Lec. 4

6 Calcium, phosphate and magnesium

Disorders of calcium metabolism are common in clinical practice and may result in hypocalcaemia or hypercalcaemia as well as bone abnormalities. Intimately associated with calcium disorders are disorders involving phosphate and magnesium metabolism.

CALCIUM METABOLISM

TOTAL BODY CALCIUM

The total body calcium depends upon the calcium absorbed from dietary intake and that lost from the body (Fig. 6.1). Ninety-eight per cent of body calcium is found in the skeleton. The extraosseous fraction, although amounting to only 1 per cent of the total, is essential because of its effect on neuromuscular excitability and cardiac muscle. An important mediator of intracellular calcium is calmodulin, a calcium-binding regulatory protein.

Factors affecting calcium intake

About 25 mmol (1 g) of calcium is ingested per day, of which there is a net absorption of 6–12 mmol (0.25–0.5 g). The active metabolite of vitamin D, 1,25-dihydroxycholecalciferol ($1,25\text{-}(OH)_2D_3$, also called calcitriol), is needed for calcium absorption.

Factors affecting calcium loss

Calcium is lost in urine and faeces. Urinary calcium excretion depends on the amount of calcium reaching the glomeruli, the glomerular filtration rate (GFR) and renal tubular function. Parathyroid hormone and 1,25-dihydroxyvitamin D increase urinary calcium reabsorption.

Faecal calcium is derived from the diet and that portion of the large amount of intestinal secretions that has not been reabsorbed. Calcium in the intestine may form insoluble, poorly absorbed complexes with oxalate, phosphate or fatty acids. An excess of fatty acids in the intestinal lumen in steatorrhoea may contribute to calcium malabsorption.

CONCEPT OF PLASMA CALCIUM AND ALBUMIN CORRECTION (ADJUSTED)

The mean plasma calcium concentration in healthy subjects is tightly controlled, at around 2.15–2.55 mmol/L, and is present in two main forms:

- *Calcium bound to proteins*, mainly albumin: this accounts for a little less than half the total calcium concentration as measured by routine analytical methods and is the physiologically inactive form.
- *Free ionized calcium* (Ca^{2+}), which comprises most of the rest. This is the physiologically active fraction.

Changes in plasma protein concentration, particularly of albumin, the principal plasma protein, alter the most commonly measured concentration, that of plasma total calcium, but not that of the free ionized fraction. The plasma total (but not free ionized) calcium concentration is lower in the supine than in the erect position because of the effect of posture on fluid distribution and therefore on plasma protein concentration. The direct measurement of the physiologically active free calcium ionized fraction is, for technical reasons, confined to special cases such as acid–base disturbance.

Formulae incorporating the albumin concentration have been devised in an attempt to calculate the active fraction of the plasma total calcium concentration, but, because binding is not simple, these are not always reliable, particularly if extremes of plasma albumin concentration occur. The following is a commonly used formula:

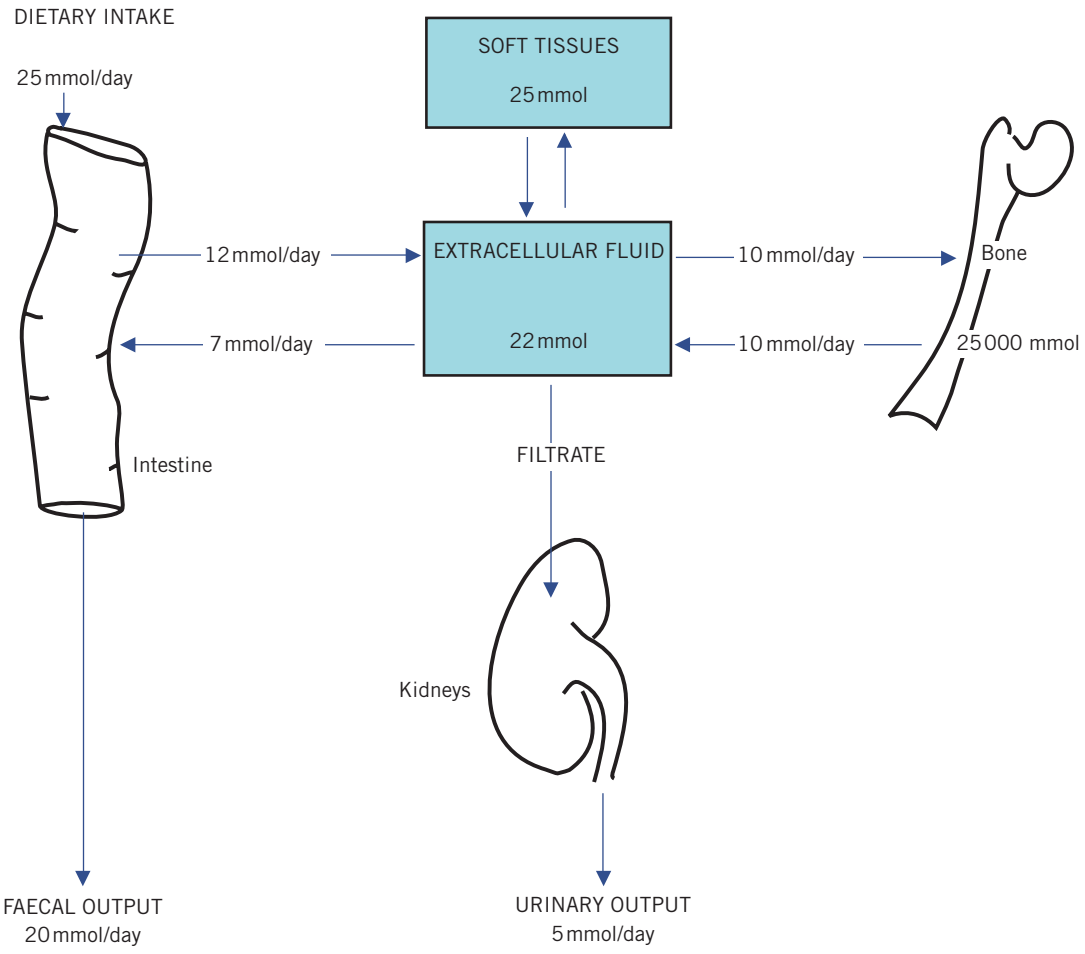

Figure 6.1 The approximate daily turnover of total body calcium.

plasma albumin-adjusted or 'corrected' calcium (mmol/L)
= plasma measured calcium
+ (40 – plasma[albumin]) (g/L) × 0.02 (6.1)

Changes in plasma hydrogen ion concentration ($[H^+]$) affect the binding of calcium to plasma proteins because H^+ competes with Ca^{2+} for binding sites. The plasma total calcium concentration is unaltered by changes in $[H^+]$. If $[H^+]$ falls, as in an alkalosis, tetany may occur, despite a normal plasma total calcium concentration. Conversely, an acidosis decreases binding and so increases the proportion of plasma calcium in the free ionized form. Also, by increasing calcium solubility, it increases the rate of release of calcium from bones into the extracellular fluid (ECF). The increased load reaching the kidneys increases the renal calcium loss. Prolonged acidosis may cause osteomalacia, partly due to the buffering effect of bone.

CASE 1

A 45-year-old man was in the intensive care unit for multiple trauma following a road traffic accident. Some of his biochemistry results were as follows:

Plasma
Calcium 1.98 mmol/L (2.15–2.55)
Albumin 30 g/L (35–45)
Phosphate 0.92 mmol/L (0.80–1.35)
What is the albumin-adjusted calcium?

DISCUSSION

Adjusted calcium = 1.98 + (40 – 30) × 0.02
= 1.98 + 0.20 = 2.18 mmol/L

Note that the plasma calcium now adjusted falls within the reference range and does not require specific treatment. Remember this if the patient has hypoalbuminaemia.

Control of plasma calcium

There are a number of mechanisms by which plasma calcium concentrations are controlled. Calcium homeostasis follows the general rule that extracellular concentrations are controlled rather than the total body content. The effectiveness of this control depends upon:

- an adequate supply of:
  - calcium,
  - vitamin D,
- normal functioning of the:
  - intestine,
  - parathyroid glands,
  - kidneys.

If any one of these factors is impaired, calcium leaves bone by passive physicochemical diffusion, and plasma concentrations may be maintained at the expense of bone calcification.

Parathyroid hormone

Parathyroid hormone (PTH) is a single-chain polypeptide containing 84 residues, with its 34 N-terminal amino acids largely determining its biological activity. It is metabolized by renal, hepatic and bone cells. Renal clearance from plasma of the physiologically inert C-terminal fragment is slower than that of the N-terminal fragment, which may accumulate in plasma in renal glomerular dysfunction. The biological actions of PTH include:

- stimulation of osteoclastic bone resorption, so releasing both free ionized calcium and phosphate into the ECF; this action increases the plasma concentrations of both calcium and phosphate,
- decreased renal tubular reabsorption of phosphate, causing phosphaturia and increased reabsorption of calcium; this action tends to increase the plasma calcium concentration but to decrease the phosphate.

The control of PTH secretion depends on the concentration of free ionized calcium in blood circulating through the parathyroid glands. A fall increases the rate of PTH secretion, which, under physiological conditions, continues until the calcium concentration returns to normal. The secretion of PTH is also affected by the extracellular magnesium concentration, being decreased by severe, chronic hypomagnesaemia.

Detectable plasma PTH, even if the concentration is within the reference range, is inappropriate in the presence of hypercalcaemia and is consistent with primary or, more rarely, tertiary hyperparathyroidism.

Parathyroid hormone-related protein

Parathyroid hormone-related protein (PTHRP) is a peptide hormone that has a similar amino acid sequence at the biologically active end of the peptide, therefore activating the same receptors as PTH. The function of PTHRP is uncertain, but it may be important in calcium metabolism in the fetus. The gene that codes for PTHRP is widely distributed in body tissues but is normally repressed. However, it may become derepressed in certain tumours, causing humoral hypercalcaemia of malignancy.

Calcitonin

Calcitonin (produced in the C cells of the thyroid gland) decreases osteoclastic activity, slows calcium release from bone and has the opposite effect on plasma concentrations of PTH. It is probably less important than PTH in physiological homeostasis. Plasma concentrations may be very high in patients with medullary carcinoma of the thyroid, although hypocalcaemia is not usually reported in this condition. However, exogenous calcitonin has been used to treat hypercalcaemia and Paget's disease of bone.

Metabolism and action of vitamin D

Vitamin D is derived from:

- ergocalciferol (vitamin D_2), obtained from plants in the diet,
- cholecalciferol (vitamin D_3), formed in the skin by the action of ultraviolet light on 7-dehydrocholesterol (Fig. 6.2); this is the form found in animal tissues, especially the liver.

In normal adults, much more cholecalciferol is derived from the action of sunlight on skin (wavelength 270–310 nm) than from food. Dietary sources are important when requirements are high, such as during growth or pregnancy, or in those elderly or chronically sick individuals who are confined indoors and not exposed to the sun.

Vitamin D is transported in plasma bound to specific carrier proteins. It is inactive until metabolized. In the liver, cholecalciferol is hydroxylated to 25-hydroxycholecalciferol (25-OHD_3) by the enzyme 25-hydroxylase. The rate of formation of 25-OHD_3 is affected by the supply of substrate in the form of calciferol, whether derived from the skin or from the

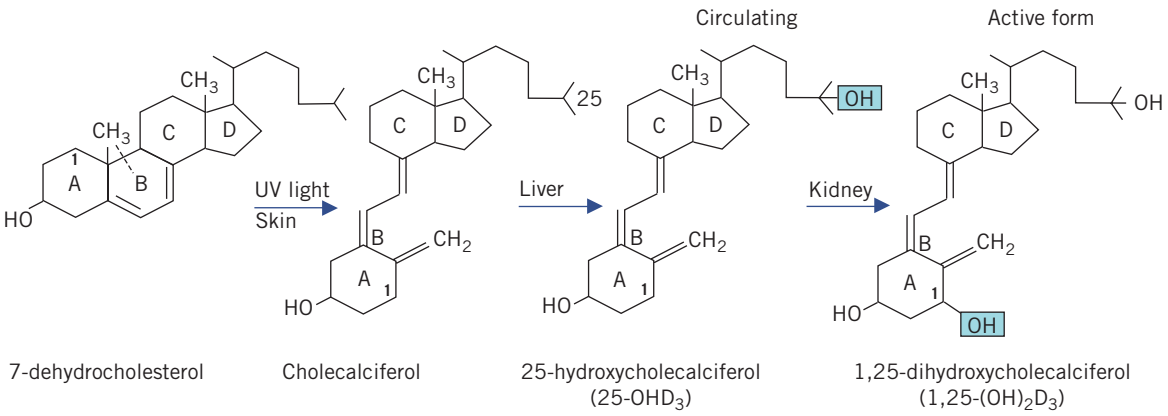

Figure 6.2 Formation of the active vitamin D metabolite from 7-dehydrocholesterol. UV, ultraviolet.

diet. It is the main circulating form and store of the vitamin. Other hydroxylated metabolites are found, such as 24,25-$(OH)_2D_3$.

In the proximal renal tubular cells of the kidney, $25\text{-}OHD_3$ undergoes a second hydroxylation, catalysed by the enzyme 1-α-hydroxylase to form the active metabolite 1,25-$(OH)_2D_3$.

The activity of 1-α-hydroxylase, and hence the production of 1,25-$(OH)_2D_3$, may be stimulated by:

- a low plasma phosphate concentration,
- an increase in plasma PTH concentration, possibly because of its phosphate-lowering effect.

Its activity is inhibited by:

- hyperphosphataemia,
- high levels of free ionized calcium.

The kidney is an endocrine organ, synthesizing and releasing the hormone 1,25-$(OH)_2D_3$; impairment of the final hydroxylation helps explain the hypocalcaemia of renal disease. This hormone increases calcium absorption by intestinal mucosal cells. In conjunction with PTH, it stimulates osteoclastic activity, releasing calcium from bone.

The action of PTH on bone is impaired in the absence of 1,25-$(OH)_2D_3$. A fall in plasma free ionized calcium concentration stimulates PTH secretion. The PTH enhances 1-α-hydroxylase activity and therefore stimulates 1,25-$(OH)_2D_3$ synthesis. The two hormones act synergistically on the osteoclasts of bone, releasing calcium into the circulation; 1,25-$(OH)_2D_3$ also increases calcium absorption from the intestinal lumen. In the short term, the homeostatic mechanisms involving the effects on bone are the more important; if hypocalcaemia is prolonged, more efficient absorption becomes important. Once the plasma free ionized calcium concentration is adjusted, the secretion of both PTH and 1,25-$(OH)_2D_3$ is suppressed.

Thus, $25\text{-}OHD_3$ is the circulating, inactive form of vitamin D and plasma concentrations fall in deficiency states. The measurement of the biologically active metabolite, 1,25-$(OH)_2D_3$, which circulates in plasma bound to vitamin D-binding protein (VDBP) in very low concentrations, is rarely indicated unless a defect in the vitamin metabolic pathway is suspected, as it does not reflect body stores.

The vitamin D receptor (VDR) is found in almost all cell nuclei with various effector systems such as endocrine, paracrine or autocrine. Calcitriol activates the receptor, which forms a heterodimer with the retinoid-X receptor and binds to hormone response elements on deoxyribonucleic acid (DNA) and is involved in the expression of various gene products. These pathways not only involve bone metabolism but also have implications for the immune system and carcinogenesis.

Calcium-sensing receptor

The calcium-sensing receptor (CaSR) is a G protein-coupled receptor. This allows the parathyroid cells and the ascending loop of Henle epithelial cells to respond to changes in extracellular calcium. The parathyroid cell surface is rich in CaSR, which allows PTH secretion to be adjusted rapidly depending on the calcium concentration.

Defects in the CaSR gene are responsible for various rare defects of calcium homeostasis. Inactivating mutations include familial benign

hypocalciuric hypercalcaemia and neonatal severe hyperparathyroidism; activating mutations include autosomal dominant hypocalcaemia with hypercalciuria. Calcimimetic agents have been devised that bind and activate the CaSR, resulting in decreased PTH release and reduced plasma calcium concentrations.

Miscellaneous mechanisms of calcium control

Thyroid hormone excess may be associated with the histological appearance of osteoporosis and with increased faecal and urinary excretion of calcium, probably following its release from bone. Hypercalcaemia is a very rare complication of severe hyperthyroidism. Unless there is gross excess of thyroid hormone, the effects on plasma calcium are over-ridden by homeostatic reduction of PTH secretion and by urinary loss.

Other hormones influencing calcium metabolism include oestrogens, prolactin and growth hormone. These may increase 1,25-$(OH)_2D_3$ production and increase calcium absorption during pregnancy, lactation and growth.

DISORDERS OF CALCIUM METABOLISM

The consequences of most disturbances of calcium metabolism can be predicted from knowledge of the actions of PTH on bone and on renal tubular cells, and from plasma concentrations of calcium and phosphate. A low plasma free ionized calcium concentration normally stimulates PTH secretion, which results in phosphaturia; the loss of urinary phosphate over-rides the tendency to hyperphosphataemia due to the action of PTH on bone.

Consequently, the plasma phosphate concentration is usually low when the plasma PTH concentration is increased. Conversely, a high plasma free ionized calcium concentration, unless due to inappropriate excess of PTH, inhibits PTH secretion and causes a high plasma phosphate concentration. Therefore plasma calcium and phosphate concentrations usually vary in the same direction unless:

- renal glomerular dysfunction is severe enough to impair the phosphaturic (and therefore hypophosphataemic) effect of PTH or PTHRP,
- there is inappropriate excess or deficiency of PTH due to a primary disorder of the parathyroid gland or to secretion of PTHRP; in such cases calcium and phosphate vary in opposite directions.

Hypercalcaemia

Clinical effects of an increased plasma albumin-adjusted calcium concentration

- Renal effects.
  - *Renal damage* is one of the most serious clinical consequences of prolonged hypercalcaemia. Because of the high plasma free ionized calcium concentration, the solubility of calcium phosphate may be exceeded and precipitate in extraosseous sites such as the kidneys (see Chapter 3).
  - *Polyuria*, characteristic of chronic hypercalcaemia, may result from impairment of renal concentrating ability owing to calcification of the tubular cells; acute hypercalcaemia may cause reversible inhibition of the tubular response to antidiuretic hormone rather than to cell damage. These effects can lead to dehydration.
  - *Renal calculi*, without significant parenchymal damage, may be caused by precipitation of calcium salts in the urine if the free ionized calcium concentration is high in the glomerular filtrate owing to hypercalcaemia (see Chapter 3).
  - *Hypokalaemia*, often with a metabolic alkalosis, is associated with hypercalcaemia. Calcium may directly inhibit potassium reabsorption from the tubular lumen (see Chapter 5).
- High extracellular free ionized calcium concentrations can depress neuromuscular excitability in both voluntary and involuntary muscle. There may also be muscular hypotonia.
- Depression, anorexia, nausea and vomiting, associated with high plasma calcium concentrations, are probably caused by an effect on the central nervous system.
- Calcium stimulates gastrin (and therefore gastric acid) secretion. There is an association between chronic hypercalcaemia and peptic ulceration. The patient may complain of constipation and abdominal pain. Hypercalcaemia may also present as an acute abdomen.
- Some patients with hypercalcaemia may be hypertensive. If renal damage is not severe, the hypertension may respond to reducing the plasma calcium concentration.
- Severe hypercalcaemia causes characteristic changes in the electrocardiogram (ECG), with shortening of

the Q–T interval and broadening of the T waves. If plasma concentrations exceed about 3.5 mmol/L, there is a risk of sudden cardiac arrest or ventricular arrhythmias. For this reason severe hypercalcaemia should be treated as a matter of urgency.
- Hypercalcaemia is also associated with bone and joint pain.

'Bones, moans, groans and stones' is a useful mnemonic to remember some of these clinical consequences of hypercalcaemia.

Causes of hypercalcaemia (Box 6.1)

Overall, thiazides are one of the most common causes of mild hypercalcaemia. However, most causes of severe hypercalcaemia are related to either primary hyperparathyroidism or malignancy. In the case of the latter, 80 per cent are due to bony metastases, with the remainder being mainly due to ectopic PTHRP. Some causes of hypercalcaemia are depicted in Box 6.1.

True free ionized or albumin-adjusted hypercalcaemia with hypophosphataemia is usually caused by inappropriate secretion of PTH or PTHRP. The term 'inappropriate secretion' is used in this book to indicate that the release of hormone into the circulation is not adequately inhibited by negative feedback control. Inappropriate PTH secretion occurs in the following clinical situations:

- production of PTH by the parathyroid glands due to:
  - primary hyperparathyroidism,
  - tertiary hyperparathyroidism.

If renal glomerular function is adequate, the high circulating PTH or PTHRP concentrations cause hypercalcaemia, which is associated with a low-normal or low plasma phosphate concentration in relation to GFR, and to phosphaturia. If glomerular damage develops due to hypercalcaemia, the kidneys cannot respond normally to the phosphaturic effect of PTH and, because of impaired hydroxylation of 25-OHD_3, plasma calcium concentrations may fall towards or within the reference range as renal failure progresses. Because plasma phosphate concentrations tend to rise, diagnosis may be difficult at this stage.

Box 6.1 Some causes of hypercalcaemia

Malignancy
Bony metastases, e.g. breast, lung, prostate, kidney, thyroid
Solid tumours with humoral effects
Haematological tumours, e.g. multiple myeloma

Parathyroid hormone abnormalities
Primary hyperparathyroidism (adenoma, hyperplasia, carcinoma or associated with multiple endocrine neoplasia)
Tertiary hyperparathyroidism
Lithium-induced hyperparathyroidism

High bone turnover
Thyrotoxicosis
Immobilization, e.g. with Paget's disease

High levels of vitamin D
Vitamin D toxicity
Granulomatous disease, e.g. sarcoidosis, tuberculosis

Drugs
Thiazides (reduced renal calcium excretion)
Vitamin A toxicity
Milk–alkali syndrome

Familial hypocalciuric hypercalcaemia

Other endocrine causes
Adrenal insufficiency
Acromegaly

Rarer causes
Williams' syndrome
Human immunodeficiency virus (HIV) infection
Leprosy
Histoplasmosis
Berylliosis

CASE 2

A 53-year-old man saw his general practitioner because of bone pain and constipation. A number of laboratory tests were requested, the results for the most relevant of which were as follows:

Plasma
Albumin-adjusted calcium 2.96 mmol/L (2.15–2.55)
Phosphate 0.62 mmol/L (0.80–1.35)
Parathyroid hormone 157 ng/L (20–65)

DISCUSSION
The patient has hypercalcaemia. Note also the hypophosphataemia and inappropriately raised PTH concentration. The diagnosis was subsequently found to be primary hyperparathyroidism due to a parathyroid adenoma associated with multiple endocrine neoplasia (MEN) type I. His symptoms are typical of chronic hypercalcaemia.

The clinical features of PTH- or PTHRP-induced hypercalcaemia are due to:

- excess circulating concentration of free ionized calcium that is the direct consequence of increased osteoclastic activity and release of calcium from bone, and enhanced absorption of calcium from the intestinal lumen by vitamin D; PTH increases the formation of 1,25-$(OH)_2D_3$,
- the effects of persistent PTH or PTHRP activity on bone in the presence of a normal supply of vitamin D and calcium (see Fig. 6.1).

The differences between the clinical presentations associated with inappropriately high plasma PTH concentrations depend on the duration of the disease. The following effects on bone become evident only in long-standing cases. Prolonged decalcification of bone causes a secondary increase in osteoblastic activity. Alkaline phosphatase-rich osteoblasts release the enzyme into the circulation and, if the number of cells is greatly increased, plasma alkaline phosphatase activity rises.

Primary hyperparathyroidism

This is caused by inappropriate secretion of PTH by the parathyroid glands, causing hypercalcaemia. It is usually due to one or more parathyroid adenomas, but occasionally to hyperplasia of all four parathyroid glands or to carcinoma of one of the glands. Ectopic parathyroid tumours do also occur. Primary hyperparathyroidism may be associated with other multiple endocrine neoplasias (MENs), such as pituitary and pancreatic adenomas (MEN type I), or with phaeochromocytomas and medullary carcinoma of the thyroid (MEN type II). The incidence of primary hyperparathyroidism increases with age, being most common in elderly females.

The majority of cases of primary hyperthyroidism are diagnosed after the chance finding of high plasma calcium, usually with low plasma phosphate concentrations.

Where there are clinical symptoms and signs at presentation, these are due to hypercalcaemia and include the following:

- *Generalized ill health* Depression, nausea, anorexia and abdominal pain and polyuria.
- *Renal calculi* About 10 per cent of patients who present with renal calculi have primary hyperparathyroidism.
- *Bone pain* In most patients, subperiosteal bone erosions or cysts may be seen on radiography of the terminal phalanges. However, extensive, severe bone disease, osteitis fibrosa cystica, is now a rare presenting feature, as patients are usually diagnosed before the disorder is extensive, and consequently plasma alkaline phosphatase activity is usually normal or only slightly increased. There are increased numbers of osteoclasts and an increased risk of bone fracture.
- *Medical emergency* Occasionally patients are admitted as an emergency with abdominal pain, vomiting and constipation. Severe hypercalcaemia is a recognized cause of acute pancreatitis and should be considered as one cause of an 'acute abdomen'.

Recently, it has been reported that an incipient form of primary hyperparathyroidism exists in which there is initially normal plasma calcium but elevated PTH.

The treatment of primary hyperparathyroidism is often surgical, with removal of the parathyroid gland(s). However, this can render the patient hypocalcaemic, and asymptomatic patients are sometimes treated conservatively.

Tertiary hyperparathyroidism

This may occur if the parathyroid glands have been subjected to long-standing and sustained positive feedback by low plasma free ionized calcium concentrations (hypocalcaemia) of secondary hyperparathyroidism which have been subsequently corrected.

The parathyroid glands hypertrophy; PTH secretion becomes partly autonomous and is not suppressed by negative feedback by the hypercalcaemia. The diagnosis is usually made when the cause of the original hypocalcaemia is removed, for example by renal transplantation or correction of long-standing calcium or vitamin D deficiency as in malabsorption. A history of previous hypocalcaemia and the finding of a very high plasma alkaline phosphatase activity due to the prolonged osteomalacia distinguish it from primary hyperparathyroidism. In some cases, the glandular hypertrophy gradually regresses and the plasma calcium concentration returns to normal.

Unlike primary or tertiary hyperparathyroidism, in which plasma PTH concentration is increased, there are other causes of hypercalcaemia where plasma levels of PTH are reduced or suppressed. These are now discussed.

Hypercalcaemia of malignancy

Malignant disease of bone

Some patients with multiple bony metastases (from, for example, breast, lung, prostate, kidney and

thyroid tumours) or with multiple myeloma show hypercalcaemia. Here there is usually a parallel rise of plasma phosphate. The hypercalcaemia is caused by direct bone breakdown due to the local action of malignant deposits and cytokine activation.

Malignant deposits in bone stimulate a local osteoblastic reaction and hence a rise in plasma alkaline phosphatase activity. This osteoblastic reaction does not occur in bone eroded by the marrow expansion of myelomatosis. Therefore, in the latter condition the plasma concentration of alkaline phosphatase of bony origin is relatively normal, despite extensive bone involvement with osteolytic lesions.

Humoral hypercalcaemia of malignancy

Parathyroid hormone-related protein is synthesized by some malignant tumours of non-endocrine tissues and is not subject to normal feedback control by the high plasma free ionized calcium concentration. Bony lesions due to circulating PTHRP are not normally present because the underlying disease is usually either fatal or successfully treated in a relatively short time. It is of note that PTHRP is not usually detected by the PTH assay.

However, the plasma alkaline phosphatase activity may be raised because of secondary deposits in bone or the liver, or both. In humoral hypercalcaemia of malignancy, the plasma calcium concentration may rise from normal to dangerously high very rapidly, in contrast to primary hyperparathyroidism. Ectopic hormone production is discussed more fully in Chapter 24.

CASE 3

A 76-year-old woman with known breast carcinoma was admitted to hospital drowsy, with weight loss and backache. The following results were returned.

Plasma

Albumin-adjusted calcium 3.96 mmol/L (2.15–2.55)
Phosphate 1.12 mmol/L (0.80–1.35)
Parathyroid hormone less than 10 ng/L (20–65)

DISCUSSION

A bone scan subsequently showed the patient to have widespread bone metastases. Note the severe hypercalcaemia and the appropriately suppressed plasma PTH, suggesting a non-parathyroid source of the hypercalcaemia. Various tumours are associated with bone metastases, including breast tumours.

Drugs/medications

Various medications can evoke hypercalcaemia, such as thiazides (decreases calcium renal excretion), lithium, and vitamin A excess.

Milk–alkali syndrome

This rare condition occurs with the excessive use of calcium-containing antacids for dyspepsia. It is also associated with a metabolic alkalosis. Milk–alkali syndrome is now rarely seen, since the advent of proton pump inhibitors and H_2 receptor antagonists for the treatment of dyspepsia.

Vitamin D excess

Vitamin D excess may be caused by overvigorous treatment of hypocalcaemia. Increased intestinal calcium absorption may cause dangerous hypercalcaemia. Vitamin D therapy, with either ergocalciferol or the active metabolite 1,25-dihydroxyvitamin D, should always be monitored by frequent estimation of plasma calcium concentrations and, if there is osteomalacia, by measuring plasma alkaline phosphatase activity. If the cause of hypercalcaemia is obscure, a careful drug history should be taken. Occasionally patients inadvertently overdose themselves with vitamin D, which is available in many countries without prescription.

Sarcoidosis

Hypercalcaemia is a rare complication. 1,25-Dihydroxycholecalciferol is synthesized in the granuloma tissue and increases calcium absorption from the intestinal tract. Chronic beryllium poisoning produces a granulomatous reaction very similar to that of sarcoidosis and may also be associated with hypercalcaemia. The same is possibly also true of tuberculosis, histoplasmosis and leprosy.

Hypercalcaemia of hyperthyroidism

Prolonged excess of thyroid hormone in severe hyperthyroidism may be associated with the histological appearance of osteoporosis and a consequent increase in urinary calcium excretion. Hypercalcaemia is a very rare complication.

Other endocrine causes of hypercalcaemia

These include acromegaly (see Chapter 7), Addison's disease (see Chapter 8) and phaeochromocytoma (see Chapter 24).

Familial hypocalciuric hypercalcaemia

Hypercalcaemia with an inappropriately high plasma PTH concentration in the presence of hypocalciuria

has been reported in some families, in none of whom was a parathyroid adenoma found at operation. The condition is inherited as an autosomal dominant trait. The aetiology of the condition is thought to be due a defect on the CaSR (see above). Low urinary calcium concentration in the face of hypercalcaemia points to the diagnosis. A useful test is the calcium excreted per litre of glomerular filtrate (CaE):

$$\text{CaE} = \frac{\text{urinary[calcium]} \times \text{plasma[creatinine]}}{\text{urinary[creatinine]}} \quad (6.2)$$

Hypocalciuric hypercalcaemia is likely if this is less than 0.015 (in mmol/L). It is important to exclude this condition, as it can mimic primary hyperparathyroidism.

Hypercalcaemia of infancy

Idiopathic hypercalcaemia of infancy includes a number of conditions that cause hypercalcaemia during the first year of life. Excessive vitamin D supplementation of cow's milk is now a very uncommon cause. Williams' syndrome is a rare familial disorder associated with increased intestinal calcium absorption and hypercalcaemia. Clinical features include growth retardation, mental deficiency and characteristic 'elfin' facies. Congenital heart disease may also be present (see Chapter 26). There is also a rare neonatal autosomal dominant hyperparathyroidism

Investigation of hypercalcaemia (Fig. 6.3)

Establish whether the high plasma total calcium concentration is due only to a high protein-bound fraction. Two groups of causes should be differentiated for raised plasma albumin-adjusted calcium concentration:

1. raised albumin-adjusted calcium concentration due to inappropriately high PTH and usually hypophosphataemia,
2. raised albumin-adjusted calcium concentration due to other causes and associated with low PTH concentrations and often hyperphosphataemia.

The following procedure may be useful to find the cause of hypercalcaemia, although the diagnosis may be obvious before all the steps have been followed:

- Establish the plasma albumin concentration.
- Check the albumin-adjusted calcium. Take a specimen without venous stasis (preferably without a tourniquet) to eliminate artefactual haemoconcentration and repeat the plasma calcium and albumin assays. If true hypercalcaemia is confirmed, a cause must be sought.
- Take a careful history, with special reference to the drug history, such as vitamin-D-containing preparations and thiazide diuretics. Is there evidence of milk–alkali syndrome, albeit rare now? If so, check acid–base status.

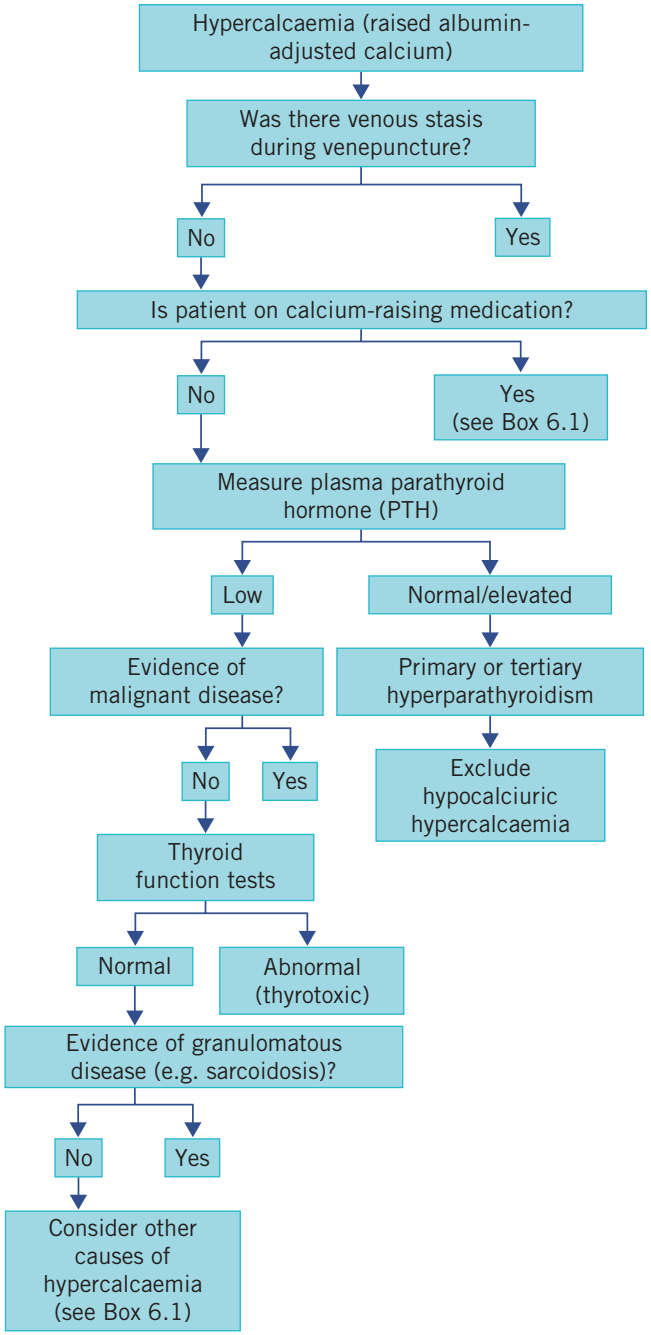

Figure 6.3 Algorithm for the investigation of hypercalcaemia.

- Is the plasma phosphate concentration low in relation to the renal function? Hypophosphataemia suggests the diagnosis of primary hyperparathyroidism.

Apart from thiazide usage, the most common causes of hypercalcaemia are either primary hyperparathyroidism or malignancy; the latter may be obvious following clinical examination and radiological and haematological tests, for example anaemia, and raised erythrocyte sedimentation rate (ESR) and biochemical investigations.

It is essential that primary hyperparathyroidism and malignant hypercalcaemia are distinguished. In the case of malignancy, pay special attention for breast, kidney, lung or prostate carcinoma. A raised plasma PTH concentration is usually seen in primary hyperparathyroidism; conversely, suppressed levels are found in malignant states and indeed in hypercalcaemia of many other causes. Very rarely PTHRP should be measured if ectopic secretion of this is suspected, for example by a tumour.

If primary hyperparathyroidism due to an adenoma is found, exclude MEN syndrome (see Chapter 24). Imaging of the parathyroid glands is often needed to distinguish adenoma from hyperplasia of the parathyroid glands. Isotope subtraction scanning or ultrasound of the neck may help to localize the adenoma, as may venous sampling for PTH levels.

Very high plasma alkaline phosphatase activity is unlikely to be due to uncomplicated primary hyperparathyroidism; near-normal activity is usual, although it may be raised if there is radiological evidence of bone involvement. If it is very high, it suggests either malignancy or some concurrent disease such as Paget's disease.

Perform serum and urinary protein electrophoresis if a multiple myeloma is suspected (see Chapter 19).

- Look for evidence of sarcoidosis; plasma angiotensin-converting enzyme (ACE) concentration is often raised (see Chapter 18) and a chest radiograph may be useful.
- Is there acromegaly, Addison's disease or thyrotoxicosis (see Chapters 7, 8 and 11)?
- A urinary calcium determination (CaE) is useful to help exclude hypocalciuric hypercalcaemia.
- Rarer causes of hypercalcaemia are listed in Box 6.1.

A steroid suppression test is rarely necessary to identify the cause of hypercalcaemia because of the development of robust PTH assays. Briefly, this test relies on the fact that hypercalcaemia of primary hyperparathyroidism is not usually suppressed by steroids, unlike many of the other causes of a raised calcium concentration such as malignant disease.

Treatment of hypercalcaemia

Mild to moderate hypercalcaemia

If the plasma albumin-adjusted calcium concentration is below about 3.5 mmol/L, and if there are no significant clinical symptoms or signs such as changes attributable to hypercalcaemia, there is no need for urgent treatment. However, therapy should be started as soon as the abnormality is found and preliminary investigations have been performed because of the danger of renal damage. If possible, the primary cause should also be diagnosed and treated.

The patient should be fluid volume repleted, if necessary by intravenous infusion of saline. The plasma total calcium concentration will often fall as the plasma albumin concentration is diluted, but the plasma free ionized calcium concentration is probably little affected. Correcting haemoconcentration enables a more realistic assessment to be made of the degree of true hypercalcaemia.

Bisphosphonates are first-line agents in the medical management of hypercalcaemia. These are structurally similar to pyrophosphate. They bind to hydroxyapatite in bone, thus inhibiting bone turnover and the mobilization of calcium. They are poorly absorbed from the intestinal tract and may have to be given intravenously to patients with severe hypercalcaemia. Cyclical administration may prevent the long-term complication of osteomalacia.

The management of apparently asymptomatic mild hypercalcaemia due to primary hyperparathyroidism is controversial. It has been suggested that prolonged hypercalcaemia does not always cause obvious renal dysfunction and that the risk of parathyroidectomy (e.g. rendering the patient hypocalcaemic) may be greater than that of mild hypercalcaemia. The decision whether to operate must be made on clinical grounds; of particular importance are the fitness of the patient for operation, plasma calcium concentration greater than 3.0 mmol/L, deteriorating renal function, renal calculi, poor bone mineral density or 24-h urinary calcium concentration greater than 10 mmol/L.

Severe hypercalcaemia

The plasma albumin-adjusted calcium concentration at which urgent treatment is indicated because of the

danger of cardiac arrest is usually about 3.5 mmol/L. If in doubt, abnormalities associated with hypercalcaemia should be sought on the ECG. Consider the following:

- *Rehydration* The patient should be volume repleted, intravenously with saline if necessary. Furosemide may also be given in an attempt to increase urinary calcium clearance and avoid fluid overload. Check electrolytes and renal function carefully.
- *Bisphosphonates* After rehydration and correction of any electrolyte abnormalities, bisphosphonates such as pamidronate are usually the treatment of choice.
- *Steroids* May sometimes lower the plasma calcium concentration in malignancy and almost always in cases of sarcoidosis and vitamin D intoxication.
- *Calcitonin* Sometimes used to treat severe hypercalcaemia. The effect lasts about 3 days; repeated doses are often less successful in maintaining a 'normal' plasma calcium concentration.

Steroids and calcitonin usually have no significant effect for about 24 h.

As with most other extracellular constituents, rapid changes in plasma calcium concentration may be dangerous because time is not allowed for equilibration across cell membranes. The aim of emergency treatment should be to lower the plasma concentration to one that is not immediately dangerous, while initiating treatment for mild hypercalcaemia as outlined above. Too rapid a reduction, even to only normal or slightly raised concentrations, may cause tetany.

Hypocalcaemia

Clinical effects of a reduced albumin-adjusted plasma calcium concentration

Low plasma albumin-adjusted calcium concentrations, including those associated with a normal total calcium concentration of alkalosis, cause increased neuromuscular activity eventually leading to tetany and carpopedal spasm, generalized seizures, laryngospasm, hyper-reflexia, paraesthesiae and hypotension.

Prolonged hypocalcaemia, even when mild, interferes with the metabolism of the lens in the eye and may cause cataracts. Because of this, asymptomatic hypocalcaemia should be sought when there has been a known risk of parathyroid damage, such as after partial or total thyroidectomy, and, if found, treated. Hypocalcaemia may also cause depression and other psychiatric symptoms as well as cardiac arrhythmias, including prolonged Q–T interval on ECG.

CASE 4

A 72-year-old woman presented to her general practitioner with tiredness, muscle aches and difficulty in standing up. The following test results were found.

Plasma

Albumin-adjusted calcium 1.76 mmol/L (2.15–2.55)
Phosphate 0.52 mmol/L (0.80–1.35)
Parathyroid hormone 138 ng/L (20–65)
Alkaline phosphatase 763 U/L (< 250)
25-hydroxyvitamin D 5 µg/L (> 75)

DISCUSSION

The patient has osteomalacia, as evidenced by the low plasma 25-hydroxyvitamin D concentration. Note also the hypocalcaemia with hypophosphataemia and raised alkaline phosphatase and secondary appropriate elevation of PTH. The symptoms are typical of osteomalacia, which can lead to proximal myopathy and bone pain. The elderly are particularly prone to osteomalacia, in part related to poor dietary vitamin D intake.

Latent neuromuscular hyperactivity, carpopedal spasm and tetany (Trousseau's sign) can be evoked by inflating a blood pressure cuff to 10–20 mmHg above systolic blood pressure for 3–5 min. Chvostek's sign can be elicited by tapping the facial nerve anterior to the ear, when ipsilateral facial muscle contraction may occur, although this can also occur in about 10 per cent of individuals without hypocalcaemia.

It is sometimes useful to divide hypocalcaemia into those cases with a low plasma phosphate concentration (hypophosphataemia) and those with high plasma phosphate concentration (hyperphosphataemia), although not all cases of hypocalcaemia fall neatly into this classification. The causes of hypocalcaemia are given in Box 6.2.

Hypocalcaemia with hypophosphataemia

Reduced intake and absorption of calcium and vitamin D

In steatorrhoea, fat (and therefore vitamin D) absorption is impaired; this malabsorption may be aggravated if calcium combines with unabsorbed fatty acids to form insoluble soaps in the lumen. Deficiency due to undernutrition is more commonly caused by deficiency of vitamin D than of calcium.

In relatively affluent countries, malabsorption is the most common cause of calcium and vitamin D

Box 6.2 Some causes of hypocalcaemia

Exclude hypoalbuminaemic states

Drugs and chemicals
Furosemide
Enzyme-inducing drugs, e.g. phenytoin
Ethylene glycol poisoning (rare)

Causes of hypocalcaemia usually with hypophosphataemia
Vitamin D deficiency
Rickets
Osteomalacia
Malabsorption states

Causes of hypocalcaemia usually with hyperphosphataemia
Chronic kidney disease
Hypoparathyrodism (low parathyroid hormone levels)
- Idiopathic or autoimmune
- Surgical removal of parathyroid glands
- Congenital absence of parathyroid glands, e.g. DiGeorge's syndrome
- Infiltration of parathyroids, e.g. tumours, haemochromatosis

Pseudohypoparathyroidism (rare)
Parathyroid hormone (PTH) resistance (raised PTH levels)

Miscellaneous causes of hypocalcaemia (rarer causes)
Acute pancreatitis
Sepsis
High calcitonin levels
Rhabdomyolysis
Severe hypomagnesaemia
Autosomal dominant hypercalciuric hypocalcaemia

deficiencies. Worldwide dietary deficiency is important. The following groups are at risk of developing osteomalacia or rickets:

- children and pregnant women, in whom increased needs may not be met by the normal supply from the skin,
- people such as the elderly and chronically sick who are less exposed to sunlight because they are confined indoors.

There is a relatively high incidence of osteomalacia and rickets among the Asian community in some urban Western societies. The causes are unclear but probably include dietary habits, relative lack of sunlight and possibly genetic factors.

Impaired metabolism of vitamin D

Chronic liver disease may occasionally be associated with mild osteomalacia, especially if there is cholestasis causing malabsorption due, for example, to primary biliary cirrhosis. However, it is unlikely that significant impairment of vitamin D hydroxylation is the cause.

Prolonged anticonvulsant therapy, especially if both barbiturates and phenytoin are taken, may be associated with hypocalcaemia and even osteomalacia. These drugs probably induce the synthesis of hepatic enzymes which catalyse the conversion of vitamin D to inactive metabolites.

In all these conditions, the low plasma free ionized calcium concentration stimulates PTH secretion; the plasma phosphate concentration tends to be low *relative to the GFR*. However, if there is renal glomerular dysfunction, the plasma phosphate concentration may be increased but tends to be lower than in those patients with the same concentration of plasma urea but normal plasma PTH concentrations. In chronic cases a rising plasma alkaline phosphatase activity indicates the onset of the bone changes of osteomalacia or rickets.

Type 1 vitamin-D-dependent rickets is due to 1-α-hydroxylase deficiency. It is an autosomal recessive disorder and results in low 1,25-$(OH)_2D_3$ concentrations.

Type 2 vitamin-D-dependent rickets is also an autosomal recessive disorder and causes a vitamin D resistance and is a defect of the vitamin D or calcitriol receptor. Thus plasma 1,25-$(OH)_2D_3$ concentrations are elevated.

Hypocalcaemia with hyperphosphataemia

Renal dysfunction

The most common causes of hyperphosphataemia include acute kidney injury and chronic kidney disease (dysfunction) (see Chapter 3).

Renal disease such as chronic kidney disease causes relative resistance to vitamin D because of the direct effect of the disease on the functioning renal tubular cells and therefore on 1-α-hydroxylation of 25-OHD_3 and inhibition of 1-α-hydroxylation by hyperphosphataemia associated with the low GFR of renal glomerular dysfunction.

Hypocalcaemia may develop within a few days of the onset of renal damage. Low plasma protein concentrations often contribute to the reduction in the total calcium concentration.

Tetany is rare in renal disease, probably because the accompanying acidosis increases the plasma free ionized

calcium concentration above tetanic concentrations. Treatment of the metabolic acidosis with bicarbonate is usually contraindicated because a rise in blood pH may cause precipitation of calcium phosphate in extraosseous sites. In the kidney it may aggravate renal dysfunction.

Primary hypoparathyroidism

Hypoparathyroidism is usually caused by surgical damage to the parathyroid glands, either directly or indirectly by impairment of their blood supply during partial thyroidectomy. Total thyroidectomy or laryngectomy is often associated with removal or damage to the parathyroid glands and it is important to monitor plasma calcium concentrations. Post-thyroidectomy hypocalcaemia is not always due to damage to the glands and may be transient.

Parathyroidectomy, carried out to treat primary or tertiary hyperparathyroidism, also carries a risk of damage to the remaining parathyroid tissue. However, there are several causes of temporary hypocalcaemia.

If the hypercalcaemia has been severe and prolonged, the remaining parathyroid tissue may have been suppressed by negative feedback for so long that there may be true hypoparathyroidism evidenced by a rising plasma phosphate concentration, which usually recovers within a few days. Unless transient it should be treated if symptomatic.

In rare cases of primary hyperparathyroidism with overt bone disease, rapid entry of calcium into bone, when plasma PTH concentrations fall, may cause true, but temporary, post-operative hypocalcaemia.

Although early post-operative parathyroid insufficiency may recover, a low plasma calcium concentration persisting for more than a few weeks should usually be treated.

Autoimmune hypoparathyroidism is rare. It may occur as a familial disorder, presenting either during childhood or in adults or as part of the polyendocrine syndrome, with antibodies against parathyroid tissue and sometimes other tissues, for example the adrenal glands and pancreatic islets. Autoimmune hypoparathyrodism can also be associated with the MEDAC syndrome (multiple endocrine deficiency, Addison's disease and candidiasis).

Congenital absence of the parathyroid glands is also rare; it is associated with impaired cellular immunity, a characteristic facial appearance and cardiac abnormalities known as DiGeorge's syndrome.

Pseudohypoparathyroidism

This is a very rare inborn error associated with an impaired response of both kidneys and bone to PTH, that is, end-organ resistance to circulating PTH. Thus plasma PTH concentration is raised with hypocalcaemia. Type 1 is a defect proximal to cyclic adenosine monophosphate (cAMP) tissue generation, and thus urinary cAMP is low; type 2 pseudohypoparathyroidism is due to a defect distal to cAMP production, so urinary cAMP levels are normal. The associated phenotype may show short stature, obesity, mental retardation and short third and fourth metacarpals.

Pseudo-pseudohypoparathyroidism shows the same phenotype but normal plasma calcium concentration.

Box 6.2 shows some miscellaneous rarer causes of hypocalcaemia that do not necessarily present with either hypophosphataemia or hyperphosphataemia.

Secondary hyperparathyroidism

High plasma PTH concentrations cause phosphaturia with hypophosphataemia if glomerular function is normal.

Secondary hyperparathyroidism ('appropriate' secretion of PTH) occurs in response to a low plasma free ionized calcium concentration. The parathyroid glands respond with appropriate secretion of PTH. If the response is effective, the plasma calcium concentration returns to normal, the stimulus to secretion is removed and hormone production is then inhibited by negative feedback. Preservation of plasma calcium concentrations occurs at the expense of bone mineralization and therefore decalcification may result. Parathyroid hormone cannot act effectively on bone in the absence of $1,25\text{-}(OH)_2D_3$. In cases of vitamin D deficiency with hypocalcaemia, plasma PTH concentrations may be very high.

Without an adequate supply of calcium and phosphate, osteoid cannot be calcified despite marked osteoblastic proliferation. The histological finding of uncalcified osteoid is characteristic of osteomalacia in adults or rickets in children. Osteomalacia, before fusion of the epiphyses, may present with a slightly different clinical, radiological and histological picture and is called rickets. Plasma alkaline phosphatase activity is increased because of osteoblastic proliferation.

Disorders of bone disease associated with secondary hyperparathyroidism may present:

- *With osteomalacia* in adults, or *rickets* in children, presenting before fusion of the epiphyses and is due

to long-standing deficiency of calcium, phosphate and vitamin D. Predisposing factors include:
  - reduced dietary intake of vitamin D, calcium and phosphate in undernutrition,
  - impaired absorption of vitamin D, for example in steatorrhoea or hepatobiliary disease,
  - impaired metabolism of vitamin D to 1,25-$(OH)_2$ D_3 due to renal disease,
  - increased inactivation of vitamin D due to anticonvulsant therapy,
  - renal tubular disorders of phosphate reabsorption.
- *Without osteomalacia or rickets*: if PTH action is inadequate to correct the abnormality, the plasma calcium concentration remains low and bone disorders are not present. Predisposing factors include:
  - early calcium and vitamin D deficiency,
  - the rare pseudohypoparathyroidism.

In secondary hyperparathyroidism the plasma calcium concentration is never high, and usually the plasma calcium and phosphate concentrations tend to be low. High-normal or high plasma calcium concentrations in renal glomerular dysfunction suggest either that primary hyperparathyroidism has caused the renal disease or that prolonged calcium deficiency has led to the development of tertiary hyperparathyroidism.

Investigation of hypocalcaemia (Fig. 6.4)

As in the case of hypercalcaemia, the causes of hypocalcaemia fall into two main groups:

- reduced albumin-adjusted calcium concentration due to primary PTH deficiency and associated with hyperphosphataemia,
- reduced albumin-adjusted calcium concentration due to other causes and associated with appropriately high PTH concentrations and usually hypophosphataemia.

Determine first if the fall in plasma total calcium concentration (albumin-adjusted calcium) is due to a low protein-bound fraction.

Patients with a low albumin concentration should not be given calcium and/or vitamin D unless there is clinical evidence of a low albumin-adjusted calcium concentration.

- Is the patient on drugs or chemicals that may cause hypocalcaemia (see Box 6.2)?
- Is the plasma phosphate concentration high? If the plasma urea and/or creatinine concentration is high, renal dysfunction is the likely cause (see Chapter 3).
- Is the plasma phosphate concentration low? If so, calcium deficiency with normal secretion of PTH in response to feedback is likely. At this point a plasma PTH assay may be useful. Is the plasma alkaline phosphatase activity high? This finding may suggest prolonged secondary hyperparathyroidism due to calcium deficiency.
- If indicated, do relevant bone radiographs show signs of rickets or osteomalacia? These may confirm prolonged calcium deficiency. Check plasma 25-hydroxyvitamin D levels; if the plasma levels are low, look for causes of undernutrition and malabsorption states.

In the rare hypocalcaemia of type 1 vitamin-D-dependent rickets there are low plasma 1,25-$(OH)_2D_3$ concentrations, whereas type 2 vitamin-D-dependent rickets causes a vitamin D resistance and plasma 1,25-$(OH)_2D_3$ concentrations are elevated.

Raised plasma phosphate in the face of hypocalcaemia and low plasma PTH concentration suggests hypoparathyroidism.

Is there a history of neck surgery which has led to hypoparathyroidism? Hypoparathyroidism may also be of autoimmune origin and associated with other autoimmune disorders. It needs to be distinguished from the even more rare 'pseudohypoparathyroidism' by measuring plasma PTH concentrations. Parathyroid hormone concentrations will be low in true hypoparathyroidism but high if there is the end-organ unresponsiveness of pseudohypoparathyroidism.

Check plasma magnesium, as severe hypomagnesaemia can cause hypocalcaemia by reducing the action of PTH.

A raised urinary calcium concentration may help diagnose the rare autosomal dominant hypercalciuric hypocalcaemia.

Treatment of hypocalcaemia

Asymptomatic hypocalcaemia

Apparent hypocalcaemia, due to low plasma albumin concentrations, should not be treated. Always look at the albumin-adjusted calcium value.

Asymptomatic true hypocalcaemia, or that causing only mild clinical symptoms, can usually be treated effectively with oral calcium supplements and vitamin D supplements. It is difficult to give enough oral calcium by itself to make a lasting and significant difference to plasma calcium concentrations. If a normal diet is

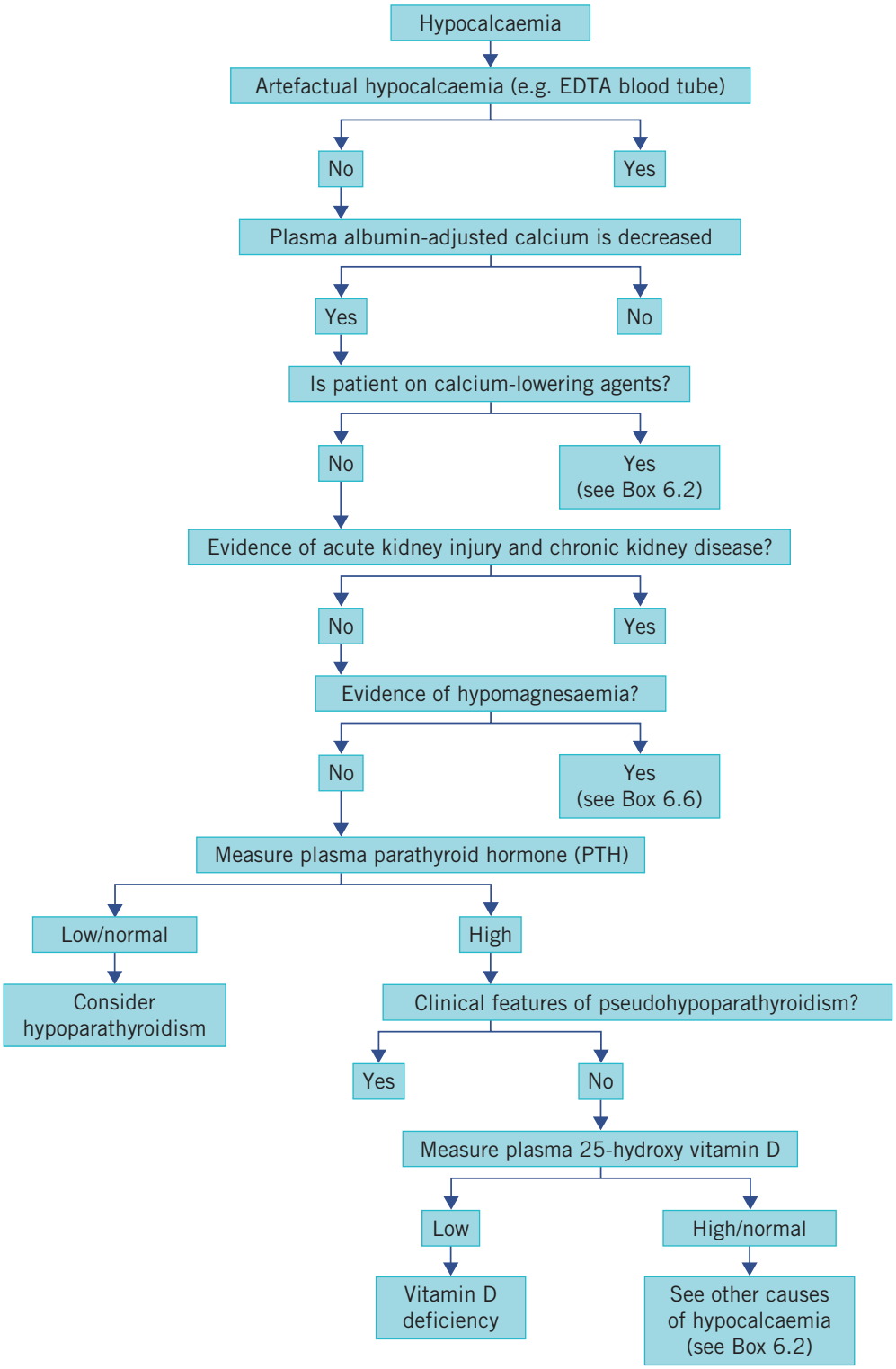

Figure 6.4 Algorithm for the investigation of hypocalcaemia. EDTA, ethylenediamine tetra-acetic acid.

being taken, vitamin D, by increasing the absorption of calcium from the intestine, is usually adequate without calcium supplements. 1,25-Dihydroxycholecalciferol and alfacalcidol (1-α-hydroxycholecalciferol) are most commonly used as they have short half-lives, particularly if there is hypoparathyroidism or a defect in vitamin D metabolism. It is important to monitor the plasma calcium closely to avoid inducing hypercalcaemia and

hypercalciuria by ensuring a normal urinary excretion of calcium.

Because of the danger of ectopic calcification by precipitation of calcium phosphate, hypocalcaemia with hyperphosphataemia in renal disease should be treated cautiously. The plasma phosphate concentration should first be lowered by giving a phosphate-binding agent that binds phosphate in the intestinal lumen. 1,25-Dihydroxycholecalciferol and alfacalcidol, the active vitamin D metabolites, have been used to treat hypocalcaemia in renal disease.

Hypocalcaemia with life-threatening symptoms

If there are cardiac arrhythmias, seizures or severe tetany including laryngospasm shown to be due to hypocalcaemia, intravenous calcium, usually as 10 mL of 10 per cent calcium gluconate, should be given over about 5 min. Treatment can then begin as above, depending upon the aetiology of the hypocalcaemia.

Post-operative hypocalcaemia

Hypocalcaemia during the first week after a thyroidectomy or parathyroidectomy should be treated only if there is tetany, and usually with calcium replacement, which, unlike vitamin D supplements, has a rapid effect and a short half-life. Persistent hypocalcaemia may indicate that the parathyroid glands are permanently damaged and that long-standing, or even life-long, vitamin D supplementation is necessary. Parathyroid bone disease may result in 'hungry bones' and prolonged post-operative hypocalcaemia.

Hypercalciuria

Hypercalciuria in the absence of hypercalcaemia (hypercalciuria normocalcaemia) may predispose to the formation of renal calculi (see Chapter 3) and may occur in:

- some cases of osteoporosis in which calcium cannot be deposited in normal amounts because the bone matrix is reduced,
- acidosis, in which the release of free ionized calcium from bone is increased.

Hypercalciuria can broadly be divided into absorptive hypercalciuria, type I (hyperabsorption of calcium), type II (diet-responsive hypercalciuria) and type III (renal phosphate leak resulting in decreased calcium resorption), and renal hypercalciuria (decreased renal calcium resorption). These can be distinguished by tests of oral calcium absorption.

Hypercalciuria can, of course, also occur in the face of hypercalcaemia, such as resorptive hypercalciuria associated with primary hyperparathyroidism.

Estimation of urinary CaE is rarely diagnostic in the differential diagnosis of hypercalcaemia except familial hypocalciuric hypercalcaemia. If glomerular function is normal, all other causes of hypercalcaemia usually increase the calcium load on the glomeruli and evoke hypercalciuria. If renal glomerular function is impaired, calcium excretion is low even if there is hypercalcaemia.

Disorders of bone not usually affecting the plasma calcium concentration

Some disorders of bone rarely alter plasma calcium concentrations but are important in the differential diagnosis of changes in mineral metabolism.

Osteoporosis

Osteoporosis is not a primary disorder of calcium metabolism. The reduction of bone mass is due to thinning of the protein on which the calcium is usually deposited. A slight increase in urinary calcium loss is secondary to this. Disorders associated with an increased incidence include the following:

- low plasma oestrogen concentrations, such as after the female menopause (the most common cause) and prolonged amenorrhoea; also low testosterone concentrations in males,
- elderly subjects in whom there may also be mild osteomalacia because of impaired renal production of 1,25-$(OH)_2D_3$,
- other endocrine disorders and other miscellaneous causes:
  - hypercortisolism, hyperthyroidism, long-term glucocorticoid use,
  - drugs such as heparin, and anticonvulsants such as phenytoin and carbamazepine,
  - prolonged immobilization,
  - smoking, alcohol abuse,
  - calcium deficiency,
  - gastrointestinal causes, including malabsorption, anorexia nervosa.

In osteoporosis plasma calcium and phosphate concentrations do not fall and, because there is no increase in osteoblastic activity, the plasma total alkaline phosphatase activity does not rise. These findings are invaluable in distinguishing between osteomalacia and osteoporosis.

Concentrations of new bone markers, such as bone-specific alkaline phosphatase (bone formation), plasma osteocalcin (bone formation), type 1 procollagen peptides (bone formation), urinary deoxypyridinoline and cross-linked N-terminal telopeptide and C-terminal telopeptide of type 1 collagen (bone resorption), urinary hydroxyproline (bone resorption) and bone-resistant or tartrate-resistant acid phosphatase (bone resorption) are raised in osteoporosis and may be useful markers of the disease process. However, these bone markers do not give information about exact bone anatomy, for which imaging studies are necessary.

Sometimes radiographs are useful, especially if fractures are suspected (Fig. 6.5). Bone mineral density (BMD) is often used and reported as a T-score that compares the patient's BMD with that of a healthy control. Normal BMD is within –1 standard deviation (SD) of this, whereas osteopenia is defined as between –1 and –2.5 SD and osteoporosis has a T-score of less than –2.5 SD.

Treatment consists of adequate calcium and vitamin D intake. The bisphosphonates increase BMD and inhibit bone resorption, probably by inhibiting osteoclast activity. Strontium ranelate is a duel action bone agent (DABA) that stimulates osteoblasts and inhibits osteoclasts. Calcitonin inhibits osteoclast reabsorption and recombinant PTH analogues such as teriparatide stimulate osteoblasts. In women, hormone replacement therapy is also used if indicated, but this may have side effects. Raloxifene has been used and is a selective estrogen receptor modulator (SERM).

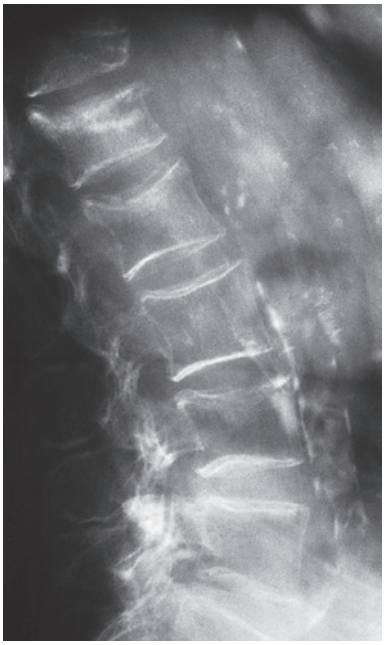

Figure 6.5 Radiograph showing osteoporosis; note compression of several vertebral bodies and compression fractures of T12 and L1. Reproduced with kind permission from Solomon L, Warwick D and Nayagam S. *Apley's System of Orthopaedics and Fractures*, 9th edition. London: Hodder Arnold, 2010.

Paget's disease of bone

Paget's disease is more common in the elderly, possibly being present in about 5 per cent of people over 60 years old. There is increased bone turnover and remodelling due to increased osteoclastic and osteoblastic function. It may be asymptomatic or may present with bone pain, pathological fractures, deafness (due to bone overgrowth) and high-output cardiac failure due to increased vascularity within the bone. Enlargement of bones such as the skull (osteoporosis circumscripta), femur and tibia (sabre tibia) can occur.

Diagnosis may necessitate radiographs and/or bone scanning. Plasma calcium and phosphate concentrations are rarely affected unless the patient is immobilized, in which case the plasma calcium concentrations may rise. Plasma alkaline phosphatase activity is typically very high. Less than 1 per cent of patients may develop osteosarcomas, and this complication may be associated with rapidly rising plasma alkaline phosphatase activity. Bisphosphonates are often used to treat Paget's disease; although calcitonin has been tried, it is probably less effective.

Rickets or osteomalacia caused by renal tubular disorders of phosphate reabsorption

In a group of inborn errors of renal tubular function, less phosphate than normal is reabsorbed from the glomerular filtrate. The consequent rickets or osteomalacia, unlike the usual form, responds poorly to vitamin D therapy. The syndrome has therefore been called 'resistant rickets'. Familial hypophosphataemia is an X-linked dominant trait; the syndrome may also be part of a more generalized reabsorption defect in Fanconi's syndrome (see Chapter 3).

In these disorders, failure to calcify bone is probably due to phosphate deficiency, although there may also be impaired vitamin D metabolism. Plasma phosphate concentrations are usually very low and fail to rise when vitamin D is given; there is phosphaturia inappropriate to the plasma concentration. The high plasma alkaline phosphatase activity reflects increased osteoblastic activity. The usually normal plasma calcium

concentrations differ from the findings in the 'classic' syndrome. As the free ionized calcium concentration is normal, the parathyroid glands are not overstimulated and therefore evidence in the bone of high PTH concentrations is rare. The conditions respond to large doses of oral phosphate and to a small dose of the active metabolite of vitamin D.

PHOSPHATE METABOLISM

Phosphate is a divalent anion, approximately 80 per cent of which is found in the bony skeleton and 20 per cent is distributed in the soft tissues and muscle. Phosphate is the major intracellular anion and shifts between the intracellular and extracellular compartments. Such transcellular movement can result from the ingestion of carbohydrate or lipid, as well as from acid–base alterations – for example, acidosis can result in shifts of phosphate out of cells into the plasma.

The daily phosphate intake is about 30 mmol, with approximately 80 per cent being absorbed in the jejunum. Protein-rich food is a major source of phosphate intake, as are cereals and nuts. The output is largely renal, with more than 90 per cent being excreted by this route. Most of the phosphate filtered at the glomeruli is reabsorbed by the proximal tubules. Gastrointestinal loss of phosphate accounts for only 10 per cent of the body's phosphate excretion.

Urinary phosphate excretion falls as the plasma phosphate, and therefore glomerular filtrate, concentrations decrease in response to reduced dietary phosphate intake. The measurement of urinary phosphate concentration may occasionally be useful to distinguish hypophosphataemia due to true depletion (low urinary phosphate) and the increased urinary phosphate excretion found in renal tubular disorders, such as X-linked hypophosphataemic rickets.

The urinary phosphate excretion threshold can be derived from nomograms, and a low value implies renal phosphate loss. Another way to assess renal phosphate loss is to calculate the fractional phosphate excretion (FEPi%):

$$\text{FEPi\%} = \frac{\text{urinary[phosphate]}}{\text{plasma[phosphate]}} \times \frac{\text{plasma[creatinine]}}{\text{urinary[creatinine]}} \times 100 \qquad (6.3)$$

An FEPi% of more than 10 per cent implies a renal phosphate loss.

THE FUNCTION OF PHOSPHATE IN VIVO

Phosphate is an important intracellular buffer as well as being essential for buffering hydrogen ions in urine. In addition, it has a structural role as a component of phospholipids, nucleoproteins and nucleic acids.

Phosphate plays a central role in cellular metabolic pathways, including glycolysis and oxidative phosphorylation. A by-product of glycolysis is 2,3-diphosphoglycerate (2,3-DPG). This is a regulator of haemoglobin oxygen dissociation. Nucleotides such as adenosine triphosphate consist of phosphate. Other actions include excitation–stimulus response coupling and nervous system conduction. Phosphate also has a role in the optimal function of leucocytes, for example chemotaxis and phagocytosis, and for platelets in clot retraction.

ABNORMALITIES OF PLASMA PHOSPHATE CONCENTRATION

Hyperphosphataemia

The causes of hyperphosphataemia are listed in Box 6.3. The majority of the clinical effects are the result of hypocalcaemia, particularly if the plasma phosphate concentration is more than 3.0 mmol/L. The reason for this is that calcium/phosphate precipitation into the tissues can ensue when the phosphate and calcium plasma concentrations exceed their solubility product. Thus, metastatic calcification is a clinical consequence of hyperphosphataemia.

The treatment for hyperphosphataemia is with oral phosphate-binding agents, for example magnesium hydroxide or calcium carbonate. These agents have been used in the management of patients with chronic

Box 6.3 Some causes of hyperphosphataemia

- Artefact due to in vitro haemolysis or old blood sample
- Inappropriately high phosphate intake, usually intravenously
- Acute kidney injury or chronic kidney disease
- Increased tissue breakdown
- Tumour lysis syndrome
- Malignant hyperpyrexia
- Crush injuries
- Acidaemia (metabolic or respiratory acidosis)
- Diabetic ketoacidosis
- Hypoparathyroidism
- Acromegaly
- Excess vitamin D intake