ACE inhibitors.

Type 2 diabetes

At 10 years following diagnosis, 25% of people have microalbuminuria. The time from the onset of diabetes to proteinuria (around 15 years) and the time from onset of proteinuria to end-stage renal disease (around 10 years) are similar in type 1 and type 2 disease.

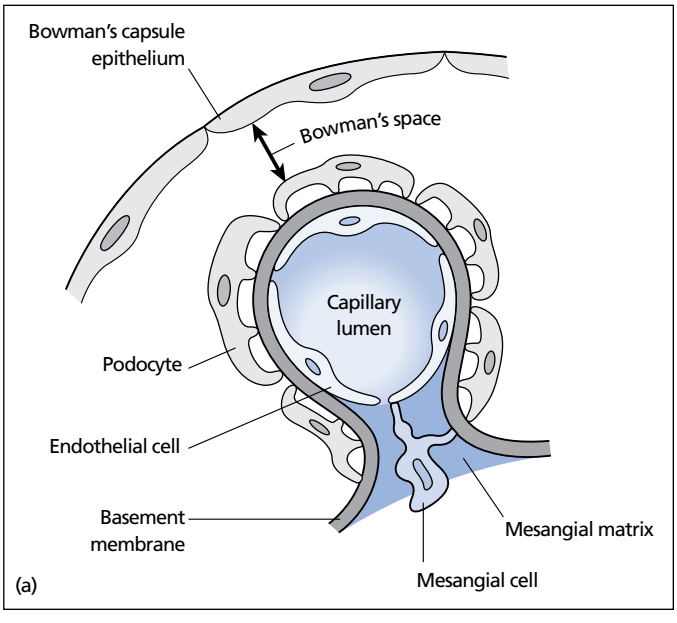
Microalbuminuria may be present in about 8% of people with type 2 diabetes at diagnosis. This may be due to an initial delay in the diagnosis. The incidence and severity of diabetic nephropathy are increased in African-Americans, Mexican-Americans, and Pima Indians.

Diagnosis

Microalbuminuria is not detected by a simple urine dipstick. As part of routine diabetes follow-up, a spot urine sample must be sent to the laboratory for measurement of urine albumin and creatinine concentrations. The latter compensates for variations in urine concentration in spot-check samples. Microalbuminuria is defined as an *albumin-to-creatinine ratio* (ACR) above 2.5 g/mol in men or above 3.5 g/mol in women.

If microalbuminuria is detected, conditions that transiently increase albumin extraction must be excluded and the test should be repeated. Urinary tract infection, fever, exercise, menstruation, cardiac failure, and poor glycaemic control can cause transient microalbuminuria. A persistent elevation in albumin excretion should be demonstrated for establishing the diagnosis of microalbuminuria. If two of the three spot urine tests are positive, treatment should be started.

If the spot urine dipstick detects proteinuria (>300 mg per day), a 24-hour urine collection may be requested to quantify the proteinuria.



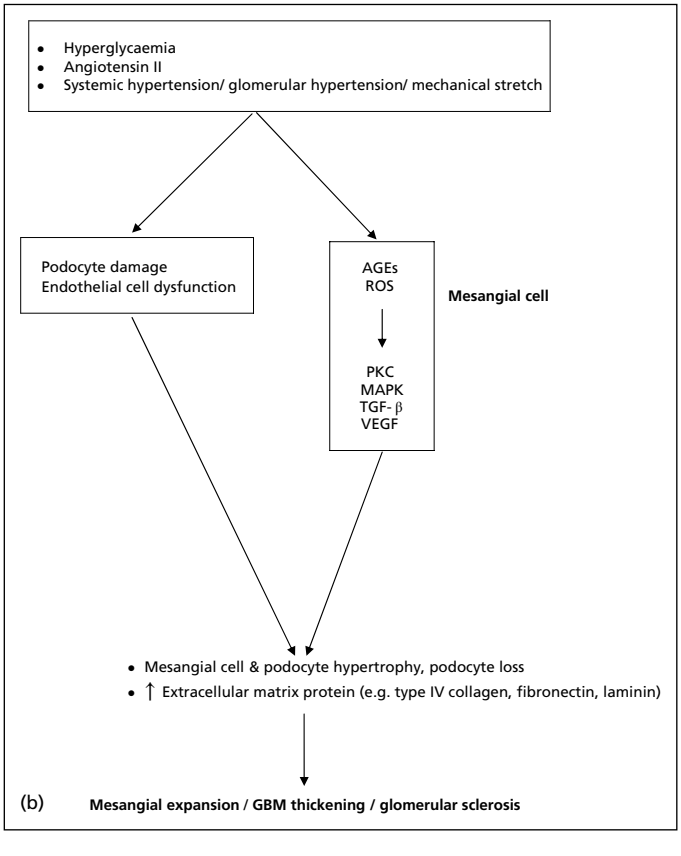


Figure 38.2 (a) Glomerular cells. (b) Simplified model of pathogenesis of diabetic nephropathy. AGEs, advanced glycation end-products; GBM, glomerular basement membrane; MAPK, mitogen-activated protein kinases; PKC, protein kinase C; ROS, reactive oxygen species; TGF, transforming growth factor; VEGF, vascular endothelial growth factor.

Serum creatinine is regularly monitored in diabetic people. However, it is an inaccurate reflection of the GFR. The *estimated glomerular filtration rate* (eGFR) should be calculated by the MDRD (Modification of Diet in Renal Disease study) equation using serum creatinine, age, sex and race.

In people with diabetes who have raised serum creatinine, other causes of kidney disease should be excluded. Blood tests for autoimmune renal disease (erythrocyte sedimentation rate, antinuclear antibodies, antineutrophil cytoplasmic antibodies, anti-double-stranded DNA antibodies, antiglomerular basement membrane antibodies, complement), myeloma (serum protein electrophoresis) and prostate-specific antigen, urine microscopy, and a renal ultrasound should be performed.

When eGFR falls below 60 mL/min/1.73 m^2, the full blood count, calcium, phosphate, and parathyroid hormone (PTH) should be monitored every 6 months. If the PTH is elevated, 25-hydroxyvitamin D should be measured.

Indications for referral to nephrologists include:

- eGFR less than 45 mL/min/1.73 m^2
- doubt about the diagnosis
- blood pressure control not achieved
- active urine sediment (i.e. urine containing red cells and cellular casts)
- anaemia
- phosphate over 1.8 mmol/L or PTH more than twice the upper limit of normal.

The clinical clues suggesting glomerular disease *other than diabetes* include:

- an acute onset of renal disease or onset of proteinuria less than 5 years from the onset of diabetes. However, this is more difficult to ascertain in type 2 diabetes as the true onset of disease is not known
- an active urinary sediment
- the absence of diabetic retinopathy or neuropathy in type 1 diabetes
- signs and/or symptoms of other systemic diseases
- a significant decrease in the GFR (>30%) within 2–3 months of starting ACE inhibitors or ARBs.

Treatment

The risk of progression of diabetic nephropathy may be reduced by:

- ACE inhibitors and ARBs
- blood pressure control
- control of glycaemia
- diet: protein restriction.

ACE inhibitors and ARBs

ACE inhibitors reduce blood pressure as well as glomerular pressure. They also antagonise the profibrotic effects of angiotensin II (see 'Pathogenesis', above). ACE inhibitors decrease microalbuminuria and reduce the risk of progression of proteinuria in both type 1 and type 2 diabetes. A drug-specific benefit in diabetic nephropathy independent of blood pressure control has been shown for ARBs in type 2 diabetes.

The dose of ACE inhibitor should be titrated up until either the microalbuminuria disappears or the maximum dose is reached. If the use of ACE inhibitors is limited by their side-effects (e.g. hyperkalaemia or cough), ARBs can be used as alternatives. Serum potassium must be monitored. A mild chronic increase in potassium is acceptable but ACE/ARB treatment should be stopped if the serum potassium level is above 6.0 mmol/L and other drugs that are known to cause hyperkalaemia have been discontinued. Combining ARBs with ACE inhibitors is not effective and not indicated because of the risk of hyperkalaemia.

Blood pressure control

The effectiveness of strict *blood pressure control* in slowing the decline in renal function has been shown in several studies. In people with nephropathy due to type 1 diabetes, higher blood pressures are associated with a worsening of microalbuminuria. In the United Kingdom Prospective Diabetes Study (UKPDS), tighter blood pressure control was associated with a reduced risk of microalbuminuria in type 2 diabetes.

Blood pressure targets for people with diabetes vary according to different guidelines, depending on age and cardiovascular risk. Blood pressure should be maintained at less than 130/80 mmHg in people with diabetes.

Glycaemic control

Improved *glycaemic control* has been shown to reduce the rate of development and progression of nephropathy. The Diabetes Control and Complications Trial (DCCT) showed that tight glycaemic control in type 1 diabetes reduces the risk of development and progression of microalbuminuria by approximately 40% and 54%, respectively. In the UKPDS, tight glycaemic control resulted in a 33% relative risk reduction for the development of microalbuminuria in type 2 diabetes. In people with albuminuria and reduced renal

function (eGFR 30–90 mL/min/1.73 m^2), canagliflozin has been shown to improve renal outcomes and reduce mortality.

Insulin requirements may decrease during the phase of declining renal function, as the kidney is a site of insulin degradation. Metformin and sulfonylureas are contraindicated in advanced renal failure.

Other treatments

In a meta-analysis of smaller studies, *protein restriction* has been shown to reduce the decline in GFR. A consensus panel of the American Diabetes Association suggests a restriction of protein intake to 0.8 g/kg per day in people with microalbuminuria or to less than 0.8 g/kg per day in overt nephropathy.

The leading cause of death in people with diabetes on dialysis is cardiovascular disease. Hyperlipidaemia should be treated aggressively with statins. Stopping smoking is also likely to be of renal benefit.

People with end-stage renal disease require dialysis. Haemodialysis in people with diabetes is associated with more frequent complications such as hypotension (caused by autonomic neuropathy) and more difficult vascular access. Following the onset of end-stage renal disease, survival is shorter in people with diabetes compared with those without diabetes but with similar clinical features.

KEY POINTS

- The earliest clinical finding of diabetic nephropathy is microalbuminuria.
- Microalbuminuria is an important predictor of progression to proteinuria, reduced GFR, and end-stage renal disease.
- The mechanisms by which diabetes leads to nephropathy involve AGEs, reactive oxygen species, signalling pathways involving protein kinase C, MAPK, growth factors, angiotensin II, and haemodynamic factors.
- The average time from the onset of diabetes to proteinuria is 15 years, and the average time from the onset of proteinuria to end-stage renal disease is 10 years.
- As part of the diabetic follow-up, a spot urine sample must be sent to the laboratory for measurement of urine ACR. Microalbuminuria is defined as an ACR above 2.5 g/mol in men or above 3.5 g/mol in women.
- Strict blood pressure and glycaemic control, ACE inhibitors, ARBs, and protein restriction reduce the risk of progression of diabetic nephropathy.

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Diabetic neuropathy

In diabetic neuropathy, both myelinated and unmyelinated nerve fibres are lost. The development of diabetic neuropathy correlates with the duration of diabetes and glycaemic control. In diabetic neuropathy, the distal sensory and autonomic fibres are preferentially affected.

Epidemiology

The prevalence of neuropathy is estimated to be around 34% in type 1 diabetes and 26% in type 2 diabetes. Clinically detectable neuropathy occurred in 10% of people with type 1 diabetes after 5 years of enrolment in the Diabetes Control and Complications Trial (DCCT). The incidence of neuropathy in type 2 diabetes is about 6% per year.

Pathogenesis

Metabolic and vascular factors and impaired nerve repair mechanisms are likely to contribute to the pathogenesis of diabetic neuropathy.

Metabolic risk factors

Metabolic factors that have been implicated in the pathogenesis of diabetic neuropathy include the following:

- *Advanced glycosylation end-products (AGEs):* AGEs are formed by non-enzymatic combination of some of the excess glucose with amino acids in proteins. Advanced glycosylation of essential nerve proteins has been implicated in the pathogenesis of diabetic neuropathy.
- *Sorbitol:* glucose that enters cells is metabolised in part by the enzyme aldose reductase to sorbitol. This process is more pronounced with chronic hyperglycaemia. The accumulation of intracellular sorbitol in tissues such as peripheral nerves results in a rise in cell osmolality, a decrease in intracellular myoinositol and Na–K-ATPase activity, and a slowing of nerve conduction velocities.
- *Oxidative stress:* hyperglycaemia results in the accumulation and stabilisation of reactive oxygen species, which may damage peripheral nerves.
- Other proposed mechanistic pathways, all mediated via hyperglycaemia, include increased glucose flux through the hexosamine pathway, high levels of protein kinase C, and activation of poly (ADP-ribose) polymerase leading to enhanced free radical formation.

Vascular risk factors

Morphological abnormalities of the vasa nervorum (small arterioles supplying the nerves) are present early in the course of diabetic polyneuropathy, and parallel the severity of the nerve fibre loss. This may be mediated through reduced oxygen tension leading to neural ischaemia.

The prospective EURODIAB study showed that the incidence of neuropathy in type 1 diabetes is associated with potentially modifiable cardiovascular risk factors, including a raised triglyceride level, raised body mass index, smoking, and hypertension.

Thrombomodulin and tissue plasminogen activator levels are reduced in peripheral nerve microvessels from people with diabetes. This suggests that an impairment of antithrombotic mechanisms may play a role in the pathogenesis of diabetic polyneuropathy.

Impairment of peripheral nerve repair

Loss of neurotrophic peptides that mediate nerve repair and regeneration may contribute to the pathogenesis of diabetic neuropathy. These peptides include

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nerve growth factor, brain-derived neurotrophic factor, neurotrophin-3, the insulin-like growth factors, and vascular endothelial growth factor.

Clinical presentations

Diabetic neuropathy may manifest as:

- distal symmetrical polyneuropathy
- polyradiculopathy
- mononeuropathy
- autonomic neuropathy.

Distal symmetrical polyneuropathy

Distal symmetrical polyneuropathy is the most common form of diabetic neuropathy. People may present with distal (glove and stocking distribution) sensory loss or paraesthesia, i.e. a sensation of numbness, tingling, burning, or sharpness that starts in the feet and spreads proximally. Some people develop neuropathic pain, typically involving the lower extremities, usually at rest and worst at night. This is occasionally preceded by improvements in glycaemic control. Painful diabetic neuropathy may be acute (lasting less than 12 months) or chronic.

Signs of distal symmetrical polyneuropathy include loss of pinprick, temperature, vibration, and joint position sensation, and diminished ankle reflexes.

Polyradiculopathy

Diabetic polyradiculopathy is characterised by severe pain in the distribution of one or more nerve roots. Diabetic polyradiculopathy usually resolves over 6–12 months. Pain over the chest or abdomen may be due to intercostal or truncal radiculopathy. Sensory symptoms may be accompanied by muscle weakness. People with involvement of the lumbar plexus may present with thigh or hip pain and weakness of the hip flexors or extensors (*diabetic amyotrophy*).

Mononeuropathy

People with diabetes may present with motor weakness and pain in the distribution of a single cranial or peripheral nerve (e.g. cranial nerves III, IV, VI, or VII, median, ulnar or peroneal nerve). Mononeuropathy is less common than polyneuropathy. The most common presentation of mononeuropathy in people with diabetes is ptosis and ophthalmoplegia due to *IIIrd cranial nerve palsy*. People may also present with simultaneous involvement of more than one nerve (mononeuropathy multiplex).

Autonomic neuropathy

Long-standing diabetes may lead to autonomic dysfunction involving the cholinergic, noradrenergic, and peptidergic (e.g. substance P, pancreatic polypeptide) systems. Autonomic neuropathy usually involves multiple systems:

- *Cardiovascular*: there may be resting tachycardia, *postural hypotension*, neuropathic oedema (due to loss of sympathetic vascular innervation and increased peripheral blood flow through arteriovenous shunts).
- *Gastrointestinal*: delayed gastric emptying (*gastroparesis*) may present with anorexia, nausea, vomiting, early satiety, and bloating. Altered small and large bowel motility (autonomic enteropathy) may present with unexplained diarrhoea (particularly at night) and/or constipation.
- *Genitourinary*: bladder dysfunction (inability to sense a full bladder, failure to void completely, incontinence, recurrent urinary tract infection), erectile dysfunction, retrograde ejaculation, and female sexual dysfunction (reduced libido, reduced vaginal lubrication and dyspareunia) can occur.
- *Hypoglycaemia unawareness* arises when reduced adrenaline release results in a loss of the adrenergic symptoms of hypoglycaemia.
- Hyperhidrosis (upper extremities), anhidrosis (lower extremities, resulting in dry skin and cracking of the feet and an increased risk of foot ulcers).

Diagnosis

Diabetic neuropathy should be suspected in all people with type 2 diabetes and in any patient with type 1 diabetes of more than 5 years' duration.

Pinprick, temperature, vibration (using a 128 Hz tuning fork) and pressure sensation (using a 10 g monofilament) must be examined to assess sensory function.

The clinical features of diabetic neuropathy are similar to those of other neuropathies (Box 39.1). Metformin can be associated with low vitamin B12 levels, and this should be checked. Other possible aetiologies should be excluded before a diagnosis of diabetic neuropathy is made.

Box 39.1 Differential diagnosis of diabetic neuropathy

Uraemia

Vitamin B12/folate deficiency

Hypothyroidism

Amyloidosis, acute intermittent porphyria

Toxins: alcohol, medications (e.g. chemotherapy), heavy metals (lead, mercury)

Inflammation: chronic inflammatory demyelinating polyneuropathy, connective tissue diseases/vasculitis

Infection: HIV, leprosy

Paraneoplastic syndromes

Hereditary sensory and motor neuropathy

In the Rochester Diabetic Study, the most sensitive tests for the diagnosis of diabetic neuropathy were nerve conduction studies and autonomic testing by using heart rate change (R–R interval on the electrocardiogram) during the Valsalva manoeuvre.

When *gastroparesis* is suspected, an upper endoscopy or a barium meal should be performed to exclude mechanical obstruction and mucosal disease. These tests may also show retained food after an overnight fast (but although supportive, are not diagnostic of gastroparesis). Computed tomographic enterography or magnetic resonance enterography or barium follow-through examination is necessary in people with colicky abdominal pain to exclude a small bowel lesion.

The best study to document gastroparesis is nuclear medicine scintigraphy after the ingestion of a radiolabelled meal. Gastric retention of more than 60% at 2 hours and more than 10% at 4 hours is abnormal. Wireless motility capsules and ^{13}C breath testing are also sometimes used. In people with type 1 diabetes and enteropathy, coeliac disease must be excluded.

Diagnostic evaluation of diabetic *bladder dysfunction* includes cystometry and urodynamic studies.

Treatment

Chronic painful diabetic neuropathy is difficult to treat. With tighter glycaemic control, clinically detectable neuropathy is reduced in both type 1 (DCCT findings) and type 2 diabetes. Although tighter glycaemic control improves nerve conduction velocity, existing symptoms may not improve. Hypoglycaemic unawareness due to autonomic neuropathy may limit efforts to optimise glycaemic control.

Pain control

Tricyclic antidepressants (e.g. amitriptyline) are useful in the treatment of painful neuropathy. However, their use may be limited by side-effects such as sedation.

Duloxetine is also effective in reducing pain scores. Side-effects include somnolence and constipation. Gabapentin and pregabalin may also be used. Tramadol should only be used for acute rescue therapy. Capsaicin cream can be used for localised neuropathic pain in people who wish to avoid or cannot take oral therapy. Other agents used for painful neuropathy in specialist settings include oxycodone, morphine, nortriptyline, desipramine, carbamazepine, phenytoin, lamotrigine, and venlafaxine. Difficult cases should be referred to pain management teams.

Surgical decompression or steroid injection should be considered for people with carpal tunnel syndrome.

Postural hypotension

Exacerbating drugs (e.g. tranquillisers, antidepressants, diuretics) should be discontinued if possible. Dorsiflexion of the feet before standing, standing slowly in 'stages', and tensing the legs by crossing them while standing may be helpful. Body stockings and gravity suits (used to increase peripheral vascular tone) may also be used but have limited success.

Medical treatment of postural hypotension consists of increasing the plasma volume with the mineralocorticoid *fludrocortisone* (100–400 µg per day), a high-salt diet and adequate hydration. However, this regimen can cause hypertension or peripheral oedema. Treatment of anaemia, if present, may also be helpful.

Other treatments that have been tried with variable success include atrial tachypacing, midodrine (alpha-adrenoreceptor agonist), fluoxetine, and desmopressin. The somatostatin analogue octreotide may be tried (50 µg three times a day, subcutaneously) in refractory and symptomatic postural or postprandial hypotension.

Neuropathic oedema

Sympathomimetic drugs such as midodrine and ephedrine can reduce arteriovenous shunting and may have a beneficial effect on neuropathic oedema.

Non-pharmacological treatments include foot elevation when sitting and support stockings.

Careful foot care is essential to prevent foot infection and ulceration. People with diabetic neuropathy should be referred to a podiatrist. The patient must be advised to carefully inspect his or her feet daily.

Gastroparesis

Symptoms of gastroparesis may be minimised by more frequent, smaller meals that are easier to digest (liquid) and are low in fat and fibre. Optimising glycaemic control may improve gastric function. Prokinetics such as metoclopramide (5–10 mg three times a day), domperidone (10–20 mg three times daily), and erythromycin (125–250 mg three times daily) may be used. Metoclopramide and domperidone are dopamine antagonists. Erythromycin interacts with the motilin receptor.

People who are unable to maintain their nutritional status or adequate hydration orally may require jejunal feeding tubes.

Autonomic enteropathy

Treatment of diabetic autonomic enteropathy includes loperamide (for diabetic diarrhoea in the absence of bacterial overgrowth), rotating antibiotics (for bacterial overgrowth), and stool softeners for constipation. Some people with intractable diarrhoea may respond to octreotide.

Bladder dysfunction

Treatment of urinary retention initially consists of a strict voluntary urination schedule. Scheduled urinations may be coupled with bethanechol, which increases detrusor muscle contraction. More advanced cases require intermittent self-catheterisation and, in extreme cases, resection of the internal sphincter at the bladder neck.

Sexual dysfunction

Oral sildenafil (a phosphodiesterase type 5 inhibitor) is an effective and well-tolerated treatment for erectile dysfunction in men with diabetes. Retrograde ejaculation has been treated with an antihistamine. Treatment for female sexual dysfunction involves vaginal lubricants and oestrogen creams.

KEY POINTS

- The development of diabetic neuropathy correlates with the duration of diabetes and with glycaemic control.
- Diabetic neuropathy may manifest as distal symmetrical polyneuropathy, polyradiculopathy, mononeuropathy, and autonomic neuropathy.
- Distal symmetrical polyneuropathy is the most common form of diabetic neuropathy.
- With tighter glycaemic control, clinically detectable neuropathy is reduced in both type 1 and type 2 diabetes.
- Tricyclic antidepressants and duloxetine are usually the first-line treatments for pain control in diabetic neuropathy.
- Medical treatment of postural hypotension consists of increasing the plasma volume with the mineralocorticoid fludrocortisone, a high-salt diet, and adequate hydration.

40

Musculoskeletal and dermatological manifestations of diabetes

Diabetic foot ulcers and infections comprise the most common dermatological and musculoskeletal complications of diabetes. Neuropathic arthropathy (Charcot joint) and other musculoskeletal and dermatological manifestations of diabetes are covered in later sections of this chapter.

Diabetic foot ulcers

Foot ulcers are a major cause of hospitalisation, morbidity, and mortality in people with diabetes. Diabetic foot ulcers account for a significant proportion of all non-traumatic amputations (e.g. about two-thirds in the USA). The lifetime risk of a foot ulcer for people with diabetes (type 1 or 2) may be as high as 25%.

Aetiology

Diabetic foot problems are often secondary to neuropathy and peripheral arterial disease.

Neuropathy is present in over 80% of people with foot ulcers. Sensory neuropathy results in decreased sensation of temperature, pain, and pressure and makes injuries and blisters less noticeable. Motor neuropathy and muscle imbalance can lead to foot deformities. Autonomic neuropathy can cause reduced sweat and sebaceous gland secretion, resulting in dry, cracked skin.

Peripheral arterial disease reduces the blood supply needed for the healing of ulcers and infections. Peripheral arterial disease in people with diabetes is often both macrovascular and microvascular.

Trauma is the usual precipitating event for diabetic foot ulcers. After the tissues are injured, the above factors can prevent normal healing and increase the risk of infection. In addition, hyperglycaemia impairs neutrophil function and host defence mechanisms.

Clinical presentations

All people with diabetes should have regular comprehensive foot evaluations. It is important to ascertain duration of diabetes, glycaemic control, presence of neuropathy, micro- or macrovascular disease, history of cigarette smoking, previous foot ulcers, and lower limb bypasses or amputation.

Assessment of the diabetic foot should look for the clinical features summarised in Box 40.1.

Peripheral neuropathy

Sensory neuropathy can be detected by a *10 g monofilament*. Monofilament testing detects people who have lost the protective pressure sensation and are susceptible to ulceration. The filament is pressed against the plantar aspects of the first and fifth toes, the first, third, and fifth metatarsal heads, and the plantar surface of the heel (Figure 40.1). The monofilament buckles at a given force of 10 g. The monofilament should not be applied at any site until callus has been removed.

Vibration sensation is assessed using a 128 Hz tuning fork. A neurothesiometer, if available, can also be used to detect sensory neuropathy. It is a device that delivers a vibratory stimulus to the foot that increases as the voltage is raised.

Endocrinology and Diabetes: Lecture Notes, Second Edition. Amir H. Sam, Karim Meeran and Neil Hill.
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Box 40.1 Clinical features in the assessment of the diabetic foot

Neuropathy
Ischaemia
Bony deformity
Callus
Swelling
Skin integrity/breakdown (especially between the toes and under the metatarsal heads)
Infection
Necrosis

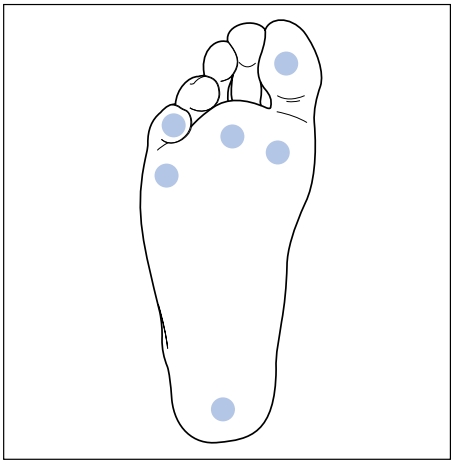

Figure 40.1 Sites for 10 g monofilament testing.

Peripheral arterial disease

Peripheral arterial disease should be suspected in people with *intermittent claudication*, cool temperature, absence of hair and presence of foot ulcers.

An absence of *pedal pulses* and a prolongation of venous filling should prompt further investigation and referral to the vascular surgical team. To measure the venous filling time, a prominent pedal vein is identified with the patient in a supine position. The leg is then elevated to 45° for 1 minute to collapse the vein. The patient then sits up and hangs the leg over the examination table. If more than 20 seconds elapse before the vein bulges above the skin, important arterial disease is likely to be present.

The *ankle–brachial pressure index* (ABPI) is calculated by measuring the systolic blood pressure (using a small hand-held Doppler) in the brachial, posterior tibial and dorsalis pedis arteries. The highest of four measurements in the ankles and feet is divided by the highest of the brachial measurements. The normal ABPI is 1.0–1.3. An ABPI of 0.90 or less is diagnostic of peripheral arterial disease. An ABPI over 1.30 suggests the presence of calcified vessels, which is common in diabetes.

Infected ulcers

Infections usually begin around cracks in the skin of the foot or around the toe nail bed (paronychia), or arise from ulcers. Diabetic foot infections are diagnosed clinically in the presence of local or systemic signs and symptoms of inflammation (including erythema, warmth, swelling, tenderness, pus coming out of an ulcer site, or a nearby sinus tract).

People with cellulitis who have sensory neuropathy often do not experience pain. In necrotising infections, purple/black discoloration of the skin, cutaneous bullae, or soft tissue gas may occur.

In any diabetic foot lesion, the severity of infection should be assessed (based on the International Working Group on the Diabetic Foot classification).

- *Grade 1 – Uninfected*: no local or systemic signs of infection. Infections are diagnosed when two or more markers of inflammation are present: erythema/cellulitis extending for >0.5 cm around the wound, local warmth, local swelling or induration, local tenderness, purulence discharge. Additionally, there should be no other explanation other than infection for an inflammatory skin response.
- *Grade 2 – Mild infection*: involvement of the skin or superficial subcutaneous tissues with no systemic manifestations and erythema not spreading >2 cm around the wound.
- *Grade 3 – Moderate infection*: more extensive infection or involvement of deeper tissues (of muscle, tendon, joint or bone resulting in abscesses, osteomyelitis, septic arthritis, or fasciitis), cellulitis extending >2 cm around the wound, with no systemic manifestations,
- *Grade 4 – Severe infection*: any foot infection an associated systemic inflammatory response (temperature >38 °C or <36 °C, heart rate >90 beats/min, respiratory rate >20 breaths/min, white blood cell count >12 000/mm^3 or <4000/mm^3).
- Where infection involves bone (osteomyelitis), infection grades 3 and 4 are described as 3O and 4O.

Gangrene (necrosis) is caused by ischaemia and is classified as wet or dry. In wet gangrene, ischaemia is caused by septic vasculitis associated with soft tissue infection. The tissues are black, brown, or grey, moist and often malodorous. In dry gangrene, ischaemia is caused by peripheral arterial disease. The

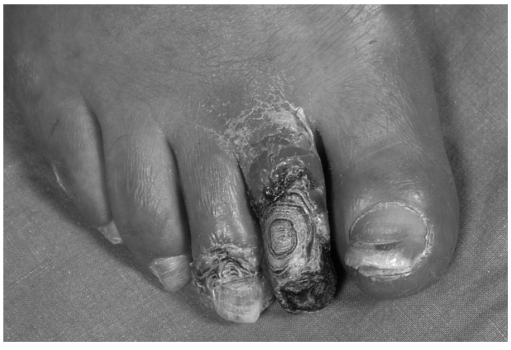

Figure 40.2 Diabetic foot with dry gangrene (caused by ischaemia), loss of hair and nail dystrophy.

Box 40.2 Characteristics suggesting more serious diabetic foot infection

Wound specific

Wound – penetrates to subcutaneous tissues (e.g. fascia, tendon, muscle, joint, or bone)
Cellulitis – extensive (>2 cm), distant from ulceration or rapidly progressive (including lymphangitis)
Local signs/symptoms – severe inflammation or induration, crepitus, bullae, discoloration, necrosis or gangrene, ecchymoses or petechiae, and new anesthesia or localised pain

General

Presentation – acute onset/worsening or rapidly progressive
Systemic signs – fever, chills, hypotension, confusion, volume depletion
Laboratory tests – leucocytosis, highly elevated C-reactive protein or ESR, severe or worsening hyperglycaemia, acidosis, new/worsening azotaemia, electrolyte abnormalities
Complicating features – presence of a foreign body (accidentally or surgically implanted), puncture wound, deep abscess, arterial or venous insufficiency, lymphoedema, immunosuppressive illness, or treatment, acute kidney injury
Failing treatment – progression while on apparently appropriate antibiotic and supportive therapy

tissues are black, hard, and mummified (Figure 40.2). There is a clean demarcation line between necrosis and viable tissue (Box 40.2).

Up to two-thirds of people with diabetic foot ulcers may have *osteomyelitis*. The following factors increase the likelihood of osteomyelitis in people with diabetic foot ulcers:

- visible bone or the ability to probe to bone (using a sterile, blunt, stainless steel probe)
- ulcer size >2 cm × 2 cm
- ulcer depth >3 mm
- ulcer duration longer than 1–2 weeks
- erythrocyte sedimentation rate (ESR) >70 mm per hour (see 'Investigations' below).

Investigations

Blood tests

Blood tests should include full blood count, urea and electrolytes, C-reactive protein (CRP) and/or ESR and/or procalcitonin, blood glucose, and glycated hemoglobin (HbA_{1c}).

Ulcer swabs and bone biopsy

Diabetic foot ulcers should be swabbed for *microscopy, culture and sensitivity*. Organisms isolated from superficial swabs may not reflect the organisms responsible for deeper infections. In the setting of deep tissue infections or osteomyelitis, cultures of deep tissue should be obtained at the time of debridement.

The correlation between superficial swab culture and bone biopsy culture is poor (up to 20%). Bone biopsy allows a histopathological diagnosis as well as microbiological culture and sensitivity. However, it is not always possible or practical to perform a bone biopsy as the incision made for a biopsy may not heal in those with peripheral arterial disease. Therefore, people may be treated empirically for the expected pathogens.

The microbiology of diabetic foot ulcers varies depending on the extent of involvement:

- *Superficial ulcers*: aerobic Gram-positive cocci including *Staphylococcus aureus*, *Streptococcus agalactiae*, *Streptococcus pyogenes* and coagulase-negative staphylococci. Methicillin-resistant *S. aureus* should be presumed and treated empirically.
- *Deep, chronic ulcers*: Gram-negative bacilli such as *Pseudomonas aeruginosa* and *Proteus mirabilis*, in addition to the above pathogens.
- *Ulcers with extensive local inflammation and signs of systemic toxicity* should be presumed to have anaerobic organisms as well as the above pathogens.

In people with chronic ulcers or those previously treated with antibiotics, infections are usually polymicrobial. When multiple organisms grow from a culture, it is difficult to determine which ones are true pathogens.

Imaging

In people with diabetic foot infections, a *foot radiograph* must be performed to look for possible osteomyelitis.

If the foot radiograph is normal, the patient is treated for soft tissue infection for 2 weeks and the foot X-ray is repeated in 2–4 weeks. If the repeat radiograph remains normal, osteomyelitis is unlikely.

If either the initial or follow-up foot radiograph is characteristic of osteomyelitis, the person is treated for osteomyelitis after obtaining appropriate specimens for culture. Those with one or more of the risk factors for osteomyelitis (see above) whose radiographs are indeterminate for osteomyelitis should have a magnetic resonance imaging (MRI) scan (see below).

Radiographs are useful for demonstrating features of chronic osteomyelitis such as cortical erosion, periosteal reaction, mixed bony lucency, sclerosis and sequestra. Radiographs are of limited sensitivity and specificity in the detection of acute osteomyelitis. Osteolysis and periosteal new bone formation may not be evident until 2 weeks after onset of infection. However, MRI scanning demonstrates abnormal marrow oedema as early as 3–5 days after the onset of infection.

MRI identifies bone marrow oedema, soft tissue inflammation, and cortical destruction. It cannot reliably differentiate between marrow oedema caused by osteomyelitis and that due to neuropathic (Charcot) arthropathy. MRI may also overestimate the extent of infection, since marrow oedema caused by osteomyelitis and surrounding reactive oedema cannot be distinguished. Furthermore, bone marrow changes may persist for weeks to months after osteomyelitis begins to respond to treatment. Gadolinium contrast-enhanced MRI is useful for demonstrating sinus tracts, fistulas, and abscesses.

Vascular investigations

Duplex ultrasonography allows anatomical localisation of arterial stenoses and assessment of blood flow haemodynamics. The normal Doppler waveform is triphasic (a forward flow systolic peak, reversal of flow in early diastole and forward flow in late diastole). With progressive peripheral arterial disease, there is elimination of the reverse flow and a decrease in systolic peak.

Magnetic resonance angiography has shown promise to become a time-efficient and cost-effective tool for the complete assessment of peripheral arterial disease. It is usually performed if revascularisation is being considered.

Angiography is considered the 'gold standard' of diagnostic evaluation for peripheral arterial disease. However, it is associated with the risks of iodinated contrast agents such as contrast nephropathy, and the risks inherent in percutaneous intervention.

Treatment

Advice for prophylactic foot care should be given to all people with diabetes (see Chapter 35). People at high risk of developing foot ulcers must be referred to a podiatrist. People are at high risk of future plantar ulceration if they have neuropathy or neuropathic foot deformities, such as bunions or calluses, peripheral arterial disease or a previous history of foot ulceration or amputation.

The management of diabetic foot ulcers includes:

- attentive wound management and debridement
- appropriate antibiotic therapy
- relief of pressure on the ulcer
- revascularisation
- glycaemic control.

Co-ordination of care among providers is important for keeping rates of amputation as low as possible.

Debridement

The management of people with superficial ulcers includes debridement by a podiatrist, good local wound care, and relief of pressure on the ulcer. People should avoid unnecessary ambulation. Open lesions are covered with a custom-fit piece of non-adherent dry dressing. People should be closely monitored. If the ulcer does not improve, hospitalisation for bed rest and intravenous antibiotic therapy may be necessary.

Prompt surgical debridement and intervention is critical in the presence of:

- a large area of infected sloughy tissue
- infections complicated by abscess: localised fluctuance and expression of pus
- crepitus with gas in the soft tissues on X-ray (gas immediately adjacent to an ulcer may have entered the foot through the ulcer and is of less importance)
- purplish discoloration of the skin, indicating subcutaneous necrosis or necrotising fasciitis
- extensive bone or joint involvement.

Following surgical debridement, vacuum-assisted wound closure may be used in the treatment of open wounds to improve healing and closure. A sponge is secured under a clear dressing with tubing extending to a collection canister. A pump applies suction and

causes fluid to flow out of the wound. Contraindications to vacuum-assisted closure include a visible vascular structure in the wound, incomplete debridement, malignancy in the wound, untreated osteomyelitis or an open fistula.

Antibiotics

Antibiotics used for the empirical treatment of mild, moderate and severe diabetic foot infections are summarised in Box 40.3. Antibiotic choice depends on the wound grade and the presence or absence of osteomyelitis. Initial treatment of diabetic foot infections is empirical and should be active against the most likely common organisms, streptococci, MRSA, aerobic Gram-negative bacilli, and anaerobes. Patient factors (allergies, compliance) should also be considered. Liaison with local microbiology is recommended. Outpatient intravenous therapy may be utilised when oral antibiotics are not tolerated or are ineffective.

Box 40.3 Antibiotics for the empirical treatment of diabetic foot infections

Oral antibiotics for empirical treatment of mild diabetic foot infections

Regimens active against streptococci and MRSA

- Clindamycin
- Linezolid
- Penicillin + doxycycline

Regimens active against streptococci, MRSA, aerobic Gram-negative bacilli, and anaerobes

- Amoxicillin–clavulanate + trimethoprim–sulfamethoxazole
- Clindamycin + ciprofloxacin (or levofloxacin)

Parenteral antibiotics for empirical treatment of moderate/severe diabetic foot infections

Vancomycin (active against MRSA) + one of the following (active against aerobic Gram-negative bacilli and anaerobes):

- Ampicillin–sulbactam
- Piperacillin–tazobactam
- Ticarcillin–clavulanate
- Imipenem
- Meropenem
- Metronidazole + one of the following: ceftazidime, ciprofloxacin or aztreonam

The duration of antibiotic therapy should be tailored to individual clinical circumstances, but longer durations (>6 weeks) may not improve healing significantly.

In people with mild infection, oral antibiotics should be continued until the infection has resolved (usually about 1–2 weeks). It is not necessary to continue antibiotics for the entire duration that the wound remains open.

In people with infections requiring surgical debridement, intravenous antibiotics should be given perioperatively. In the absence of osteomyelitis, antibiotics should be continued until signs of infection appear to have resolved (usually 2–4 weeks). If there is a good response to intravenous antibiotics, oral agents can be used to complete the course of treatment. The optimal regimen and when to switch to oral antibiotics depend on the clinical features of each case.

Those requiring amputation of the involved limb should receive intravenous antibiotics perioperatively. If the entire area of infection is fully resected, a brief course of oral antibiotics (for about a week) after surgery is usually sufficient.

If clinical evidence of infection persists beyond the expected duration, issues of compliance, antibiotic resistance, undiagnosed deep abscess, and ischaemia should be considered.

The optimal duration of antibiotic therapy for osteomyelitis is not certain. Parenteral antibiotics should be continued at least until debrided bone has been covered by vascularised soft tissue. This usually takes at least 6 weeks from the last debridement. Long-term parenteral antibiotic administration may be accomplished on an outpatient basis via a long-term intravenous catheter with close monitoring. Monitoring may include weekly serum drug levels, renal function, liver function and/or haematological function, depending on the antibiotic used.

Relief of pressure: footwear and total contact casting

Devices used to relieve pressure on the ulcer ('mechanical off-loading') include removable cast walkers, half-shoes, and total contact casts.

Total contact casting is an alternative to prolonged bed rest for the relief of pressure on the ulcer. This allows ambulation and is often preferred by people. As many of the people have markedly impaired sensation in their feet and legs, it is important to check regularly that pressure from the cast is not causing the formation of new ulcers. Total contact casting is contraindicated in people with soft tissue infection or osteomyelitis.

Extra-depth and extra-width therapeutic shoes with special inserts are frequently prescribed for individuals with diabetes to prevent recurrence of foot ulcers.

Revascularisation

In people with diabetes who have peripheral arterial disease, revascularisation and improvement of tissue perfusion help to control infection and promote healing of foot ulcers.

Angioplasty is indicated for single or multiple stenoses or short-segment occlusions of less than 10 cm. If angioplasty is not possible due to long arterial occlusions or widespread lesions, revascularisation may be achieved by *arterial bypass surgery*. However, this is a major operation with its own inherent risks and should be reserved for people who do not respond to conservative treatment and antibiotics, and require operative debridement with toe or ray amputation.

In arterial bypass surgery, an autologous vein is used to fashion a conduit from either the femoral or the popliteal artery down to a tibial artery in the lower leg, or the dorsalis pedis artery on the dorsum of the foot. After surgery, the leg has wounds at the sites of graft insertion and vein harvesting. Wounds overlying the arterial graft must be kept free from infection to avoid blockage of the graft. Postoperative oedema is common, and it is important to elevate the leg.

Charcot arthropathy

The following factors have been suggested to contribute to the pathogenesis of neuropathic (Charcot) arthropathy.

- Peripheral neuropathy and lack of proprioception may result in ligamentous laxity, increased range of joint movement, instability, and damage by minor trauma.
- Autonomic neuropathy results in vasomotor changes, the formation of arteriovenous shunts, and reduced effective skin and bone blood flow.
- There may be an exaggerated local inflammatory response to trauma (mediated by proinflammatory cytokines).

Neuropathic arthropathy in people with diabetes most commonly affects the joints of the foot and ankle: the tarsus and tarsometatarsal joints, metatarsophalangeal joints, and ankle.

Neuroarthropathy affects about one in 700 people who have either type 1 or type 2 diabetes. These people typically have longstanding diabetes and are in their sixth or seventh decade. However, younger people may also be affected.

Clinical presentations

People with Charcot arthropathy may present with:

- A sudden onset of unilateral warmth, redness, and oedema over the foot or ankle, usually with a history of minor trauma. About 30% of people complain of pain or discomfort.
- Slowly progressing arthropathy with insidious swelling over months or years, collapse of the arch of the midfoot, and bony prominences and deformities.

The neuroarthropathy is bilateral in about 20% of cases.

Investigations

In acute Charcot arthropathy, the inflammatory markers may be increased. A plain radiograph of the foot may show mild or non-specific changes. Abnormalities that may be seen on a foot radiograph include:

- soft tissue swelling, loss of joint space and osteopenia
- forefoot: bone resorption, osteolysis of the phalanges, partial or complete disappearance of the metatarsal heads, and 'pencil-pointing' of the phalangeal and metatarsal shafts
- midfoot and hindfoot: osseous fragmentation, sclerosis, new bone formation, subluxation, and dislocation.

A *radioisotope bone scan* may show an increased uptake in neuropathic arthropathy. However, increased isotope uptake may be seen in both people with diabetic neuroarthropathy and those with peripheral neuropathy alone.

MRI scanning may facilitate the diagnosis of stress fractures and the visualisation of torn ligaments and intra-articular fragmentation. However, the changes of acute neuropathic arthropathy may be indistinguishable from those of osteomyelitis.

Treatment

Acute-onset Charcot arthropathy is treated with *avoidance of weight bearing* on the affected joint until oedema and erythema have resolved, and radiological signs have improved. A minimum of 8 weeks without weight bearing is recommended for disease

of the midfoot. People may progress through partial weight bearing in a cast brace to full weight bearing in approximately 4–5 months. Good chiropody and well-fitting shoes are essential.

Alternatively, a *total contact cast* may be used from the time of diagnosis. This is a very efficient method of redistributing plantar pressure. The cast should be changed every 2 weeks. A transition to custom-made orthoses and commercial footwear accommodating the patient may be possible at about 9–10 weeks.

The swollen, uncomfortable, hot foot of active Charcot arthropathy may improve with an intravenous infusion of *pamidronate*. Oral bisphosphonates (alendronate) may also be useful. In people with both Charcot arthropathy and renal insufficiency in whom bisphosphonates are contraindicated, intranasal calcitonin may potentially be useful.

Joint disorganisation may be severe and irreversible in chronic cases of Charcot arthropathy. Common deformities such as the 'rocker-bottom foot' transfer weight bearing to areas that may lack sensation and tolerate it poorly, leading to ulceration and infection. Surgical correction is best avoided in most people but in carefully selected cases, acceptable alignment may be achieved by surgery, thereby preserving soft tissue viability and avoiding ulceration and amputation.

Other musculoskeletal manifestations of diabetes

A number of musculoskeletal conditions have been associated with diabetes mellitus (Box 40.4).

Box 40.4 Musculoskeletal conditions associated with diabetes

Diabetic foot infections
Neuropathic (Charcot) arthropathy
Limited joint mobility
Carpal tunnel syndrome
Dupuytren contracture
Flexor tenosynovitis
Shoulder: adhesive capsulitis, calcific periarthritis
Diffuse idiopathic skeletal hyperostosis
Diabetic muscle infarction

Limited joint mobility

Limited joint mobility is common in people with diabetes mellitus. It is characterised by a limitation of joint movement, particularly in the small joints of the hands. Limited joint mobility is painless. It is commonly associated with thickening and waxiness of the skin on the dorsal surface of the fingers.

The risk increases with poor glycaemic control, duration of diabetes, and cigarette smoking. It may be secondary to the deposition of abnormal collagen in connective tissue around the joints. Enzymatic and non-enzymatic glycosylation of collagen, abnormal cross-linking of collagen resulting in resistance to degradation, and increased collagen hydration may all play a role. Microangiopathy and neuropathy may contribute to contractures via fibrosis and disuse.

Stiffness and contractures result in decreased grip strength and difficulties with hand function. Examination of the hands may show contractures of the metacarpophalangeal, proximal and sometimes distal interphalangeal joints. Other joints may occasionally be involved. The 'prayer sign' test is performed by asking the patient to flatten the hands together as in prayer. This helps to identify contractures in the metacarpophalangeal, proximal and distal interphalangeal joints. Imaging studies are not typically used to diagnose limited joint mobility.

Limited joint mobility is difficult to treat. Glycaemic control should be optimised. Physiotherapy with passive palmar stretching and occupational therapy may improve hand function. People must be advised to stop smoking. Injection of the palmar tendon sheath with corticosteroids has been used.

Osteoporosis

The association between diabetes mellitus and osteoporosis remains controversial. Bone mineral density is lower in those with type 1 diabetes and normal or increased in those with type 2 diabetes. However, fracture risk appears to be increased in people with both type 1 and type 2 diabetes. This is possibly related to factors in addition to bone mineral density, such as duration of diabetes, diabetic complications, treatment, and risk of falling.

Diabetic muscle infarction

Diabetic muscle infarction is a rare condition characterised by an acute or subacute onset of muscle pain, swelling, and tenderness, usually in the muscles of the thigh and calf. It affects people with relatively longstanding diabetes. The pathogenesis is uncertain.

The differential diagnosis includes infective myositis, intramuscular haematoma due to coagulopathy, venous thrombosis, and neoplasm.

Investigations should include full blood count, creatine kinase, CRP, clotting screen, blood culture, plain radiograph, venous Doppler ultrasound, and MRI of the affected and contralateral limb. MRI may show increased T2 signal in affected muscle, fascia, and subcutaneous tissues.

The definitive diagnosis of diabetic muscle infarction requires biopsy of the affected area of muscle to demonstrate ischaemic necrosis and exclude infection. Surgical exploration and excisional biopsy are recommended in people in whom a rapidly progressive infection of muscle or fascia cannot be excluded. People with diabetic muscle infarction should also receive low-dose aspirin.

Dermatological manifestations of diabetes

Protracted wound healing and skin ulcerations are the most common dermatological manifestations of diabetes.

Diabetic dermopathy (or 'pigmented pretibial papules') begins as erythematous areas that evolve into areas of circular hyperpigmentation. The lesions are more common in elderly men with diabetes and are caused by mechanical trauma in the pretibial region. Bullous diseases are also seen.

Necrobiosis lipodica diabeticorum is a rare skin manifestation of diabetes that predominantly affects young females with type 1 diabetes, retinopathy and neuropathy. These lesions start in the pretibial region as erythematous papules or plaques, gradually darken and develop irregular margins, with shiny atrophic centres. Treatment is best started early under the supervision of a dermatologist. Topical steroids or calcineurin inhibitors (tacrolimus 0.03% or 0.1% ointment) may be used. Intralesional steroid injections can help but can cause thin skin. A variety of oral treatments have been tried, as has light therapy (psoralen ultraviolet A).

Acanthosis nigricans (hyperpigmented velvety plaques on the neck or axillae) is a sign of insulin resistance.

Granuloma annulare (localised or generalised) are erythematous papules coalescing in rings, especially on the backs of the hands and fingers.

Lipoatrophy and lipodystrophy can occur at insulin injection sites. Diabetic sclerodactyly is characterised by thickening and waxiness of the skin on the dorsa of the fingers and may be associated with limited joint mobility. Pruritus and dry skin are common in people with diabetes and are relieved by moisturisers.

KEY POINTS

- Foot ulcers are a major cause of hospitalisation, morbidity, and mortality in people with diabetes.
- Diabetic foot problems often occur secondary to neuropathy and peripheral arterial disease.
- Clinical evaluation of the diabetic foot should look for neuropathy, ischaemia, bony deformity, callus, swelling, skin integrity/breakdown, infection, and necrosis.
- Investigations in a diabetic patient with foot problems include blood tests for full blood count, urea and electrolytes, ESR, CRP, blood glucose and HbA_{1c}, an ulcer swab for microscopy, culture and sensitivity, a foot radiograph, and duplex ultrasonography.
- The management of diabetic foot ulcers includes debridement, antibiotic therapy, relief of pressure, revascularisation, and glycaemic control.
- Neuropathic arthropathy in individuals with diabetes most commonly affects the joints of the foot and ankle.
- Acute-onset Charcot arthropathy is treated with avoidance of weight bearing on the affected joint or total contact casts.

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Endocrinology and Diabetes: Lecture Notes, Second Edition. Amir H. Sam, Karim Meeran and Neil Hill.

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