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).

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 hydrolyase 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
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 homeostatic 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 homeostatic 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).
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:
• 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

**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 1α-hydroxylase.

**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).
### 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

### Table 5.2 Clinical features of hypercalcaemia

<table>
<thead>
<tr>
<th>System</th>
<th>Feature</th>
</tr>
</thead>
<tbody>
<tr>
<td>Neurological and psychiatric</td>
<td>Drowsiness and altered conscious level</td>
</tr>
<tr>
<td></td>
<td>Headache</td>
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<tr>
<td></td>
<td>Sleep disturbance</td>
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<td></td>
<td>Depression</td>
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<td></td>
<td>Muscle weakness</td>
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<tr>
<td>Renal</td>
<td>Hyperreflexia</td>
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<tr>
<td>Gastrointestinal</td>
<td>Constipation</td>
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<tr>
<td>Renal impairment</td>
<td>Polyuria</td>
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<td></td>
<td>Polydipsia</td>
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<td></td>
<td>Nephrolithias</td>
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<tr>
<td>Cardiovascular</td>
<td>Hypertension</td>
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<tr>
<td></td>
<td>ECG abnormalities (shortened QT interval)</td>
</tr>
<tr>
<td>Articular</td>
<td>Chondrocalcinosis</td>
</tr>
<tr>
<td>Miscellaneous</td>
<td>Pruritus and skin necrosis</td>
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<tr>
<td></td>
<td>Band keratopathy</td>
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</table>

### Table 5.3 Clinical features of hypocalcaemia

<table>
<thead>
<tr>
<th>System</th>
<th>Feature</th>
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</thead>
<tbody>
<tr>
<td>Neurological and psychiatric</td>
<td>Peripheral paraesthesia</td>
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<tr>
<td></td>
<td>Circumoral numbness</td>
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<tr>
<td>Tetany</td>
<td>Cramp-like spasms</td>
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<td></td>
<td>Laryngeal stridor</td>
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<tr>
<td>Convulsions</td>
<td>Chvostek’s and Trousseau’s signs</td>
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<tr>
<td>Convulsions</td>
<td>Tetany</td>
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<tr>
<td></td>
<td>Chvostek’s and Trousseau’s signs</td>
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<tr>
<td>Cardiovascular</td>
<td>Arrhythmias</td>
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<tr>
<td></td>
<td>ECG abnormalities (prolonged QT interval)</td>
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<tr>
<td>Ocular</td>
<td>Papilloedema</td>
</tr>
<tr>
<td></td>
<td>Cataracts (if long-standing)</td>
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</table>

### 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.
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...
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...
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, alfalcacidol, 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.)

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### 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.

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

Table 5.7 Causes of rickets and osteomalacia

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

Chapter 5

Table 5.8 Common causes for an increased fracture tendency

<table>
<thead>
<tr>
<th>Increased skeletal fragility</th>
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<tbody>
<tr>
<td>Osteoporosis</td>
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<tr>
<td>Osteomalacia</td>
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<tr>
<td>Malignant deposits</td>
</tr>
<tr>
<td>Paget’s disease of bone</td>
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<table>
<thead>
<tr>
<th>Increased risk of falling</th>
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</thead>
<tbody>
<tr>
<td>Neurological disorders</td>
</tr>
<tr>
<td>Stroke</td>
</tr>
<tr>
<td>Cognitive impairment</td>
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<tr>
<td>Parkinson’s disease</td>
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<tr>
<td>Poor visual acuity</td>
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<tr>
<td>Locomotor disorders and other causes of postural instability</td>
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<tr>
<td>Cardiovascular disease</td>
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<tr>
<td>Drugs</td>
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<tr>
<td>Diuretics</td>
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<td>Antihypertensives</td>
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<tr>
<td>Sedatives</td>
</tr>
</tbody>
</table>

- 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 \( \text{D}_2 \)) 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 hypercalcæmia.

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.
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 5.9 Causes of secondary osteoporosis

<table>
<thead>
<tr>
<th>Endocrine causes</th>
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<tbody>
<tr>
<td>Cushing’s disease</td>
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<tr>
<td>Thyrotoxicosis</td>
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<td>Hypogonadism</td>
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<tr>
<td>Hyperparathyroidism</td>
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<tr>
<td>Drugs</td>
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<tr>
<td>Glucocorticoids</td>
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<td>Heparin</td>
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<td>Antiepileptics</td>
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<tr>
<td>Inflammatory</td>
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<td>Rheumatoid arthritis</td>
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<td>Ankylosing spondylitis</td>
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<td>Ulcerative colitis</td>
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<td>Gastrointestinal</td>
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<td>Malabsorption</td>
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<td>Primary biliary cirrhosis</td>
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<td>Hereditary causes</td>
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<td>Osteogenesis imperfecta</td>
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<tr>
<td>Homocystinuria</td>
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<td>Ehlers–Danlos syndrome</td>
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<tr>
<td>Miscellaneous</td>
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<tr>
<td>Chronic renal failure</td>
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<tr>
<td>Immobilization (e.g. long-term bed rest)</td>
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<tr>
<td>Weightlessness (e.g. astronauts)</td>
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<td>Alcohol</td>
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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
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...
assessing future risk of osteoporosis in those with other risk factors, thereby targeting possible patients for preventive therapy (Table 5.10).

**Histopathology**

*Iliaz 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, arthritis, alcoholism, chronic heparin therapy, systemic mastocytosis, anorexia nervosa

*Localized osteoporosis*

Limb immobilization

*Algodystrophy* (reflex sympathetic dystrophy, Sudeck’s atrophy)

*Transient regional osteoporosis*

**Increased fracture tendency**

• Increased skeletal fragility
• Increased risk of falling

**Blood tests**

- **Calcium**
- **Phosphate**
- **Alkaline phosphatase**
- **PTH**
- **25-OH-D**
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.
  - **Vertebral 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.
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.
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

**Psychological**
- Weakness
- Drowsiness
- Depression
- Sleep disturbance

**Eye**
- Band keratopathy

**Kidney**
- Polyuria and polydipsia
- Nephrolithiasis
- Nephrocalcinosis
- Renal impairment

**GI tract**
- Nausea
- Anorexia
- Constipation
- Peptic ulceration
- Pancreatitis

**Muscle**
- Neuropathic proximal myopathy

**Bones**
- Diffuse osteopaenia
- Osteitis fibrosa cystica
- ‘Salt-and-pepper’ skull

**Blood tests**

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<th>Blood test</th>
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<tr>
<td>Calcium</td>
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<td>↑ or ↑</td>
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<tr>
<td>Phosphate</td>
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<td>Alkaline phosphate</td>
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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
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- 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; post-menopausal 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.
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
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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.

**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
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.

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

<table>
<thead>
<tr>
<th>Cause</th>
<th>Features</th>
</tr>
</thead>
<tbody>
<tr>
<td>Idiopathic hypoparathyroidism</td>
<td>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</td>
</tr>
<tr>
<td>DiGeorge’s syndrome</td>
<td>Severe hypocalcaemia and T-cell immunodeficiency</td>
</tr>
<tr>
<td>Hereditary disorder</td>
<td>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)</td>
</tr>
<tr>
<td>Pseudopseudohypoparathyroidism</td>
<td>Skeletal and developmental abnormalities of pseudohypoparathyroidism, but calcium metabolism is normal</td>
</tr>
<tr>
<td>Hypomagnesaemia</td>
<td>Causes hypocalcaemia by inhibiting PTH release and antagonizing its peripheral effects</td>
</tr>
</tbody>
</table>
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**

<table>
<thead>
<tr>
<th>Blood tests</th>
<th>Chronic renal failure</th>
<th>Vitamin D dependent causes</th>
<th>Pseudohypoparathyroidism</th>
</tr>
</thead>
<tbody>
<tr>
<td>Calcium</td>
<td>Present</td>
<td>Present</td>
<td>Present</td>
</tr>
<tr>
<td>Phosphate</td>
<td>Present</td>
<td>Present</td>
<td>Present</td>
</tr>
<tr>
<td>PTH</td>
<td>Present</td>
<td>Present</td>
<td>Absent</td>
</tr>
<tr>
<td>Urinary cAMP response to PTH</td>
<td>Present</td>
<td>Present</td>
<td>Absent</td>
</tr>
</tbody>
</table>

**Past medical history**
- Recent parathyroid surgery

**Psychological**
- Anxiety
- Psychosis

**Larynx**
- Laryngeal stridor

**Eye**
- Papilloedema
- Cataracts

**Face**
- Circumoral numbness
- Chvostek's sign

**Brain**
- Convulsions
- Calcification of basal ganglia and extrapyramidal regions

**Hand**
- Trousseau's sign
- Peripheral paraesthesia
- Cramp-like muscle spasms
- Skeletal abnormalities such as short 4th or 5th metacarpals

**Kidney**
- Chronic renal failure

**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

- **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.
Chapter 5 Metabolic bone disease

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

Journals
Osteoporosis International, Springer Verlag.

Websites
National Osteoporosis Society: www.nos.org.uk
Paget’s Society: www.paget.org.uk
International Bone and Mineral Society: www.bonekey-ibms.org