Metabolic Bone Disease

5

Introduction

Metabolic bone diseases are a heterogeneous group of disorders characterized by abnormalities in calcium metabolism and/or bone cell physiology. They lead to an altered serum calcium concentration and/or skeletal failure. The most common type of metabolic bone disease in developed countries is osteoporosis. Because osteoporosis is essentially a disease of the elderly, the prevalence of this condition is increasing as the average age of people in developed countries rises. Osteoporotic fractures may lead to loss of independence in the elderly and is imposing an ever-increasing social and economic burden on society. Other pathological processes that affect the skeleton, some of which are also relatively common, are summarized in Table 3.20 (see Chapter 4).

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Structure and function

Structure of bone

Bone consists of an extracellular matrix and cellular constituents. The structure of the extracellular matrix is maintained throughout life by constant remodelling by its cellular constituents.

Extracellular matrix

- *Type 1 collagen:* forms a fibrillar structure by cross-linkage of the precursor peptide procollagen, and provides tensile strength. The fibrils are generally arranged in parallel or concentric sheets to form lamellar bone, but in newly laid 'woven bone' this arrangement appears more random.
- *Calcium- and phosphate-containing crystals:* set in a structure similar to hydroxyapatite and deposited in holes between adjacent collagen fibrils, which provide rigidity.
- *At least 11 non-collagenous matrix proteins* (e.g. osteocalcin, osteonectin): these form the ground substance and include glycoproteins and proteoglycans. Their exact function is not yet defined, but they are thought to be involved in calcification.

Cellular constituents

- *Mesenchymal-derived osteoblast lineage:* consist of osteoblasts, osteocytes and bone-lining cells. Osteoblasts synthesize organic matrix in the production of new bone.
- *Osteoclasts:* derived from haemopoietic precursors, and resorb bone tissue by the local release of hydrolase enzymes.

Anatomy of bone

- *Cortical bone:* the external part of each bone consists of dense skeletal tissue known as cortical (compact) bone, which contributes to most of the skeleton's mechanical strength.
- *Trabecular bone:* within the vertebrae and the ends of long bones, the internal space is filled with a fine network of bone tissue called trabecular (cancellous) bone. This is in intimate contact with the bone marrow and is largely responsible for the skeleton's metabolic role as a reservoir for body calcium. In addition, trabecular elements are thought to contribute to the ability of vertebrae to withstand compressive forces, with loss of these contributing to the vertebral collapse seen in osteoporosis.

Function of bone

Bone has two main functions: to provide an endoskeleton and to act as a reservoir for body calcium (bone contains

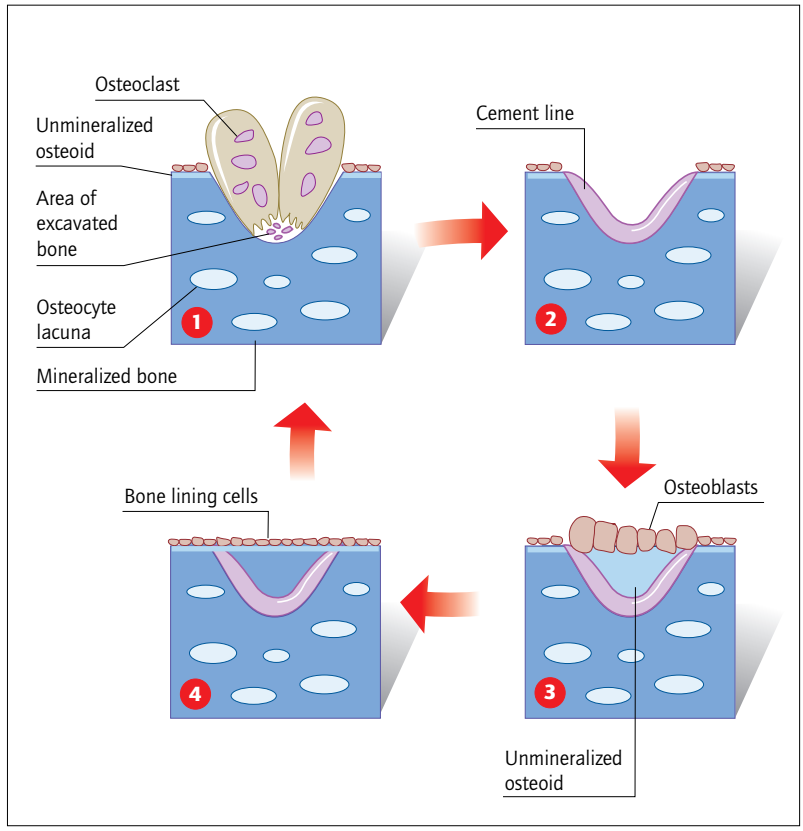


Figure 5.1 The remodelling cycle. (1) On activation of bone resorption the surface layer of unmineralized osteoid is removed and bone resorption by osteoclasts starts, the membrane of the osteoclasts taking on a ruffled appearance at the site of active bone resorption. (2) When bone resorption is complete the cement line is laid down during the reversal phase. (3) The unmineralized osteoid synthesized by osteoblasts fills the resorption cavity. (4) The osteoid is then mineralized, the bone surface finally being covered by lining cells and a thin layer of unmineralized osteoid.

1–2 kg of calcium compared with 1–2 g of calcium in the extracellular fluid). These two functions are normally independent. However, as 25% of extracellular calcium is replaced daily, prolonged calcium stress can ultimately affect skeletal integrity.

Skeletal maintenance

During growth, bone formation and resorption are regulated as part of the modelling process that results in the micro- and macroarchitecture of the adult skeleton.

- *Modelling:* involves resorption secondary to bone formation
- *Remodelling:* consists of repeated cycles of bone resorption followed by formation, at discrete sites throughout the skeleton (Fig. 5.1)

The mechanisms regulating modelling and remodelling are not clear, but local responses to mechanical stimuli are thought to have a major role.

Calcium balance

Many essential intracellular processes are critically dependent on the concentration of ionized extracellular calcium. The average western diet provides 0.5–1.0 g calcium/day; 20–40% of this is absorbed, which is usually sufficient to match minimal renal and intestinal losses (Fig. 5.2). However, if calcium intake or absorption is reduced, or requirements increase, a negative calcium balance may ensue. As powerful homoeostatic mechanisms preserve the concentration of extracellular calcium by using skeletal calcium stores, this can ultimately lead to a significant loss of calcium from bone. The homoeostatic mechanisms affecting bone include parathyroid hormone, vitamin D and other factors.

Parathyroid hormone

Parathyroid hormone (PTH) is an 84 amino acid polypeptide that is secreted by the chief cells of the parathyroid gland in response to hypocalcaemia. It is the principal regulator of extracellular calcium concentration (Fig. 5.3) and increases it by:

- Stimulating calcium release from bone by increasing osteoclast bone resorption
- Promoting renal tubular calcium reabsorption
- Increasing renal tubular phosphate excretion
- Enhancing renal conversion of 25-hydroxyvitamin D (25-OH-D) to 1,25-dihydroxyvitamin D (1,25-$(OH)_2$-D).

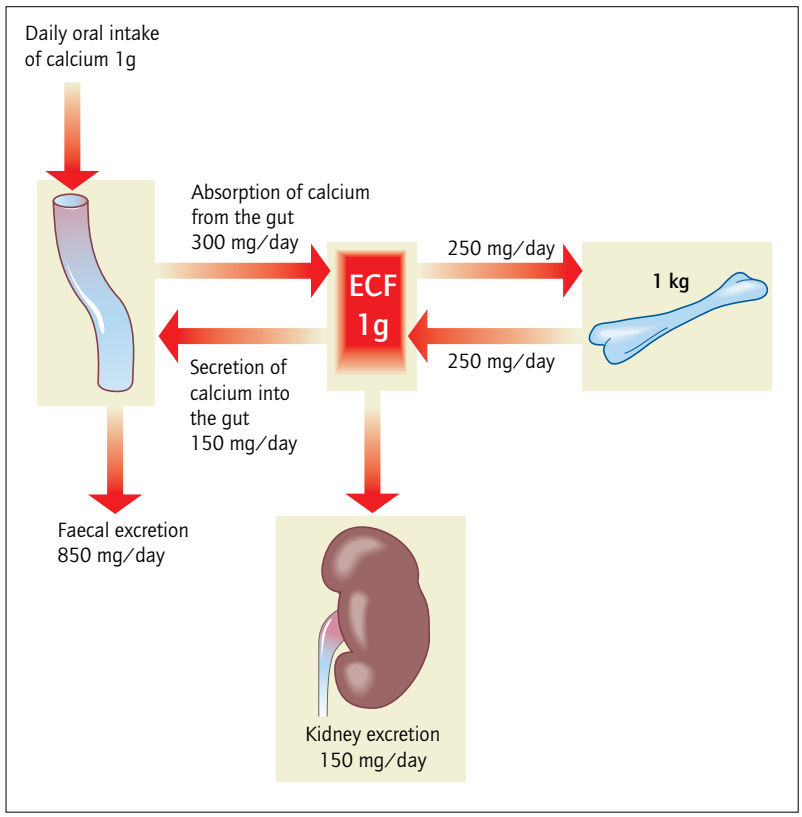


Figure 5.2 Pathways in calcium balance. The size of the extracellular fluid (ECF) and skeletal calcium compartments (1 g and 1 kg, respectively), the degree of exchange between them, the daily oral intake of calcium and the daily faecal and urinary excretion of calcium refer to a typical subject in zero calcium balance. A negative calcium balance may occur if calcium intake falls, the efficiency of calcium absorption from the gut is reduced and/or urinary calcium excretion is increased.

Vitamin D

Vitamin D is a steroid hormone, which is either ingested in the diet or produced in the skin from 7-dehydrocholesterol after exposure to sunlight.

Vitamin D is a pro-hormone; the active form (1,25-$(OH)_2$-D) is produced by successive hydroxylations in the liver and kidney by the enzymes 25-hydroxylase and 1-α-hydroxylase, respectively (Fig. 5.3). 1-α-Hydroxylase is stimulated not only by PTH, but also by low ambient inorganic phosphate, growth hormone, prolactin and oestrogen. This enables vitamin D levels to become adapted to the higher calcium requirements of growth and reproduction.

In conjunction with PTH, 1,25-$(OH)_2$-D acts to maintain serum calcium levels by:

- Increasing the efficiency of calcium absorption from the proximal small intestine
- Stimulating calcium release from bone

1,25-$(OH)_2$-D also acts to maintain phosphate levels by promoting phosphate absorption from the gut. In vitamin D deficiency, renal phosphate excretion is increased as a consequence of raised levels of PTH.

Other factors

- *Other hormones*: steroid hormones such as glucocorticoids, oestrogen and androgens are thought to influence bone metabolism
- *Local factors:* regulate bone cell activity in response to systemic hormones and mechanical strain such as members of the transforming growth factor-β (TGF-β) superfamily and osteoclast stimulatory factor
- *Local mechanical strain:* also an important controlling influence on osteoblast and osteoclast activity, with its loss in disuse states leading to rapid bone loss

Calcium measurement

Most calcium in the blood is bound or complexed to plasma proteins. However, only ionized calcium is biologically active.

Ionized serum calcium can be measured directly, but conventional analysers measure only total levels (normal range 2.2–2.6 mmol). Such total levels require correction for albumin concentration because albumin is the predominant calcium binder. The most convenient correction is to:

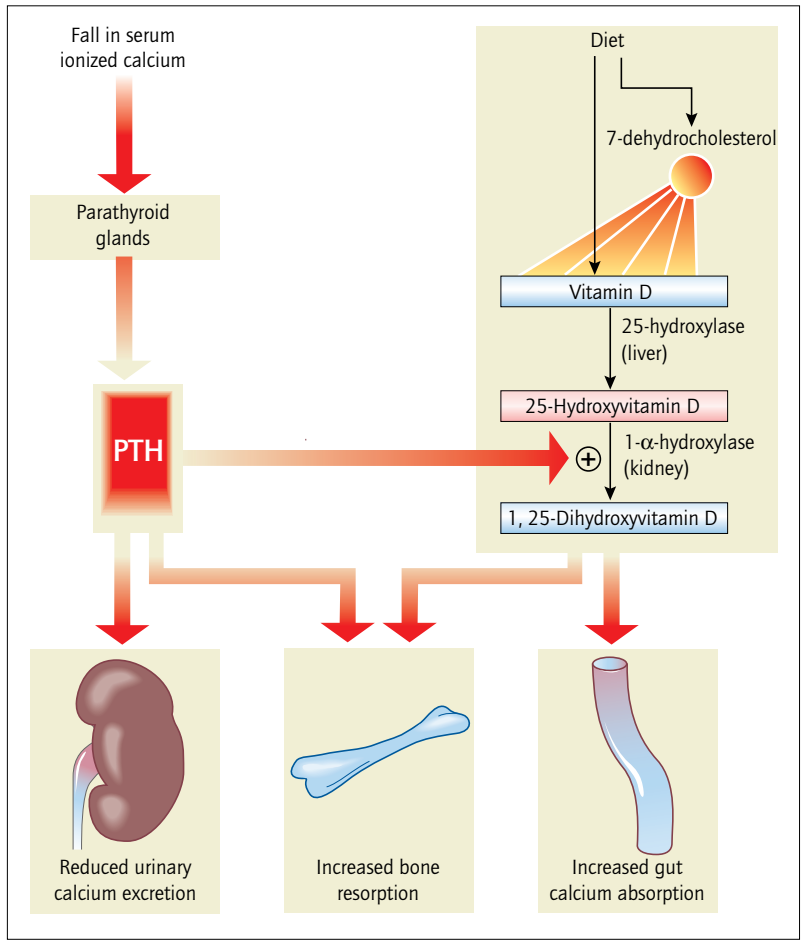


Figure 5.3 Regulation of calcium metabolism by parathyroid hormone (PTH) and vitamin D. PTH and vitamin D are the principal hormones responsible for calcium homoeostasis. Note that these two regulatory mechanisms are interdependent because of the stimulatory action of PTH on renal 1-α-hydroxylase.

- Add 0.02 mmol to the total calcium level for every g/l that the albumin is below 40 g/l
- Subtract 0.02 mmol from the total calcium level for every g/l that the albumin is above 40 g/l

Approach to the patient

History and examination

Findings from the history and examination vary according to the metabolic bone disease in question (see under separate disease headings). In general, people with chronic diseases such as rickets, osteomalacia and osteoporosis present with features specific to the musculoskeletal system such as bone pain, proximal weakness and deformity (Table 5.1). In contrast, people with disorders of short duration associated with an acute disturbance in calcium metabolism, such as hypercalcaemia of malignancy or postparathyroidectomy hypocalcaemia, present with features of hyper- or hypocalcaemia (Tables 5.2 and 5.3). Musculoskeletal features may occur in combination with long-standing symptoms of altered serum calcium concentration as in rickets and primary hyperparathyroidism. There are rare familial forms of metabolic bone disease such as X-linked hypophosphataemic rickets, so a family history should always be sought (see HISTORY & EXAMINATION BOXES 5.1 and 5.2).

Metabolic bone disease: Clinical presentations at a glance

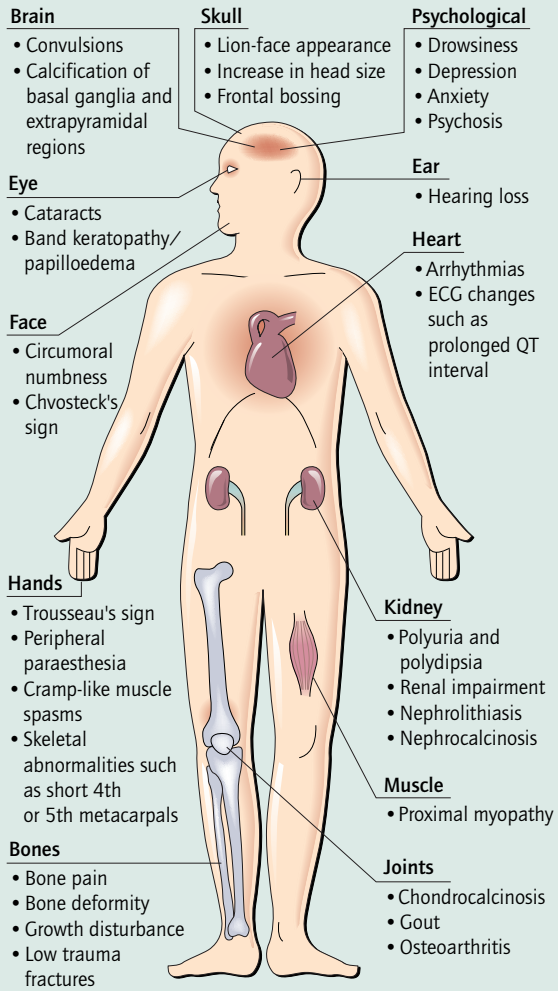


Table 5.1 Musculoskeletal abnormalities in rickets and osteomalacia

Hypotonia, proximal muscle weakness and waddling gait
Impaired skeletal growth
Bowing deformity of long bones
Rib deformities
Prominence of costochondral junction (rachitic rosary)
Indentation of the lower ribs (Harrison's groove)
Kyphosis and lordosis of the thoracolumbar spine
Skull abnormalities
Softened calvarium (craniotabes)
Parietal flattening and frontal bossing
Delayed eruption of permanent dentition and enamel defects

Investigation

In metabolic bone disease, the findings of the history and examination are usually relatively non-specific. Further investigations are therefore needed to diagnose the nature of any underlying metabolic bone disease before starting treatment.

Table 5.2 Clinical features of hypercalcaemia

System	Feature
Neurological and psychiatric	Drowsiness and altered conscious level
	Headache
	Sleep disturbance
	Depression
	Muscle weakness
	Hyporeflexia
Renal	Polyuria
	Polydipsia
	Nephrolithiasis
	Nephrocalcinosis
	Renal impairment
Gastrointestinal	Constipation
	Nausea and anorexia
	Peptic ulceration
	Pancreatitis
Cardiovascular	Hypertension
	ECG abnormalities (shortened QT interval, first-degree heart block)
Articular	Chondrocalcinosis
	Gout
Miscellaneous	Pruritus and skin necrosis
	Band keratopathy

Table 5.3 Clinical features of hypocalcaemia

System	Feature
Neurological and psychiatric	Peripheral paraesthesia
	Circumoral numbness
	Tetany
	cramp-like spasms
	laryngeal stridor
	Chvostek's and Trousseau's signs
	Convulsions
	Anxiety
	Psychosis
	Basal ganglia and/or extrapyramidal calcification (if long-standing)
Cardiovascular	Arrhythmias
	ECG abnormalities (prolonged QT interval)
Ocular	Papilloedema
	Cataracts (if long-standing)

History & Examination 5.1: Important questions to ask a patient with a metabolic bone disease

About symptoms

Do you have any bone, joint or muscle symptoms such as pain, tenderness or weakness? (People with metabolic bone diseases may have a history of musculoskeletal symptoms)

Have you ever broken a bone with only minimal trauma? (Low impact fractures, e.g. fall from a standing height or less, are a feature of many metabolic bone diseases)

Is your sleep disturbed? Do you have headaches? Nausea? Constipation? Do you pass much water? Are you particularly thirsty? (Ask about symptoms of hypercalcaemia that can occur with primary hyperparathyroidism or disseminated malignancy)

Do you have any pins and needles or tingling in your hands and/or feet? Do you have any numbness around your mouth? Do you have any muscle twitching or cramps? (Ask about symptoms of hypocalcaemia that can occur with severe osteomalacia, chronic renal failure or after a parathyroidectomy)

About the onset and progression of disease

When did your symptoms start? How old were you? (Onset in childhood is a feature of rickets and hereditary hypocalcaemic disorders)

Over how long have your symptoms been getting worse? (Metabolic bone diseases usually progress slowly over months or years but hypercalcaemia of malignancy can progress rapidly)

About past medical history

Do you have or have you had any intestinal or liver disorder? (Osteomalacia and osteoporosis are relatively common complications of gastrointestinal diseases associated with malabsorption and/or liver dysfunction)

Do you have or have you had any kidney disorders? (Chronic renal failure can cause osteomalacia and/or hypocalcaemia)

Have you had cancer, and if so what sort? (Patients with hypercalcaemia should be asked about a history of malignancy, particularly breast or lung cancer)

What age were you at your menopause and were your periods previously regular? Have you ever had a disorder of the thyroid or adrenal gland? (Osteoporosis can occur at a relatively young age following hysterectomy and in association with ovarian dysfunction. It may also occur in association with endocrine disorders such as hyperthyroidism and Cushing's disease)

About drug history

Have you received treatment for epilepsy? Have you received prolonged treatment with steroids? What medicines and tonics are you currently taking? (Glucocorticoids can cause osteoporosis; use of phenytoin can lead to osteomalacia; hypercalcaemia can result from vitamin A or D intoxication, antacids and thiazide diuretics)

About social history

Do you have a balanced diet? (A poor diet lacking in vitamin D-enriched foods such as milk products and cereals can cause osteomalacia. Osteomalacia is also associated with a strict vegetarian diet and increased intake of phytic acid, which are common in certain Asian populations. Calcium insufficiency in the elderly is common)

Do you smoke and if so how much? Do you drink alcohol and if so how much? Do you take regular exercise? (Osteoporosis is associated with cigarette smoking, increased alcohol intake and lack of exercise)

About family history

Has anyone in your family had similar symptoms? (Rare metabolic bone diseases can be inherited, e.g. X-linked hypophosphataemic rickets and primary hyperparathyroidism may be part of multiple endocrine neoplasia (MEN) which is autosomal dominant)

Has your mother broken her hip? (There is an increased risk of osteoporosis associated with maternal hip fracture)

Haematology

Full blood count. Anaemia can be caused by conditions that underlie metabolic bone disease such as gastrointestinal malabsorption and chronic renal failure. It is not a direct result of the metabolic bone disease itself.

Biochemistry

Serum biochemistry results are frequently diagnostic of the underlying metabolic bone disease (Table 5.4):

- *Serum creatinine:* may be elevated in associated chronic renal failure or multiple myeloma, or caused by dehydration resulting from polyuria resulting from hypercalcaemia.
- *Serum calcium:* may be increased (Table 5.5), normal in osteoporosis or decreased (Table 5.6).
- *Serum phosphate:* increased in chronic renal failure and hypoparathyroidism, and decreased in primary hyperparathyroidism and hyperparathyroidism secondary to deficiency, malabsorption or abnormal metabolism of vitamin D.
- *Serum alkaline phosphatase:* increased when there is

History & Examination 5.2: Examination of a patient with a metabolic bone disease

General examination

Is there evidence of underlying gastrointestinal disease? [Look for cholestasis (see EXAMINATION BOX 9.1) or signs of malnutrition]

Is there evidence of endocrine disorders? [Such as Cushing's disease (see p. 852) and hyperthyroidism (see p. 843)]

Is there evidence of malignancy? [Such as lung or breast the patient has hypercalcaemia]

Is there evidence of renal disease? [If the patient has osteomalacia and/or hypocalcaemia]

Neurological examination

Look for signs of hypercalcaemia such as hyporeflexia and band keratopathy (in long-standing cases)

Look for signs of hypocalcaemia such as papilloedema and tetany

Look for hypotonia and proximal myopathy, which are features of rickets and osteomalacia

Examination of the locomotor system

General

Stunted growth, rib deformities and long bone deformities occur in rickets. Abnormal skeletal development is a feature of congenital disorders such as pseudohypoparathyroidism

Record the patient's height

Height records are of vital importance in the diagnosis and monitoring of metabolic bone disease in both children and adults. Normally, height is equal to span

Observe the gait

A waddling gait is a feature of rickets and osteomalacia, and occurs secondary to skeletal deformity and/or proximal myopathy

Look at the spine

A kyphotic deformity is a common feature of osteoporosis

	Calcium	Phosphate	ALP	PTH
Osteomalacia	N or ↓	↓	↑	↑
Osteoporosis	N	N	N	N
Hyperparathyroidism	↑	↓	↑	↑
Hypercalcaemia of malignancy	↑	N or ↓	N or ↑	↓
Hypoparathyroidism	↓	↑	N	↓

Table 5.4 Serum biochemistry in metabolic bone disease

↑ Increased; ↓ decreased; ALP, alkaline phosphatase; N, normal; PTH, parathyroid hormone.

osteoblastic hyperactivity (e.g. in osteomalacia/rickets, hyperparathyroidism, osteoblastic skeletal malignant deposits).

- *Serum PTH:* increased in deficiency, malabsorption or abnormal metabolism of vitamin D, and in primary, secondary and tertiary hyperparathyroidism; it is reduced in hypocalcaemia resulting from hypoparathyroidism. Relatively rapid degradation of PTH can result in falsely low levels of PTH where the assay uses an antibody against intact PTH.
- *Serum 25-OH-D levels:* may be increased or reduced in abnormal vitamin D metabolism, according to the site of the metabolic defect. 25-OH-D levels are measured in preference to other vitamin D metabolites because they give a better reflection of current vitamin D nutritional status.
- *Bone markers:* urinary and serum markers such as telopeptides (e.g. N-telopeptide) measure breakdown products of type I collagen and indicate the level of bone resorption. They can be used to measure the effectiveness of therapy with antiresorptive agents such as bisphosphonates.

Diagnostic imaging

Plain radiography

Metabolic bone disease can be associated with adverse effects on the skeleton that can be readily recognized on plain radiographs. Although changes such as low bone density are non-specific, specific changes pointing to a particular diagnosis such as Looser's zones in osteomalacia may be evident.

Isotope bone scan

Metabolic bone diseases can be associated with local areas of increased technetium uptake, especially if there are associated fractures. Widespread changes are most commonly a result of skeletal secondary malignant deposits but also occur in osteomalacia and Paget's disease of bone.

Bone densitometry

A number of techniques have been developed to quantify the amount of bone mineral present at a given skeletal site, from which other values such as bone mineral density can be derived. They largely consist of dual energy X-ray

Table 5.5 Causes of hypercalcaemia

Endocrine disorders
Primary hyperparathyroidism
Tertiary hyperparathyroidism
Hyperthyroidism
Addison's disease
Phaeochromocytoma

Malignancy
Solid tumours, especially breast and lung
Haematological tumours

Drugs
Thiazides
Lithium
Theophylline toxicity
Vitamin A intoxication
Vitamin D intoxication

Renal disorders
Acute and chronic renal failure

Granulomatous disorders
Sarcoidosis
Tuberculosis
Histoplasmosis

Familial
Multiple endocrine neoplasia (MEN) I and II
Familial hypocalciuric hypercalcaemia

Prolonged immobilization
Paget's disease of bone
Young patients

Table 5.6 Causes of hypocalcaemia

Vitamin D-dependent
Vitamin D deficiency or malabsorption
Impaired vitamin D metabolism
  Chronic renal failure
  Chronic liver failure
  Phenytoin
  Congenital renal 1-α-hydroxylase deficiency

Hypoparathyroidism/PTH resistance
Hypoparathyroidism
  Postoperative
  Idiopathic
DiGeorge's syndrome
Infiltrative (e.g. haemochromatosis)
Hypomagnesaemia
Pseudohypoparathyroidism

Miscellaneous
Phosphate therapy
Acute rhabdomyolysis
Pancreatitis
Massive citrated blood transfusion

absorptiometry (DXA) and ultrasound-based approaches to assess fracture risk when preventative therapy is being considered.

DXA measures bone mineral density (BMD), which is bone mineral content partially corrected for size, either centrally (spinal BMD) or peripherally (forearm or heel BMD). Quantitative ultrasound analyses transmission of high-frequency sound through bone at the calcaneus, phalanges and other skeletal sites.

Histopathology

Bone biopsy

Because metabolic bone diseases generally affect the whole skeleton, the underlying diagnosis can usually be confirmed by performing a bone biopsy at a convenient site such as the iliac crest. In this way, abnormalities such as defective osteoid mineralization, loss of trabecular bone and excessive osteoclastic activity can be detected. However, although bone biopsy may be the most accurate means of defining an underlying metabolic bone disease, it is invasive and so its use is generally confined to patients in whom there is diagnostic difficulty.

Management

Lifestyle modification

Lifestyle modification is an important aspect of management of all diseases. In metabolic bone diseases it can be very useful but should not be used in isolation; correction of dietary deficiency of calcium and vitamin D, stopping smoking, reducing alcohol consumption and increasing exercise is beneficial in patients with osteoporosis.

Physiotherapy

Increasing exercise capacity is important for all patients with skeletal diseases. Improving strength and balance can help prevent fractures by decreasing the likelihood of falls. Transcutaneous electrical nerve stimulation (TENS) and acupuncture, for example, can all help in the management of skeletal pain.

Occupational therapy

A thorough assessment of impairment and disability can be provided by occupational therapists so that intervention is appropriate to the social context.

Drug treatments

Drug treatment in metabolic bone disease is aimed

at correcting the underlying metabolic disturbance, which may be calcium deficiency, vitamin D deficiency, malabsorption or abnormal metabolism, or a result of excessive bone breakdown. Brief information is presented below; however the information—especially that relating to adverse effects and contraindications—is not complete. Fuller information is given in a formulary; for example, the *British National Formulary* (*BNF*). Drug regimens should also be checked in the *BNF*.

Bisphosphonates

The bisphosphonates disodium etidronate, risedronate sodium, alendronic acid and intravenous disodium pamidronate are used for the prevention and treatment of postmenopausal osteoporosis including corticosteroid-induced osteoporosis. Alendronic acid is also licensed for the prevention and treatment of osteoporosis in men. In addition, bisphosphonates can be used in Paget's disease of bone (e.g. risedronate sodium or tiludronic acid) or hypercalcaemia of malignancy (e.g. intravenous disodium pamidronate).

The main adverse effects are on the gastrointestinal system, ranging from nausea to oesophageal ulceration and stricture formation. They are contraindicated in pregnancy and breastfeeding, and should be used with caution in renal impairment or hypocalcaemic states.

Hormone replacement therapy and selective oestrogen receptor modulators

Hormone replacement therapy (HRT) may be useful in postmenopausal women at risk of osteoporosis. Selective oestrogen receptor modulators (SERMs) such as raloxifene are indicated for the prevention of postmenopausal osteoporosis and the treatment of osteoporotic fractures in postmenopausal women. Adverse effects include thromboembolism, leg cramps and mastalgia. HRT is contraindicated in women with oestrogen-dependent cancers (e.g. breast) and both HRT and SERMs should not be used in women with active thromboembolic disorders.

Calcium

Calcium salts are used where there is dietary deficiency of calcium, and also in the treatment of osteoporosis and chronic hypocalcaemia. Adverse effects are mild and usually related to gastrointestinal upset.

Vitamin D and its metabolites

Vitamin D (cholecalciferol) and its metabolites (ergocalciferol, alfacalcidol, calcitriol, dihydrotachysterol) are used in dietary deficiency of vitamin D, chronic renal failure, vitamin D malabsorption or abnormal metabolism, and in hypoparathyroidism. It can be given orally or via the intramuscular approach. Adverse effects include symptoms of hypercalcaemia from overdosage, and so it is contraindicated in hypercalcaemia or hypercalciuria.

Calcitonin

Calcitonin is given via subcutaneous injection, or intranasally for the treatment of hypercalcaemia, postmenopausal osteoporosis or Paget's disease of bone. Adverse effects include inflammatory reactions at injection sites and nausea or diarrhoea.

Surgery

(See primary hyperparathyroidism, p. 293.)

Diseases and their management

Rickets and osteomalacia

Rickets and osteomalacia consist of a number of heterogeneous disorders characterized by defective mineralization of newly synthesized organic bone matrix. Rickets results when defective mineralization during skeletal growth leads to impaired epiphyseal growth plate calcification and bony deformity. Osteomalacia refers to defective mineralization of the adult skeleton.

Epidemiology

Prevalence. Osteomalacia and rickets brought about by dietary deficiency are relatively common. Non-nutritional causes are rare.

Age. In childhood and the elderly.

Sex. X-linked hypophosphataemic rickets most commonly affects males.

Race. Osteomalacia is relatively common amongst Asian immigrants in the UK.

Genetics. Rare causes may be familial (e.g. congenital renal 1-α-hydroxylase deficiency, hypophosphatasia, hereditary renal tubular disorders).

Geography. Vitamin D deficiency is most frequently seen in those developing countries where food is not fortified with vitamin D and reduced sunlight exposure is common.

Disease mechanisms

The cause of osteomalacia and rickets is usually a reduced serum level of 1,25-$(OH)_2$-D. This results in lowering of the calcium-phosphate product to below normal, leading to impaired matrix mineralization. A direct effect of 1,25-$(OH)_2$-D on osteoblast activity and the mineralization process has also been suggested.

There are many causes of reduced 1,25-$(OH)_2$-D levels (Table 5.7). Insufficient dietary intake of vitamin D associated with reduced skin synthesis because of low levels of sunlight is the most common. Rarely, rickets and osteomalacia are unrelated to deficiency or abnormal metabolism of vitamin D (e.g. excessive use of phosphate-binding antacids).

Skeletal deformities caused by childhood rickets are now rare since the widespread supplementation of food and milk with vitamin D. However, osteomalacia is relatively common amongst the elderly and in immigrant Asian populations, especially those who adhere to a strict vegetarian diet.

Table 5.7 Causes of rickets and osteomalacia

Vitamin D deficiency
Increased vitamin D requirements in childhood because of skeletal growth
Poor diet combined with reduced sunlight exposure
Vitamin D malabsorption
Gastric surgery
Small bowel malabsorption syndrome (e.g. coeliac disease, Crohn's disease)
Chronic cholestasis
Chronic pancreatic insufficiency
Impaired vitamin D metabolism
Chronic renal failure
Chronic liver failure
Drugs (e.g. phenytoin, barbiturates)
Congenital renal 1-α-hydroxylase deficiency (vitamin D-dependent rickets)
Drugs, toxins
Fluoride therapy
Bisphosphonates
Aluminium poisoning
Hypophosphataemia
Isolated renal tubular defects in phosphate handling (e.g. X-linked hypophosphataemic vitamin D-dependent rickets)
Urinary phosphate wasting resulting from a generalized renal tubular defect (Fanconi's syndrome)
Miscellaneous
Distal renal tubular acidosis
Hypophosphatasia (inherited alkaline phosphatase deficiency)
Malignancy

Rickets and osteomalacia are characterized by defective mineralization of newly synthesized organic bone matrix. This leads to impaired epiphyseal growth in children, resulting in the characteristic skeletal deformities of rickets. In adults, unmineralized osteoid accumulates on bone surfaces, leading to a deficit in skeletal bone mineral. Ultimately, this compromises the mechanical strength of the skeleton, resulting in an increased susceptibility to fractures.

Clinical features

The clinical features of rickets are impaired skeletal growth, bony deformities such as bowing of long bones and rib deformities (rachitic rosary, Harrison's groove) (Table 5.1), weakness and symptoms of hypocalcaemia (see Table 5.3).

Osteomalacia is characterized by widespread bone pain and tenderness, muscle weakness, proximal myopathy (causing a waddling gait) and an increased risk of fracture.

Diagnosis

Childhood rickets is readily diagnosed from its characteristic skeletal deformities. However, the clinical manifestations of osteomalacia in the adult are relatively non-specific. Although typical radiographical changes such as Looser's zones may be seen, osteomalacia is most commonly diagnosed from serum biochemistry on the basis of a decreased phosphate concentration and an elevated alkaline phosphatase. Measurement of 25-OH-D provides useful confirmatory evidence of vitamin D deficiency, but this may be normal (e.g. in chronic renal failure). Iliac crest bone biopsy should be carried out if there is diagnostic difficulty.

Differential diagnosis

The differential diagnosis of osteomalacia includes:

- Other causes of proximal myopathy (see p. 954)
- Other causes of increased skeletal fragility (Table 5.8)

Investigation

If vitamin D deficiency is confirmed, further investigation to detect malabsorption is indicated if dietary deficiency seems unlikely, or if there are other features to suggest malabsorption (e.g. a history of gastric surgery, associated iron or folic acid deficiency).

If vitamin D levels are normal in a child with rickets, primary urinary phosphate wasting is the probable cause. Further studies of renal tubular function should then be

Rickets and osteomalacia at a glance

A heterogeneous group of disorders characterized by defective bone matrix mineralization. Rickets occurs in childhood and consequent bone softening leads to characteristic skeletal deformities. Osteomalacia is defective mineralization of the adult skeleton.

Epidemiology

Prevalence
Nutritional vitamin D deficiency is common

Age
In childhood and the elderly

Race
Asian immigrants in the UK are particularly at risk

Genetics
Rare causes may be familial

Geography
Nutritional vitamin D deficiency in childhood is largely confined to developing countries

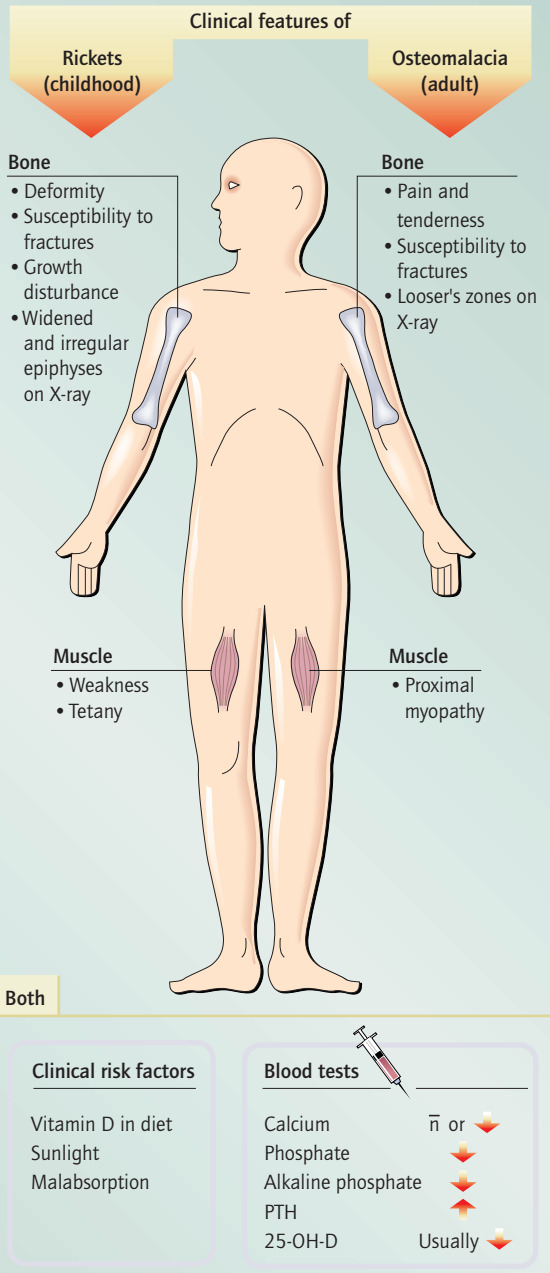
Aetiology

Dietary
Dietary deficiency of vitamin D combined with reduced vitamin D skin synthesis because of poor sunlight exposure

Malabsorption
Of vitamin D

Impaired vitamin D metabolism

Hypophosphataemia



carried out to investigate whether this is part of a generalized tubular disorder (e.g. Fanconi's syndrome).

Haematology

There may be evidence of associated iron or folic acid deficiency if malabsorption is responsible.

Biochemistry

- *Serum calcium:* usually at the lower end of the normal range, but in children there can be a severe hypocalcaemia
- *Serum phosphate:* reduced in the absence of renal failure
- *Serum alkaline phosphatase:* may be elevated
- *Serum PTH:* elevated

Table 5.8 Common causes for an increased fracture tendency

Increased skeletal fragility
Osteoporosis
Osteomalacia
Malignant deposits
Paget's disease of bone
Increased risk of falling
Neurological disorders
Stroke
Cognitive impairment
Parkinson's disease
Poor visual acuity
Locomotor disorders and other causes of postural instability
Cardiovascular disease
Drugs
Diuretics
Antihypertensives
Sedatives

- *Serum 25-OH-D:* usually reduced in vitamin D deficiency or malabsorption

Diagnostic imaging
Plain radiography may show:
- Appearance of low density because of impaired mineralization and may resemble that of osteoporosis
- Bone deformity and widened irregular epiphyses in rickets
- Pseudofractures (Looser's zones) in osteomalacia most commonly seen in the scapulae, ribs, pubic rami and proximal femur.

Histopathology
Iliac crest bone biopsy can be useful if there is diagnostic difficulty. Impaired mineralization of collagenous bone matrix leads to its accumulation on actively forming bone surfaces. This is recognized as a widening of the layer of unmineralized osteoid on undecalcified sections.

Management

Dietary deficiency of vitamin D
Dietary vitamin D deficiency is readily corrected by giving vitamin D supplements. Body stores of vitamin D can be replenished by administering a single oral dose of ergocalciferol (vitamin D_2) 150 000–300 000 IU (1.25 mg). Low-dose ergocalciferol 200–400 IU (5–10 μg/day), which is available in combination with calcium supplements, should be taken if a continued dietary deficiency is anticipated. Regular administration of high-dose vitamin D should be avoided as it can cause hypercalciuria and/or hypercalcaemia.

Vitamin D malabsorption
Vitamin D malabsorption can usually be overcome with daily high-dose vitamin D and calcium supplements taken orally, although parenteral administration may be necessary. Alternatively, small doses of more potent metabolites such as calcitriol (1,25-$(OH)_2$-D) and alfacalcidol (1-α-OH-vitamin D) may be used. In either case, serum calcium should be regularly monitored.

Osteomalacia associated with renal disease
Although many forms of renal disease respond to high-dose vitamin D supplementation, there is often significant 1-α-hydroxylase deficiency and so α-hydroxylated vitamin derivatives (e.g. calcitriol or alfacalcidol) should be prescribed.

Prognosis

Vitamin D deficiency resulting from dietary deficiency or malabsorption usually responds well to vitamin D replacement. Osteomalacia associated with chronic renal failure can be difficult to manage in the long term, particularly if there is associated hypocalcaemia, which may be hard to correct.

Osteoporosis

Osteoporosis can be defined as a decrease in the quantity of bone per unit volume that is sufficient to compromise its mechanical function. The bone tissue is mineralized normally, but there is not enough of it to preserve the normal skeletal architecture.

Epidemiology

Prevalence. Thirty per cent of women living in developed countries are likely to sustain an osteoporotic fracture at some time in their life.

Age. Osteoporotic fractures are more common with increasing age. The annual UK incidence of hip fractures is 4.3/100 000 women aged 45–64 years, rising to 90.1/100 000 women aged 75–85 years. UK prevalence of vertebral fractures rises from 1–2% in women aged 44–54 years, to more than 10% in women over 65 years of age.

Sex. Osteoporotic fractures at all sites are more common in women than men (about 70% occur in women).

Race. The incidence of osteoporotic fractures is similar in different ethnic groups living in the same country, except in Afro-Caribbeans in whom it is relatively low.

Genetics. There may be a family history, and twin studies suggest a significant genetic component.

Geography. Osteoporosis is most common in developed countries.

Table 5.9 Causes of secondary osteoporosis

Endocrine causes
Cushing's disease
Thyrotoxicosis
Hypogonadism
Hyperparathyroidism
Drugs
Glucocorticoids
Heparin
Antiepileptics
Inflammatory
Rheumatoid arthritis
Ankylosing spondylitis
Ulcerative colitis
Gastrointestinal
Malabsorption
Primary biliary cirrhosis
Hereditary causes
Osteogenesis imperfecta
Homocystinuria
Ehlers–Danlos syndrome
Miscellaneous
Chronic renal failure
Immobilization (e.g. long-term bed rest)
Weightlessness (e.g. astronauts)
Alcohol

Classification

Idiopathic osteoporosis

Osteoporosis usually occurs in the absence of any disorder known to cause osteoporosis (Table 5.9), when it is termed idiopathic osteoporosis. A combination of low adult peak bone mass and excessive age-related bone mass is thought to be responsible. Because bone loss is relatively rapid for 5–10 years following the menopause, idiopathic osteoporosis is most common in postmenopausal women (postmenopausal osteoporosis). A number of factors that predispose to postmenopausal osteoporosis by adversely affecting peak bone mass or subsequent bone loss have been identified (Table 5.10). Occasionally, idiopathic osteoporosis occurs in childhood before puberty (juvenile osteoporosis), and in younger adults of either sex when the cause is unknown.

Secondary osteoporosis

Secondary osteoporosis develops as a result of a disorder known to cause osteoporosis. Of these disorders ovarian hormone deficiency (premature ovarian failure) and glucocorticoid treatment are relatively common (Table 5.9).

Table 5.10 Predisposing factors for postmenopausal osteoporosis

Age
Family history of osteoporosis (particularly history of maternal hip fracture)
Episodes of unexplained amenorrhoea for more than 6 months
Early menopause
Low calcium and vitamin D dietary intake
Smoking
Prolonged immobilization

Localized osteoporosis

Localized osteoporosis frequently develops where a limb is immobilized, such as after wearing a plaster cast, and in association with paraplegia and poliomyelitis. Localized osteoporosis can also be caused by algodystrophy (reflex sympathetic dystrophy, Sudeck's atrophy), whereby pain, swelling and autonomic dysfunction of a limb extremity develops after a precipitating event such as trauma.

Transient regional osteoporosis can occur in association with pregnancy. The spine and hip are the most commonly involved sites, and bone loss may largely recover.

Disease mechanisms

Osteoporosis arises as a result of a low peak bone mass and/or excessive bone loss.

- *Low peak bone mass:* insufficient bone tissue is formed during skeletal development. This may be because of genetic or environmental factors such as poor dietary calcium intake.
- *Excessive bone loss:* bone loss normally occurs as an age-related process following the attainment of peak bone mass. It may be excessive resulting from elevated bone resorption and/or reduced bone formation.

A significant reduction in bone mass (osteopaenia) does not necessarily cause any adverse effects. However, it is usually associated with an increase in skeletal fragility. This leads to a high risk of skeletal fractures, resulting in low trauma fractures and established osteoporosis. Any bone can be involved, but fractures of the hip, wrist and vertebral bodies are the most common.

Clinical features

Osteoporosis may predispose to fractures of any part of the skeleton. The most common sites are vertebral bodies, wrist and hip:

Vertebral body osteoporosis. This leads to wedge fractures of the vertebral body that may progress to near-complete vertebral body collapse. It is particularly associated with osteoporosis secondary to sex-hormone deficiency or glucocorticoid excess, and patients present either with sudden pain during an episode of vertebral collapse, or with a

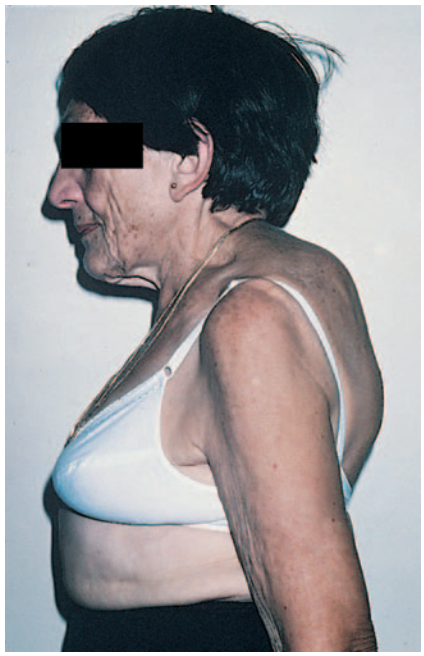


Figure 5.4 Dowager's hump. Kyphotic deformity of the thoracic spine in a patient with osteoporosis.

progressive kyphotic deformity (dowager's hump) associated with a loss of height (Fig. 5.4). The cumulative effect of vertebral collapse and associated deformity may reduce mobility. Although spinal cord compression is extremely rare, aggravation of nerve root irritation resulting from coexisting lumbar spondylosis is relatively common.

Wrist osteoporosis. A Colles' fracture in a middle-aged woman should be assumed to be secondary to osteoporosis until proven otherwise.

Hip osteoporosis. Osteoporotic hip fractures usually occur in people over 65 years of age. The risk of such fractures is considerably influenced by the presence of factors that increase the risk of falling (Table 5.8).

Diagnosis

Osteoporosis should be considered when a person in a high-risk group for osteoporosis (e.g. postmenopausal women) presents with a fracture at a typical site such as the hip, wrist or spine associated with relatively low levels of trauma (e.g. falling from a standing height).

Differential diagnosis

Secondary causes of osteoporosis should be excluded by clinical assessment and serum biochemistry.

Other causes of increased skeletal fragility should be considered for minimal-trauma fractures, particularly those of the vertebrae (Table 5.8). In general, symptoms from a single episode of osteoporotic vertebral body collapse tend to improve over a few days, whereas malignant spinal deposits cause continuous pain that fails to resolve. In addition, laboratory investigations may be helpful (e.g. to exclude osteomalacia and multiple myeloma).

Investigation

Haematology

Full blood count is normal.

Biochemistry

- *Serum biochemistry:* characteristically normal
- *Serum alkaline phosphatase:* may be marginally elevated if there has been a recent fracture

Diagnostic imaging

Plain radiography. This is essential for the diagnosis of a fracture. In patients with established osteoporosis, early changes consist of wedge fractures and/or vertebral body height loss. In patients with more advanced osteoporosis, marked vertebral body compression or biconcave vertebral body fractures may occur. Plain radiographs may also be suggestive of osteopaenia, pointing to an underlying diagnosis of osteoporosis.

Isotope bone scan. This may differentiate between vertebral body collapse resulting from osteoporosis and that from malignant deposits. Multiple areas of uptake throughout the skeleton suggest malignancy.

Bone densitometry. This may reveal that the bone mineral density is below the threshold for diagnosis of osteoporosis according to the World Health Organization (WHO) criteria defining those who need further treatment (Fig. 5.5). Bone densitometry has also been used as a means of

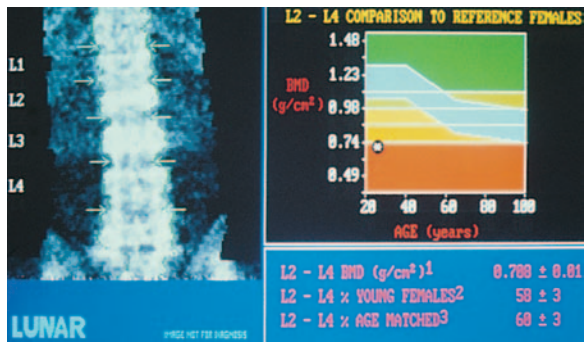


Figure 5.5 Bone densitometry. Bone densitometer reading of a female patient with spinal osteoporosis. Note the normal range for bone mineral density (BMD) at different ages (blue band) and the patient's result plotted according to age.

assessing future risk of osteoporosis in those with other risk factors, thereby targeting possible patients for preventive therapy (Table 5.10).

Histopathology

Iliac crest bone biopsy. This is useful for distinguishing between osteoporosis, osteomalacia, malignant deposits and Paget's disease of bone. Osteoporosis is seen as a generalized loss of trabecular bone and thinning of the cortex. However, a bone biopsy is only indicated if there is diagnostic difficulty.

Management of acute vertebral collapse

Initially, this should be treated with bed rest and analgesia followed by early mobilization. In addition, calcitonin by subcutaneous injection or intranasally may be given during acute episodes to relieve bone pain. Physiotherapy and TENs machines can play an important part in early mobilization. Measures to prevent further osteoporotic fractures need to be remembered.

Prevention of postmenopausal osteoporosis

Lifestyle modification. This is an important part of the

Osteoporosis at a glance

A decrease in the amount of bone tissue, resulting in a reduction of skeletal strength and an increased tendency to sustain fragility fractures.

Epidemiology

Prevalence
Occurs in up to 30% of menopausal women

Age
Predominantly a disease of the elderly

Race
Low prevalence in Afro-Caribbeans

Genetics
Significant genetic component

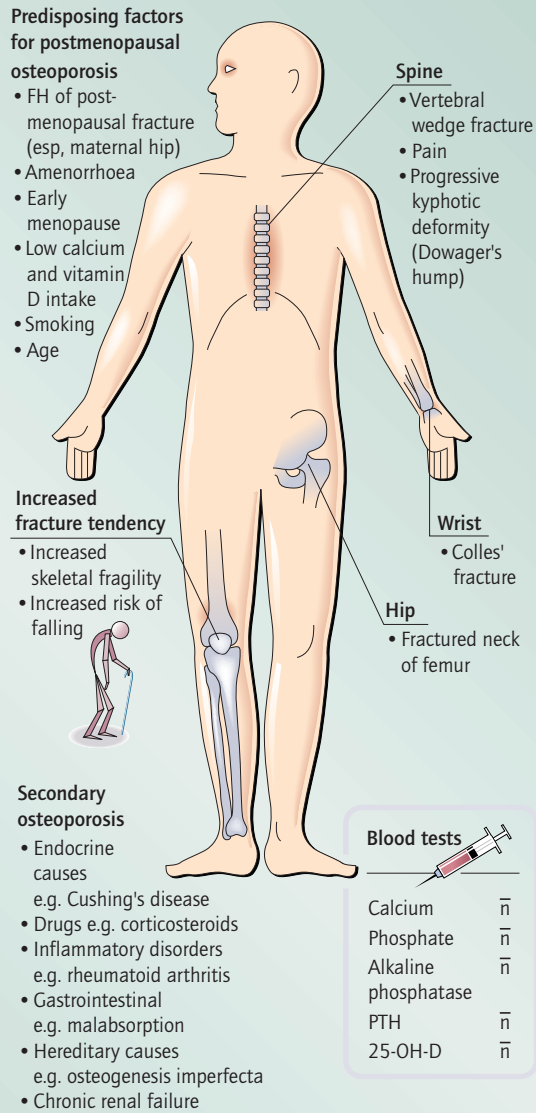
Geography
Most common in developed countries

Aetiology

Idiopathic osteoporosis
Most commonly affects postmenopausal women

Secondary osteoporosis
Endocrine disorders: sex hormone deficiency, Cushing's syndrome and thyrotoxicosis
Prolonged treatment with glucocorticoids
Metabolic disorders: chronic renal failure, malabsorption states
Hereditary causes: osteogenesis imperfecta, homocystinuria, Ehlers–Danlos syndrome
Miscellaneous: multiple myeloma, arthritides, alcoholism, chronic heparin therapy, systemic mastocytosis, anorexia nervosa

Localized osteoporosis
Limb immobilization
Algodystrophy (reflex sympathetic dystrophy, Sudeck's atrophy)
Transient regional osteoporosis



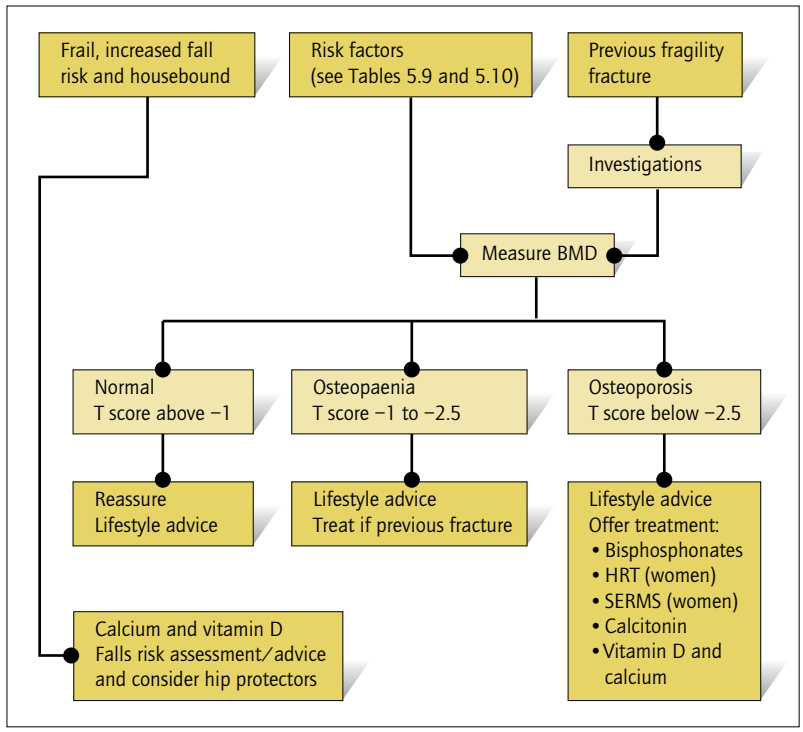


Figure 5.6 Management of women aged over 45 years who have or are at risk of osteoporosis. (Adapted from the Royal College of Physicians and Bone and Tooth Society of Great Britain Osteoporosis Clinical Guidelines for Prevention and Treatment, July 2000.)

management of osteoporosis. Encouraging people to stop smoking, take regular exercise and improve their dietary intake of calcium can help.

Medical therapy. Several drugs are available for the prevention and treatment of postmenopausal osteoporosis:

1 *Bisphosphonates:* the most widely used drugs to treat osteoporosis. They have been shown to reduce the risk of further fractures at both the spine and hip. Examples include disodium etidronate, risedronate sodium, alendronic acid, disodium pamidronate and tiludronic acid. They are indicated for the prevention and treatment of postmenopausal osteoporosis including corticosteroid-induced osteoporosis. Alendronic acid is also licensed for the prevention and treatment of osteoporosis in men. The main adverse effects are on the gastrointestinal system ranging from nausea to oesophageal ulceration and stricture formation. They are contraindicated in pregnancy and breastfeeding, and should be used with caution in renal impairment or hypocalcaemic states.

2 *Hormone replacement therapy:* reduces bone loss and fracture incidence in postmenopausal women. Its use in older women is limited by patient tolerance rather than lack of efficacy (e.g. withdrawal bleed; Fig. 5.6).

3 *Selective oestrogen receptor modulators:* can be used for prevention of postmenopausal osteoporosis and for the treatment of osteoporotic vertebral fractures in postmenopausal women.

4 *Anabolic agents:* these are currently under investigation for their role in stimulating osteoblastic activity; e.g. PTH, which has powerful effects on bone density.

Prevention of osteoporotic fractures in frail housebound people

- *Calcium and vitamin D supplementation:* many people who are frail or institutionalized are vitamin D-deficient and have a poor calcium intake. Use of these supplements in this population has been shown to decrease the risk of fracture.
- *Falls risk assessment and advice:* in this population it is especially important to look not only for increased skeletal fragility but also an increased risk of falling (Table 5.8).
- *Hip protectors:* foam or rubber shields that are worn over the greater trochanter and reduce the likelihood of hip fractures if the patient falls. However, they can be uncomfortable, conspicuous and difficult to put on, and this probably limits their usefulness.

Prognosis

Hip fracture is the most serious complication of osteoporosis, being associated with a 20% mortality within the first 3 months. In addition, many patients fail to regain their premorbid level of mobility and independence, with approximately 30% of patients requiring some form of institutional care.

Recurrent vertebral fractures in spinal osteoporosis

can cause pain and progressive deformity, and in some patients this leads to significant morbidity.

Paget's disease of bone

Paget's disease of bone is a localized disorder of bone remodelling that results in a disorganized structure of woven and lamellar bone.

Epidemiology

Prevalence. Approximately 3.6% of the population over 40 years of age in the UK.

Age. Rare before 40 years of age. Prevalence increases with age.

Sex. Sixty per cent of patients are male.

Race. Common in the UK. Rare in Scandinavia, India, Japan, China, Arab Middle East and black Africans.

Genetics. Family clustering occurs and siblings of patients with Paget's disease are 10 times more likely to develop the condition. In some families, Paget's disease is linked to a susceptibility locus on chromosome 18q21-22, which also contains the gene responsible for familial expansile osteolysis (FEO). FEO is a rare bone dysplasia with many similarities to Paget's disease of bone.

Disease mechanisms

Measles virus, respiratory syncytial virus and canine distemper virus have been suggested as causative agents.

There are three pathological stages:

1 Initially the bone is invaded by huge multinucleated osteoclasts, resulting in intense bone resorption and accompanied by vascular hypertrophy.

2 The bone resorption is then accompanied by disorganized woven bone formation.

3 The amount of bone resorption then decreases, resulting in irregularly shaped trabecular bone and bone enlargement.

Clinical features

About 30% of pagetic lesions are associated with pain, which is the presenting symptom in 80% of cases. Any bone may be involved, but most commonly affected sites are the pelvis, lumbar spine and femur. The skeletal distribution of these lesions in any one individual tends to be multifocal and asymmetrical. Whereas lesions at any one anatomical site may progress relentlessly within the same bone, contiguous spread to adjacent bones is not seen.

- *Limb involvement:* causes pain at the affected site. Deformity may be present such as the 'sabre tibia', which is caused by a combination of bony enlargement and bowing as a result of skeletal softening. Long bone deformities can also cause osteoarthritis of adjacent joints. Paget's disease may result in transverse fractures because of localized skeletal fragility, particularly where aggressive lytic lesions are present in weight-bearing bones. In addition, small fissure fractures can occur along the convex surface of bowed lower limb bones.
- *Skull involvement:* leads to an increase in head size with or without frontal bossing. Hearing loss may also occur (conductive and/or sensorineural), while other cranial nerves may be affected less commonly. When the skull base is involved, the resulting softening can lead to basilar invagination. Increased vascularization of skull lesions may also result in the so-called vascular steal syndrome, which causes blood to be diverted away from the cerebrum, leading to somnolence and apathy.
- V*ertebral involvement:* may lead to vertebral compression fractures and secondary degenerative changes. Rarely, spinal cord compression and caudal ischaemia secondary to vascular steal syndrome may occur.
- *Facial involvement:* may cause facial deformity, leading to dental problems and a characteristic 'lion face' appearance (leontiasis ossea).
- *Osteosarcoma:* the most devastating complication of Paget's disease, occurring in approximately 0.2% of patients. Patients present with new pain in an existing affected site, the pelvis, femur and humerus being affected most commonly.
- *High output cardiac failure:* a rare complication of Paget's disease, which results from excess skeletal blood flow.
- *Hypercalcaemia:* may occur during periods of prolonged immobilization.

Diagnosis

Paget's disease of bone is readily diagnosed in patients presenting with localized bone pain by performing X-rays of the affected site. Alternatively, Paget's disease may be diagnosed in asymptomatic individuals with an isolated elevation in serum alkaline phosphatase.

Differential diagnosis

Other causes of localized bone pain need to be considered such as malignant deposits.

Investigation

Biochemistry

Serum alkaline phosphatase. This is nearly always elevated, and may reach beyond 10 times the upper normal limit, highest levels being found in association with skull involvement. This measure is particularly useful in monitoring the response of patients to therapy.

Paget's disease at a glance

A localized disorder of bone remodelling that results in a disorganized structure of woven and lamellar bone.

Epidemiology

Prevalence

Occurs in approximately 3.6% of people over 40 years old in the UK

Age

Rare before 40 years old. Increases with age

Sex

60% are male

Race

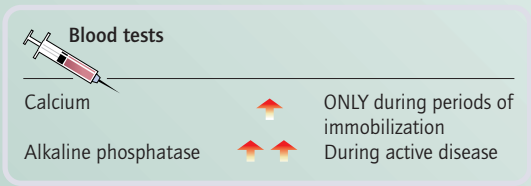
Common in the UK

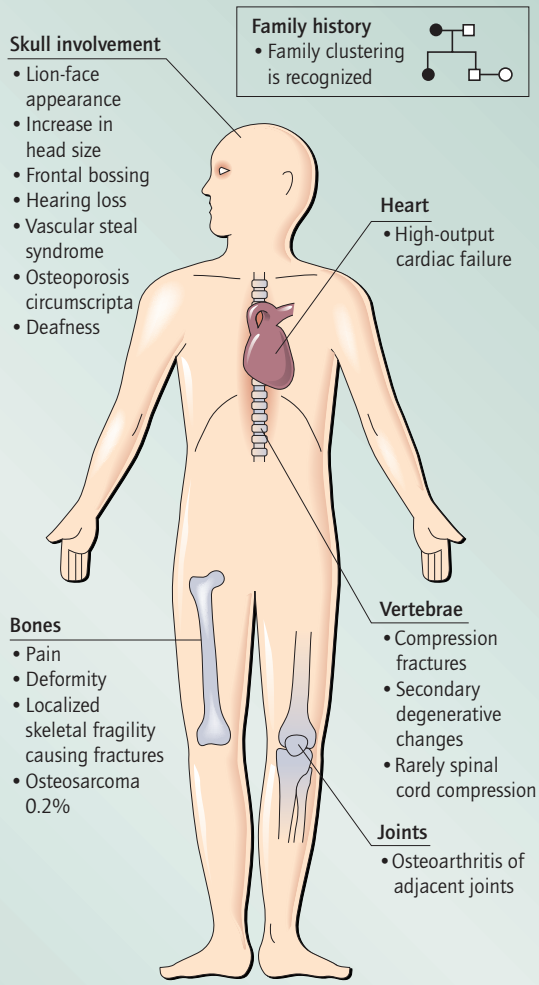
Genetics

Familial clustering occurs

Aetiology

Unknown





Diagnostic imaging

Plain radiography. This reveals generalized expansion and deformity of affected long bones, with a characteristic lytic leading edge ('blade of grass' appearance). There may also be areas of sclerotic bone at sites of osteoblastic reaction. When Paget's disease affects the skull, characteristic widening of the skull vault may be seen (Fig. 5.7), or broad scalloped areas of lysis (osteoporosis circumscripta).

Isotope bone scan. This is useful for showing the extent of pagetic involvement. Characteristically, affected bones show intense and uniform uptake over a considerable length.

Management

Bisphosphonates. These are the mainstay of treatment for Paget's disease of bone. Treatment should be offered to all symptomatic individuals, and should be considered in younger asymptomatic patients particularly where a weight-bearing bone is affected.

Bisphosphonates act to suppress osteoclast activity following their uptake within the skeleton. Higher doses for a shorter duration are used, compared to the treatment regimen for osteoporosis (e.g. risedronate sodium 30 mg/day for 8 weeks for Paget's disease of bone but 5 mg/day continuously for postmenopausal osteoporosis). In the great majority of cases, bisphosphonates cause significant symptomatic relief and lowering—if not normalization—of the serum alkaline phosphatase. Although patients frequently relapse within a few years, they generally respond to further courses of treatment.

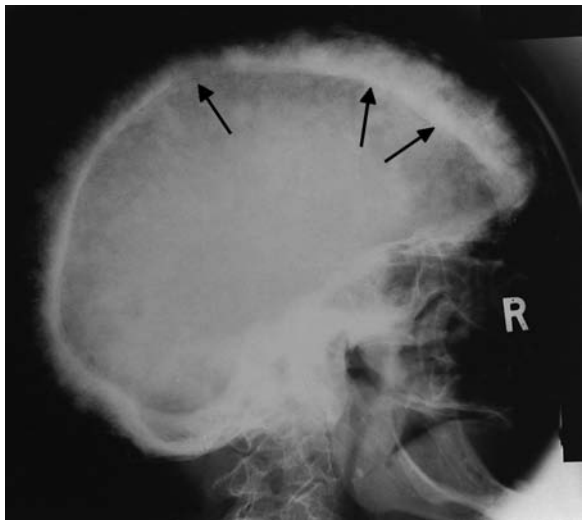


Figure 5.7 Radiograph demonstrating Paget's disease of bone. There is thickening of the skull vault and regions of lucency and sclerosis (arrows).

Prognosis

With the use of bisphosphonates, pagetic bone pain can be treated effectively and long-term complications such as deformity and secondary osteoarthritis can largely be prevented. However, this treatment does not appear to prevent the development of osteosarcoma, which remains a life-threatening complication affecting a small fraction of patients.

Hyperparathyroidism

Hyperparathyroidism is defined as increased PTH secretion from the parathyroid glands. The most common form, primary hyperparathyroidism, is a common endocrine disorder characterized by chronic hypercalcaemia (Table 5.2).

Epidemiology

Prevalence. Approximately 1/1000 men and 2/1000 women at 60 years of age.

Age. Incidence of primary hyperparathyroidism increases with age.

Sex. Approximately 70% of patients are female.

Genetics. A small proportion of cases are familial, when primary hyperparathyroidism is usually a component of multiple endocrine neoplasia (MEN) type I or II.

Classification

Hyperparathyroidism may be primary, secondary or tertiary:

- *Primary hyperparathyroidism:* usually caused by a single benign parathyroid gland adenoma (85% of cases). Otherwise, it results from chief cell hyperplasia of all four parathyroid glands. Carcinoma of a single parathyroid gland is rare, as are familial forms such as MEN types I and II.
- *Secondary hyperparathyroidism:* occurs as a physiological response in chronic renal failure secondary to hypocalcaemia and/or hyperphosphataemia. PTH levels return to normal following correction of the calcium and phosphate levels.
- *Tertiary hyperparathyroidism:* occurs when the increased PTH release of secondary hyperparathyroidism becomes autonomous. Raised PTH levels then persist, despite correction of calcium and phosphate levels, and can lead to troublesome hypercalcaemia, requiring treatment by parathyroidectomy.

Disease mechanisms

In primary hyperparathyroidism, PTH release by the parathyroid gland is no longer under negative feedback control by serum calcium, leading to hyperparathyroidism and hypercalcaemia. This results in:

- Reversible symptoms of hypercalcaemia, reflecting the influence of serum ionized calcium on cellular functions such as neuromuscular activity
- Bone complications resulting from the excessive action of PTH on the skeleton
- Renal damage secondary to prolonged exposure to raised extracellular calcium levels causing nephrolithiasis and nephrocalcinosis
- Calcium deposition at other sites, such as joints, eyes and the skin

Clinical features of primary hyperparathyroidism

Primary hyperparathyroidism most commonly presents as incidental hypercalcaemia on routine serum biochemistry. Symptoms of hypercalcaemia are likely if the serum calcium concentration is higher than 3.0 mmol and consist of:

- Polyuria and polydipsia
- Nausea, anorexia and constipation
- Depression and sleep disturbance

Such symptoms may have existed for some time before diagnosis, but older patients can present acutely with dehydration, drowsiness and confusion. Alternatively, hyperparathyroidism may manifest with complications as a result of organ damage, most commonly involving the kidney or skeleton.

Renal involvement. This is the most common complication of primary hyperparathyroidism, affecting 20–40% of patients. It manifests as either nephrolithiasis or nephrocalcinosis, which do not usually coexist in the same patient; nephrolithiasis is the more common. Primary hyperparathyroidism is detected in 5–10% of people with recurrent calcium-containing renal stones. In nephrocalcinosis, calcium and phosphate precipitate in the renal tubules and interstitium, leading to renal impairment.

Skeletal involvement. In primary hyperparathyroidism this comprises the characteristic histological and clinical entity of osteitis fibrosa cystica. Early histological changes are present in most people with primary hyperparathyroidism, but less than 15% have symptoms such as bone pain at the time of diagnosis. The full clinical picture of osteitis fibrosa cystica is now rare. It consists of bone cysts, fractures and deformity. Osteopenia on bone densitometry is a fairly common finding.

Hypertension. This frequently coexists with primary hyperparathyroidism, but hyperparathyroidism has not been found to have a causal role and the hypertension does not usually resolve following parathyroidectomy.

Gastrointestinal complications. In MEN type I there is an association between primary hyperparathyroidism and peptic ulceration resulting from Zollinger–Ellison syndrome. There is also an association between primary hyperparathyroidism and peptic ulceration in the absence of MEN type I, with peptic ulceration reported by up to 20% of patients with primary hyperparathyroidism. There is an infrequent association with pancreatitis, but the pathophysiological basis for this is unknown.

Neurological complications. A syndrome of reversible proximal muscle weakness and wasting resulting from denervation and atrophy of type II muscle fibres can occur.

Articular manifestations. Chondrocalcinosis.

Pruritus and skin necrosis. Resulting from skin involvement.

Band keratopathy. Occurs following the deposition of calcium salts below the corneal epithelium.

Diagnosis

Increased PTH in the presence of raised serum calcium is considered diagnostic of primary and tertiary hyperparathyroidism.

Differential diagnosis

Other causes of hypercalcaemia should be considered (Table 5.5). It is particularly important to exclude malignancy which, together with primary hyperparathyroidism, accounts for more than 90% of patients with hypercalcaemia. In general, mild hypercalcaemia that remains asymptomatic suggests primary hyperparathyroidism.

Investigation

Haematology

Full blood count. Anaemia is common in secondary and tertiary hyperparathyroidism resulting from the associated chronic renal failure.

Biochemistry

- *Serum creatinine:* increased, and creatinine clearance decreased if there is renal impairment.
- *Serum calcium:* elevated in primary and tertiary hyperparathyroidism. Repeated measurements are required to confirm the elevation.
- *Serum phosphate:* usually reduced in primary hyperparathyroidism (urinary phosphate wasting) and elevated in secondary hyperparathyroidism resulting from renal failure.
- *Serum alkaline phosphatase:* increased if there is any associated bone disease.
- *Serum PTH:* usually elevated. It is usually suppressed in hypercalcaemia from other causes.
- *Serum 25-OH-D:* usually elevated. It is also elevated in hypercalcaemia caused by granulomatous diseases and lymphoma.
- *24-h Urinary calcium excretion:* normal or increased, and should be measured to exclude familial hypocalciuric hypercalcaemia in which it is less than 100 mg/g creatinine. Familial hypocalciuric hypercalcaemia can mimic asymptomatic primary hyperparathyroidism.

Diagnostic imaging

Plain radiography. This commonly shows a diffuse reduction in bone density. Radiological evidence of osteitis fibrosa cystica is present in less than 5% of patients at diagnosis. It consists of subperiosteal bone resorption (best seen along the radial aspect of middle phalanges), erosions of the tufts of the terminal phalanges, mottling of the skull vault ('salt-and-pepper appearance'), cystic lesions and loss of the lamina dura. There may also be radiological evidence of nephrocalcinosis.

Bone densitometry. Measurement of skeletal calcium at both cortical and trabecular sites may reveal osteopaenia, which may be monitored by serial measurements.

Other techniques. High-resolution ultrasonography, high-resolution computed tomography, subtraction scan with technetium and thallium radioisotopes and parathyroid arteriography with selective venous sampling may

Hyperparathyroidism at a glance

Increased parathyroid hormone (PTH) secretion from the parathyroid glands.

Epidemiology

Prevalence

1/1000 men and 2/1000 women of 60 years of age

Age

Increased incidence with increasing age

Sex

Approximately 70% of patients are female

Genetics

Familial hyperparathyroidism with multiple endocrine neoplasia (MEN) types I and II

Aetiology

Primary hyperparathyroidism

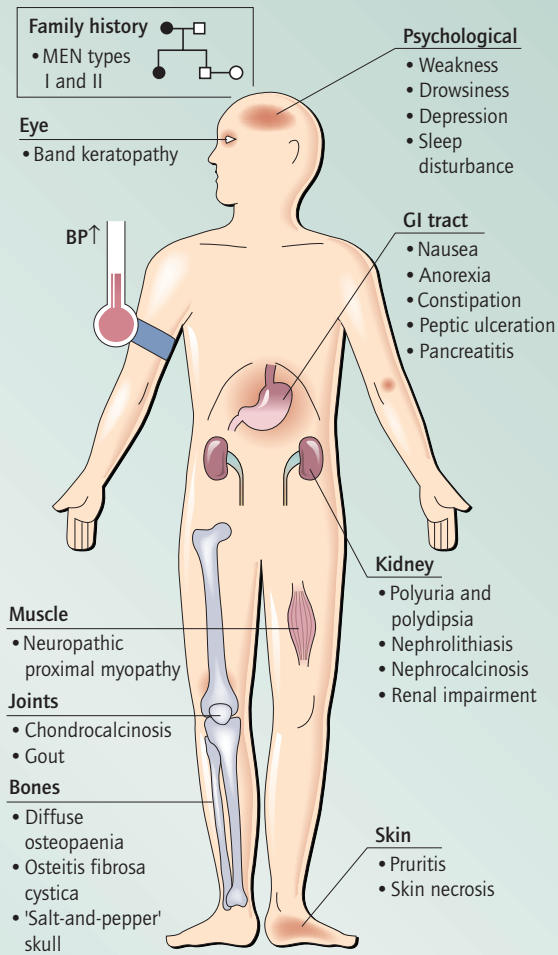
Most commonly caused by a benign adenoma of a single parathyroid gland (85% of all cases), or hyperplasia of all four glands

Secondary hyperparathyroidism

Increased PTH secretion in response to hypercalcaemia and/or hyperphosphataemia of chronic renal failure

Tertiary hyperparathyroidism

Autonomous increase in PTH secretion in patients with secondary hyperparathyroidism



Blood tests	Hyperparathyroidism		
	Primary	Secondary	Tertiary
Calcium	↑	n̄ or ↓	↑
Phosphate	↓	n̄ or ↑	↓
Alkaline phosphate	↑	–	–
PTH	↑	↑	↑

05

localize parathyroid adenomas prior to surgical removal.

Histopathology

Biopsy of cystic lesions seen on plain radiography reveals either a true bone cyst filled with fibrous tissue, or an appearance similar to an osteoclastoma ('brown tumour').

Management

Life-threatening hypercalcaemia

Life-threatening hypercalcaemia needs prompt treatment with:

- Intravenous fluids such as 0.9% saline, 4–6 l in 24 h as needed
- Intravenous disodium pamidronate

- Glucocorticoids (intravenous hydrocortisone, oral prednisolone)
- Calcitonin

Symptomatic hypercalcaemia in people unfit for surgery
People with symptomatic hypercalcaemia who are unfit for surgery may benefit from long-term oral treatment with phosphate or a bisphosphonate drug; postmenopausal women may benefit from oestrogen replacement.

Asymptomatic primary hyperparathyroidism with no evidence of renal or skeletal impairment
Asymptomatic primary hyperparathyroidism in people with no evidence of renal or skeletal impairment at the time of diagnosis may follow a benign course, with little organ damage developing. It may therefore be reasonable to treat these people, particularly older patients with mild hypercalcaemia (serum calcium less than 2.9 mmol/l), conservatively if there are facilities for regular monitoring of renal function and bone density.

Surgery
Surgery is the only curative treatment for primary hyperparathyroidism. It should be offered to patients with symptomatic hypercalcaemia or evidence of skeletal or renal complications. Unfortunately, there are no definitive means of predicting the development of complications in asymptomatic people. Surgery is usually considered for younger patients, who have longer to develop complications, and those with a higher serum calcium (e.g. more than 2.9 mmol/l), who are presumed more likely to sustain significant organ damage.

Parathyroid surgery should only be undertaken by experienced surgeons as there may be associated complications which include:

- Difficulty in identifying parathyroid tissue at surgery (an ectopic site occurs elsewhere within the neck or upper mediastinum in 5–10% of patients)
- Transient postoperative hypocalcaemia, which is maximal 4–7 days postoperatively and persists for up to 2–3 weeks
- Prolonged hypocalcaemia secondary to significant parathyroid gland damage (hypocalcaemia persisting for longer than 6 months suggests permanent hypoparathyroidism)

Prognosis
Surgery cures 90% of patients with uncomplicated primary hyperparathyroidism. For the remaining 10%, re-exploration of the neck following preoperative localization of parathyroid tissue may be successful.

Untreated hyperparathyroidism can lead to irreversible renal failure and skeletal deformity, but this is now rare. In secondary and tertiary hyperparathyroidism, the prognosis largely depends on that of the underlying renal failure.

Hypercalcaemia of malignancy
Hypercalcaemia of malignancy is usually an indicator of advanced disease with secondary skeletal deposits and is rarely the first manifestation.

Epidemiology
Prevalence. Five per cent of hospital inpatients with malignancy.

Disease mechanisms
Nearly 50% of people with hypercalcaemia of malignancy have squamous cell carcinoma of the lung or adenocarcinoma of the breast. Hypercalcaemia is also a common feature of squamous cell tumours of the head and neck, renal and ovarian tumours, and haematological tumours such as multiple myeloma.

Hypercalcaemia of malignancy is most commonly associated with secondary malignant deposits in the skeleton. Such deposits stimulate osteoclast activity. This results in hypercalcaemia when calcium release from the bone exceeds renal calcium excretion.

Two mechanisms have been implicated in this increased osteolysis and involve the release of local factors or PTH-related peptide (PTHrP):

1 *Release of local factors:* skeletal secondary deposits are thought to stimulate resorption of surrounding bone by locally releasing bone-resorbing cytokines such as interleukin-1, tumour necrosis factor and prostaglandins.

2 *PTHrP:* hypercalcaemia of malignancy sometimes resembles hyperparathyroidism biochemically (reduced renal calcium excretion, increased phosphate excretion) despite reduced serum PTH levels. This is now attributed to the release of PTHrP by tumour cells. PTHrP is a calcium-regulating peptide with PTH-like activity and has been isolated from a number of solid tumours causing hypercalcaemia. As well as contributing to the hypercalcaemia complicating skeletal deposits, PTHrP is probably responsible for the hypercalcaemia that occasionally occurs as a non-metastatic paraneoplastic manifestation of malignancy.

Clinical features
The elevated serum calcium that occurs in malignancy is frequently high enough to cause symptoms of hypercalcaemia (Table 5.2). These may be relatively non-specific, and hypercalcaemia should therefore be sought in all patients with malignancy who feel unwell.

Bone pain from skeletal secondary deposits is common. There is often mild renal impairment because of dehydration, but significant renal failure is suggestive of multiple myeloma.

Diagnosis

Hypercalcaemia of malignancy usually presents in patients with malignancy associated with metastatic bone disease, in which case the diagnosis is clear and further investigation of the cause of hypercalcaemia is not usually helpful. Although occult malignancy is an infrequent cause of hypercalcaemia, it should be sought if primary hyperparathyroidism and rarer causes such as sarcoidosis and familial hypocalciuric hypercalcaemia have been excluded.

Differential diagnosis

Other causes of hypercalcaemia should be considered if hypercalcaemia is found in patients with malignancy rarely associated with hypercalcaemia such as cancer of the colon or cervix, or in those without skeletal metastases (Table 5.5).

Investigation

If hypercalcaemia is discovered when there is no history of malignancy, and the PTH level is suppressed, investigations should be carried out to look for an underlying malignancy. If no malignancy is discovered, and the patient remains asymptomatic during follow-up, a rarer cause of hypercalcaemia such as sarcoidosis should be considered.

Haematology

- *Full blood count:* There may be anaemia
- *ESR:* May be elevated, particularly in multiple myeloma

Biochemistry

- *Serum creatinine:* frequently elevated because of dehydration
- *Serum calcium:* elevated
- *Serum phosphate:* may be reduced (urinary phosphate wasting)
- *Serum alkaline phosphatase:* may be increased if there are solid tumour metastases to bone causing an osteoblastic response, but normal in the presence of osteolytic metastases (e.g. in association with multiple myeloma)
- *Serum PTH:* usually suppressed
- *Serum 25-OH-D:* usually suppressed, but may be elevated if hypercalcaemia is associated with lymphoma

Diagnostic imaging

- *Plain radiography:* may reveal an osteolytic bone lesion or evidence of a primary malignancy such as lung neoplasm
- *Isotope bone scan:* may reveal previously unsuspected secondary malignant deposits of the skeleton

Management

Hypercalcaemia should generally be treated aggressively if there are associated symptoms. However, if there is severe life-threatening hypercalcaemia, the overall prognosis and quality of life may be such that aggressive treatment is not indicated.

Intravenous saline

People with hypercalcaemia are frequently dehydrated as a result of polyuria from renal tubular impairment. This reduces renal calcium excretion further and aggravates the hypercalcaemia. Mild hypercalcaemia may respond to an increase in oral fluid intake, but volume replacement with intravenous normal saline is mandatory for severe hypercalcaemia. This treatment usually lowers calcium levels significantly but only transiently in the absence of additional therapy to inhibit bone resorption.

Bisphosphonates

Intravenous administration of bisphosphonates (e.g. disodium pamidronate) combined with intravenous saline is an effective treatment for acute hypercalcaemia.

Glucocorticoids

Glucocorticoids (e.g. prednisolone 30–60 mg/day) are usually a helpful treatment for hypercalcaemia caused by haematological tumours such as multiple myeloma. They may be conveniently administered orally if the hypercalcaemia is long-standing. They are less effective for hypercalcaemia resulting from solid tumours. Glucocorticoids are also useful in the treatment of hypercalcaemia associated with non-malignant causes such as sarcoidosis and vitamin D intoxication.

Calcitonin

Calcitonin is a non-toxic agent that usually causes a rapid lowering of calcium levels in acute hypercalcaemia. Its action is relatively transitory, but may be prolonged if used in combination with glucocorticoids.

Specific treatment

Hypercalcaemia of malignancy is usually caused by disseminated malignancy, in which case specific therapy aimed at eradicating the underlying tumour is not usually helpful. The exception to this is hypercalcaemia occurring as a non-metastatic paraneoplastic manifestation of malignancy, in which case the hypercalcaemia may resolve following successful ablation of the primary tumour.

Prognosis

Hypercalcaemia of malignancy can generally be satisfactorily treated with the measures outlined above. The

Hypercalcaemia of malignancy at a glance

A high serum calcium occurring with malignancy usually indicating advanced disease with secondary skeletal deposits.

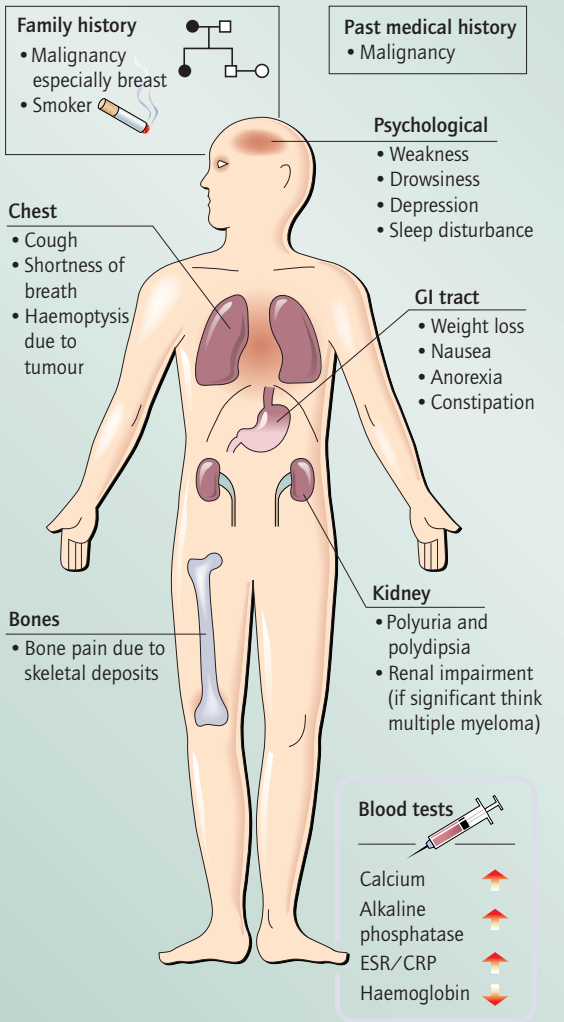
Epidemiology

Prevalence

5% of hospital inpatients with malignancy

Aetiology

Squamous cell carcinoma of the lung
Adenocarcinoma of the breast
Squamous cell tumours of the head and neck
Renal carcinoma
Ovarian carcinoma
Haematogenous tumours, especially multiple myeloma



overall prognosis is dictated by that of the underlying malignancy.

Hypocalcaemia

Hypocalcaemia is a less common clinical problem than hypercalcaemia and has fewer causes. Like hypercalcaemia, its presentation varies from an asymptomatic biochemical abnormality to a life-threatening condition.

Disease mechanisms

Hypocalcaemia usually results from chronic renal failure or other vitamin D-dependent causes (Table 5.6). Alternatively, it may be caused by hypoparathyroidism, which is most frequently seen as a postoperative complication of parathyroidectomy. There are a number of rare hypocalcaemic disorders characterized by hypoparathyroidism or PTH resistance (Table 5.11).

A decrease in ionized calcium concentration increases neuromuscular irritability. In addition, chronic hypocalcaemia can lead to mineralization of soft tissues, causing basal ganglia calcification and cataracts.

Hypocalcaemia caused by chronic renal failure results from a combination of phosphate retention and impaired vitamin D metabolism.

Clinical features

Clinical features of hypocalcaemia include (Table 5.3):

- *Paraesthesia:* peripherally and/or circumoral numbness.
- *Tetany:* cramp-like muscle spasms, which in milder forms are predominantly distal (carpopedal spasm) but may become generalized, causing, for example, laryngeal stridor.
- *Convulsions.*
- *Mental changes:* anxiety, psychosis.
- *Chvostek's sign:* gentle tapping over the facial nerve causes twitching of the muscles within its distribution. This is positive in 10% of people who do not have hypocalcaemia.
- *Trousseau's sign:* inflation of a sphygmomanometer cuff above diastolic pressure for 3 min to obliterate the radial pulse causes distal tetanic spasm.
- *Papilloedema:* if hypocalcaemia is long-standing.
- *Arrhythmias and/or ECG changes* (e.g. prolonged QT interval).

Differential diagnosis

The differential diagnosis of hypocalcaemia is shown in Table 5.6. If it is not caused by chronic renal failure, severe osteomalacia (associated with a raised PTH and reduced serum phosphate) can be readily distinguished from hypoparathyroidism (associated with a

Table 5.11 Hypocalcaemic disorders caused by hypoparathyroidism or parathyroid hormone (PTH) resistance

Cause	Features
Idiopathic hypoparathyroidism A rare autoimmune disorder	Often associated with cutaneous candidiasis and other autoimmune disorders such as Addison's disease. It usually presents in childhood. There is also an adult-onset form
DiGeorge's syndrome Congenital absence of the parathyroid and thymus glands	Severe hypocalcaemia and T-cell immunodeficiency
Pseudohypoparathyroidism Hereditary disorder characterized by end-organ resistance to PTH	Hypocalcaemia. It is associated with intellectual impairment, short stature and skeletal abnormalities such as short 4th and 5th metacarpals and metatarsals (Albright's hereditary osteodystrophy)
Pseudopseudohypoparathyroidism Hereditary disorder	Skeletal and developmental abnormalities of pseudohypoparathyroidism, but calcium metabolism is normal
Hypomagnesaemia Most commonly caused by malabsorption	Causes hypocalcaemia by inhibiting PTH release and antagonizing its peripheral effects

reduced PTH and elevated phosphate). Hypomagnesaemia should be excluded by measuring serum magnesium concentration.

If hypoparathyroidism is suspected, skeletal abnormalities such as short stature and short fourth and fifth metacarpals and metatarsals may suggest pseudohypoparathyroidism.

Investigation

Haematology

Full blood count. There may be anaemia if there is underlying chronic renal failure.

Biochemistry

- *Serum calcium:* reduced
- *Serum phosphate:* increased in chronic renal failure and hypoparathyroidism; decreased in vitamin D-dependent causes other than chronic renal failure
- *Serum PTH:* increased in chronic renal failure and other vitamin D-dependent causes; decreased in hypoparathyroidism
- *Serum magnesium:* reveals or excludes hypomagnesaemia
- *Urinary cyclic adenosine monophosphate (cAMP) response to PTH:* absent in pseudohypoparathyroidism, confirming the end-organ resistance to PTH
- *Assay of the GS protein on red cells:* this protein binds guanine triphosphate (GTP) and is deficient in most patients with pseudohypoparathyroidism

Immunology

Antibodies to the parathyroid and other endocrine glands have been found in patients with idiopathic hypoparathyroidism.

Diagnostic imaging

Plain radiography. Changes of renal osteodystrophy or osteomalacia/rickets are likely if chronic renal failure or vitamin D deficiency is severe enough to cause hypocalcaemia. In childhood hypoparathyroidism, radiographs may reveal skeletal abnormalities characteristic of pseudohypoparathyroidism.

Management

Acute life-threatening hypocalcaemia

Acute life-threatening hypocalcaemia is treated with 10 ml calcium gluconate 10% by slow intravenous infusion followed by an infusion of 20 ml calcium gluconate 10% in 5% dextrose 6-hourly, adjusted according to the serum calcium. Patients receiving intravenous calcium should have cardiac monitoring because of the risk of arrhythmias.

Chronic hypocalcaemia

Chronic hypocalcaemia is difficult to manage. Recurrences of the symptoms of hypocalcaemia and complications of overtreatment are common.

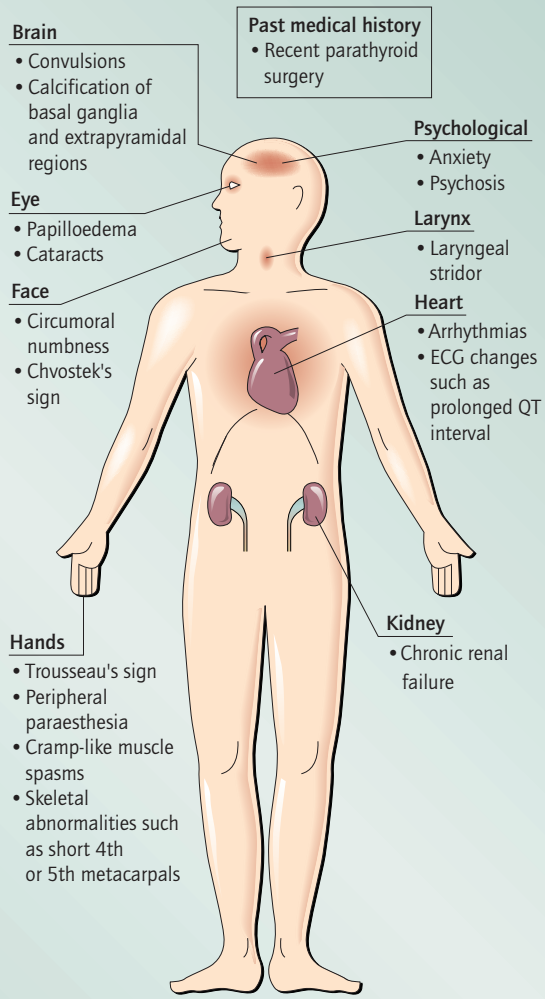
- *Calcium:* should be delayed until any associated hyperphosphataemia has been treated, to avoid extraskeletal calcification.

Hypocalcaemia at a glance

Low serum calcium ranging from an asymptomatic biochemical abnormality to a life-threatening condition.

Aetiology
Hypoparathyroidism
Chronic renal failure
Severe vitamin D deficiency
Pseudohypoparathyroidism

Blood tests	Hypoparathyroidism	Chronic renal failure	Vitamin D dependent causes	Pseudohypoparathyroidism
Calcium	↓	↓	↓	↓
Phosphate	↑	↑	↓	↑
PTH	↓	↑	↓	↑
Urinary cAMP response to PTH	Present	Present	Present	Absent



• *Vitamin D formulations:* usually given in combination with calcium supplements and include ergocalciferol, dihydrotachysterol, alfacalcidol and calcitriol. In general, the more potent metabolites of vitamin D are preferred because their shorter half-life allows more rapid restoration of normocalcaemia and faster recovery in the event of vitamin D intoxication. Vitamin D intoxication causes hypercalcaemia or hypercalciuria, leading to nephrolithiasis and/or nephrocalcinosis. It should be prevented by regular monitoring of serum and urinary calcium during treatment with vitamin D.

Prognosis

Complications of hypocalcaemia depend largely on its severity and duration, which in turn reflect the underlying cause:

• *Hypocalcaemia of chronic renal failure:* may be associated with osteomalacia and/or secondary hypoparathyroidism, leading to renal osteodystrophy

• *Hypocalcaemia resulting from hypoparathyroidism and pseudohypoparathyroidism:* usually long-standing, and basal ganglia or extrapyramidal calcification may result, causing significant mental impairment

! Must know checklist

- Useful investigations in metabolic bone disease
- Predisposing factors for postmenopausal osteoporosis
- Causes of secondary osteoporosis
- Diagnosis and treatment of osteoporosis
- Causes of rickets and osteomalacia
- Clinical features of osteomalacia
- Clinical features and causes of hypercalcaemia
- Clinical features and causes of hypocalcaemia
- Management of acute hypercalcaemia
- Clinical features of Paget's disease of bone

Further reading

Books

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Klippel JH, Dieppe PA. Chapters on osteoporosis and metabolic bone disease. In: *Rheumatology*. London: Mosby, 1997.

Journals

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Journal of Bone and Mineral Research (www.jbmr-online.org), American Society for Bone and Mineral Research.

Websites

National Osteoporosis Society: www.nos.org.uk

Paget's Society: www.paget.org.uk

International Bone and Mineral Society: www.bonekey-ibms.org