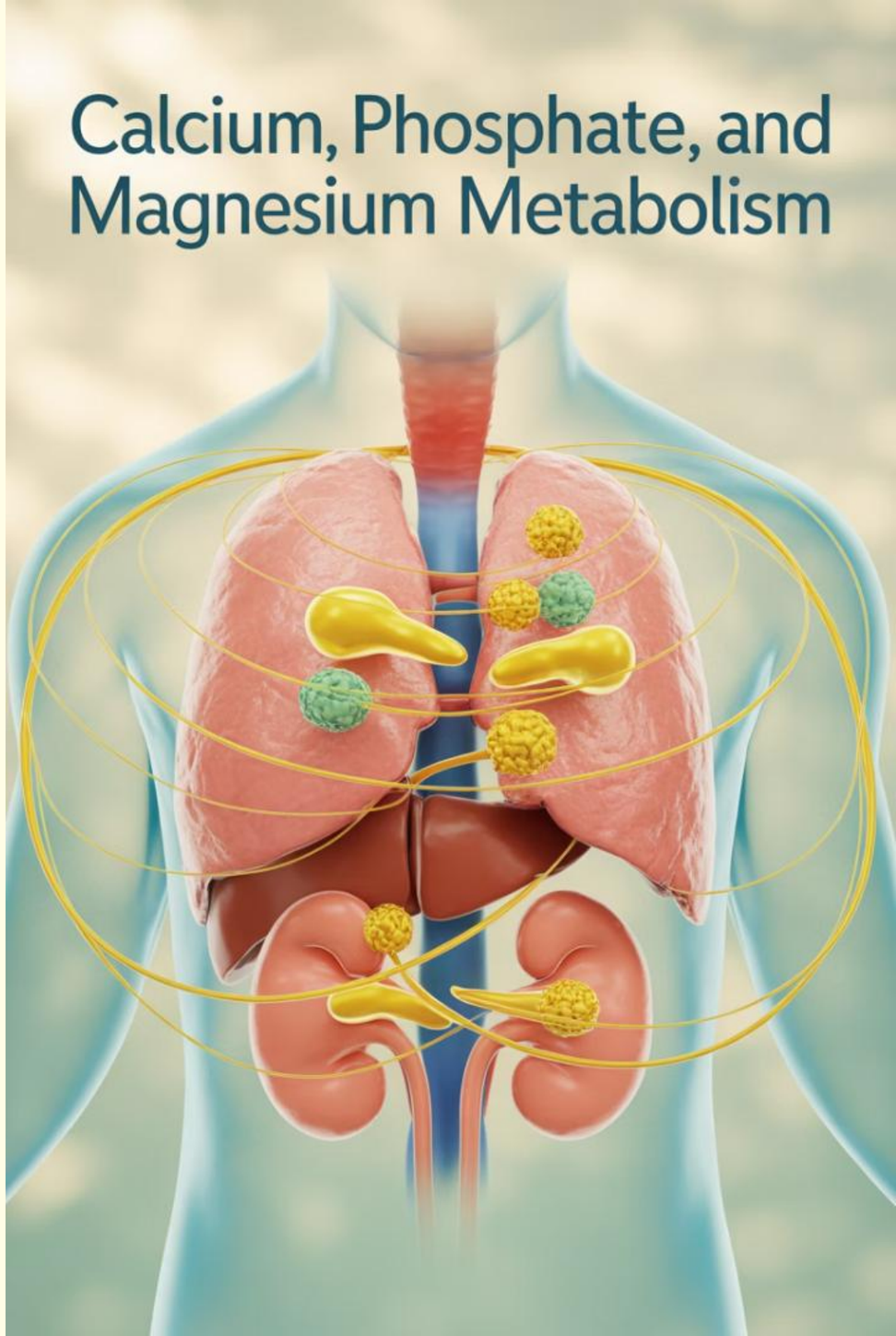
Disorders of Calcium Metabolism

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.

by Assist.Prof.Dr.Qutaiba Alhajjaj

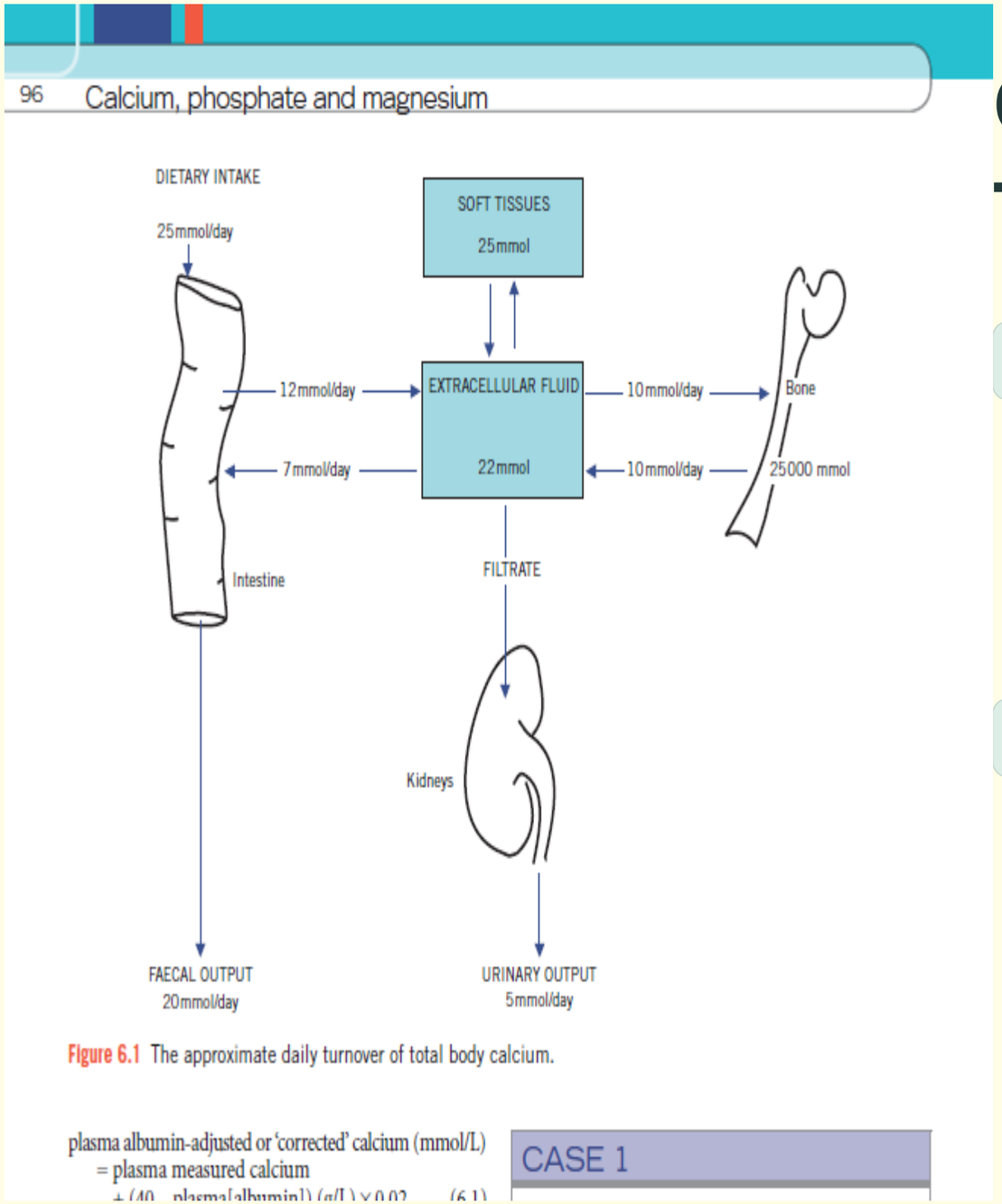


Total Body Calcium

The total body calcium depends upon the calcium absorbed from dietary intake and that lost from the body. 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-(OH)2 D3, also called calcitriol), is needed for calcium absorption.



Calcium Loss and Daily Turnover

Urinary 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 Loss

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.

Plasma Calcium and Albumin Correction

Forms of Plasma Calcium

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 (Ca2+), which comprises most of the rest. This is the physiologically active fraction.

Albumin Correction Formula

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

Case 1: Calcium Correction in Trauma

1.98

Measured Calcium

Patient's plasma calcium in mmol/L (reference range: 2.15-2.55)

30

Albumin Level

Patient's plasma albumin in g/L (reference range: 35-45)

2.18

Adjusted Calcium

Calculated as: 1.98 + (40 – 30) × 0.02 = 1.98 + 0.20 = 2.18 mmol/L

A 45-year-old man was in the intensive care unit for multiple trauma following a road traffic accident. The adjusted calcium falls within the reference range and does not require specific treatment. Remember this if the patient has hypoalbuminaemia.

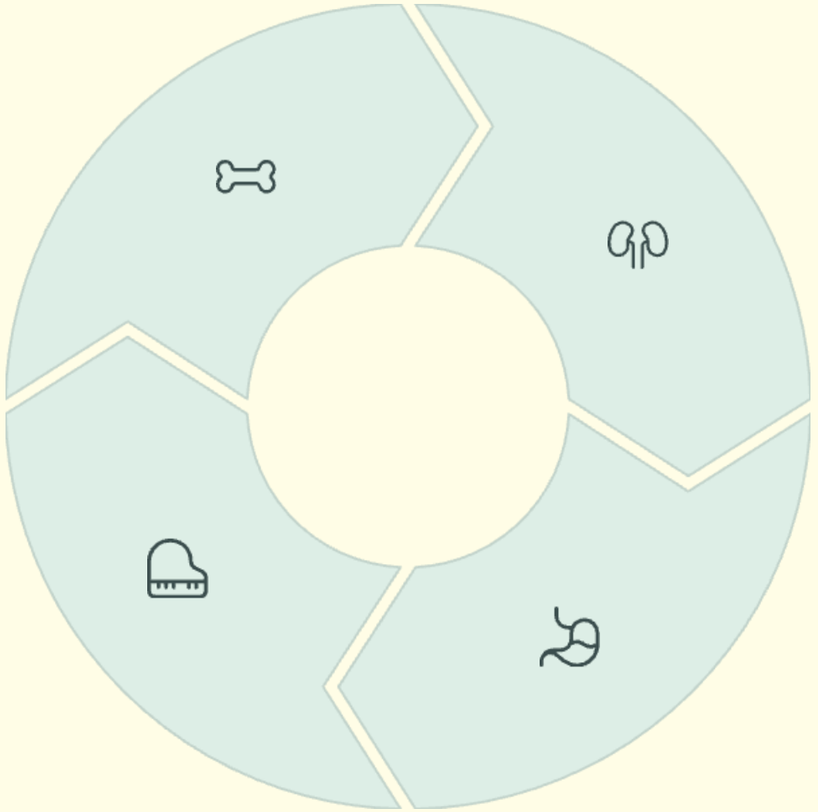
Control of Plasma Calcium

Bone

Calcium storage and release regulated by PTH and vitamin D

Kidneys

Regulate calcium excretion and vitamin D activation



Parathyroid Glands

Secrete PTH in response to low calcium levels

Intestine

Absorbs dietary calcium under vitamin D influence

The effectiveness of calcium control depends upon an adequate supply of calcium and vitamin D, and normal functioning of the intestine, parathyroid glands, and kidneys.

Parathyroid Hormone (PTH)

1

Structure and Metabolism

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.

2

Bone Effects

Stimulation of osteoclastic bone resorption, releasing both free ionized calcium and phosphate into the ECF; this action increases the plasma concentrations of both calcium and phosphate.

3

Kidney Effects

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.

4

Control of Secretion

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 continues until the calcium concentration returns to normal.

PTH-Related Protein and Calcitonin

Parathyroid Hormone-Related Protein (PTHRP)

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.

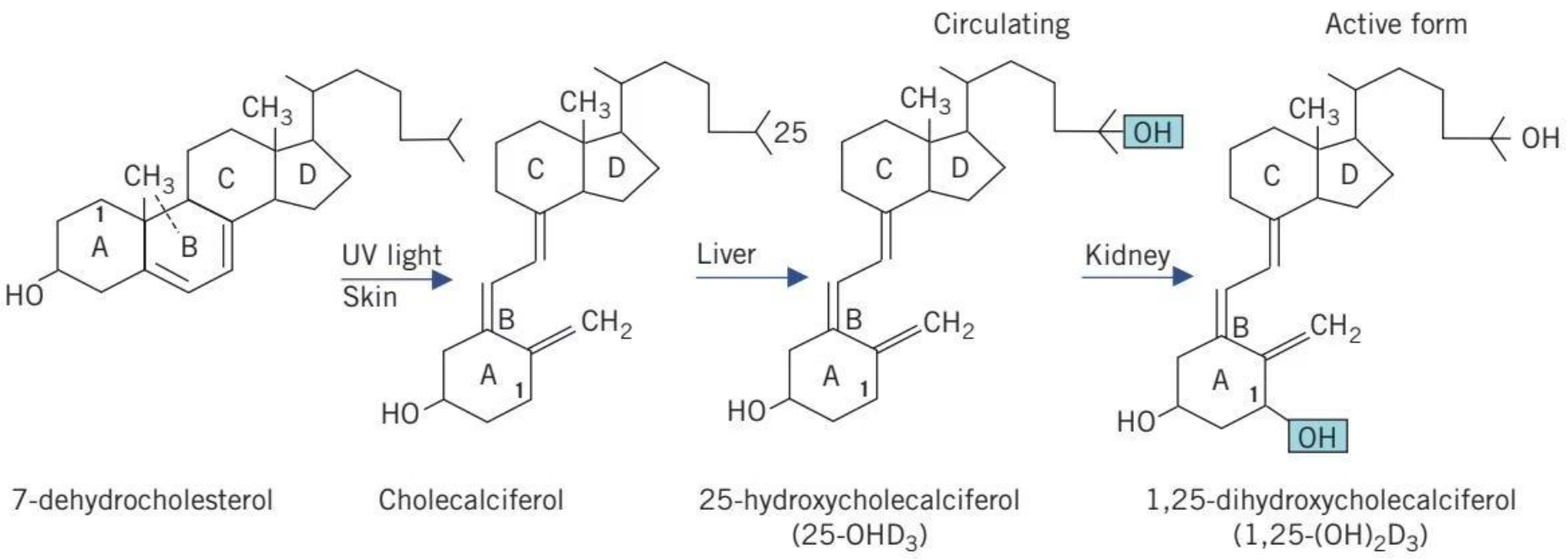
The gene that codes for PTHRP is widely distributed in body tissues but is normally repressed. However, it may become derepressed in certain tumours, causing humoral hypercalcaemia of malignancy.

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.

Vitamin D Metabolism



1

Sources of Vitamin D

Vitamin D is derived from ergocalciferol (vitamin D2), obtained from plants in the diet, and cholecalciferol (vitamin D3), formed in the skin by the action of ultraviolet light on 7-dehydrocholesterol.

2

Liver Metabolism

In the liver, cholecalciferol is hydroxylated to 25-hydroxycholecalciferol (25-OHD3) by the enzyme 25-hydroxylase. The rate of formation of 25-OHD3 is affected by the supply of substrate in the form of calciferol.

3

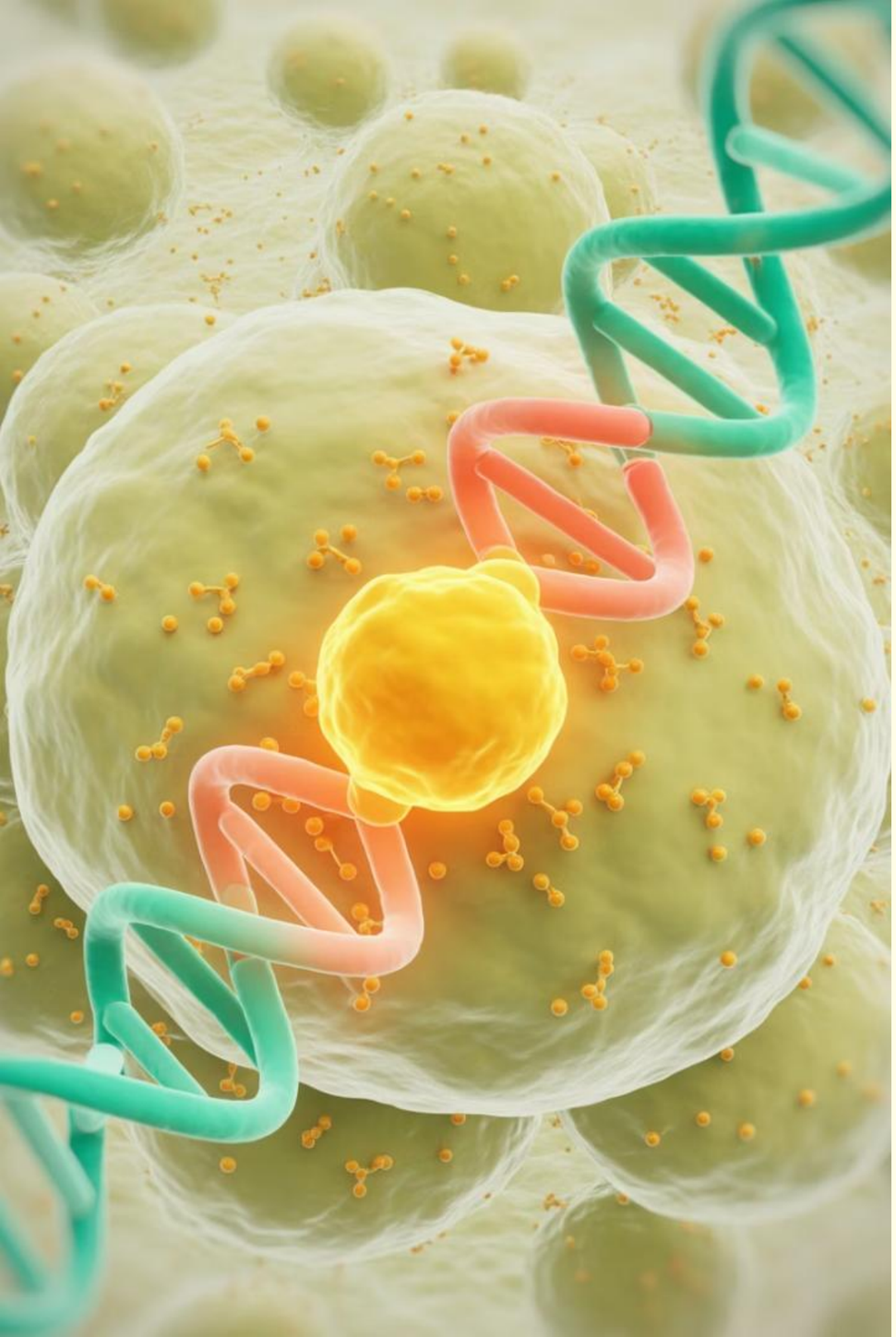
Kidney Activation

In the proximal renal tubular cells of the kidney, 25-OHD3 undergoes a second hydroxylation, catalysed by the enzyme 1-α-hydroxylase to form the active metabolite 1,25-(OH)2 D3.

4

Regulation of Activation

The activity of 1-α-hydroxylase is stimulated by a low plasma phosphate concentration and an increase in plasma PTH concentration. Its activity is inhibited by hyperphosphataemia and high levels of free ionized calcium.



Vitamin D Action and Receptor

Vitamin D Production

In normal adults, much more cholecalciferol is derived from the action of sunlight on skin than from food.

2

Kidney as Endocrine Organ

The kidney is an endocrine organ, synthesizing and releasing the hormone 1,25-(OH)2 D3; impairment of the final hydroxylation helps explain the hypocalcaemia of renal disease.

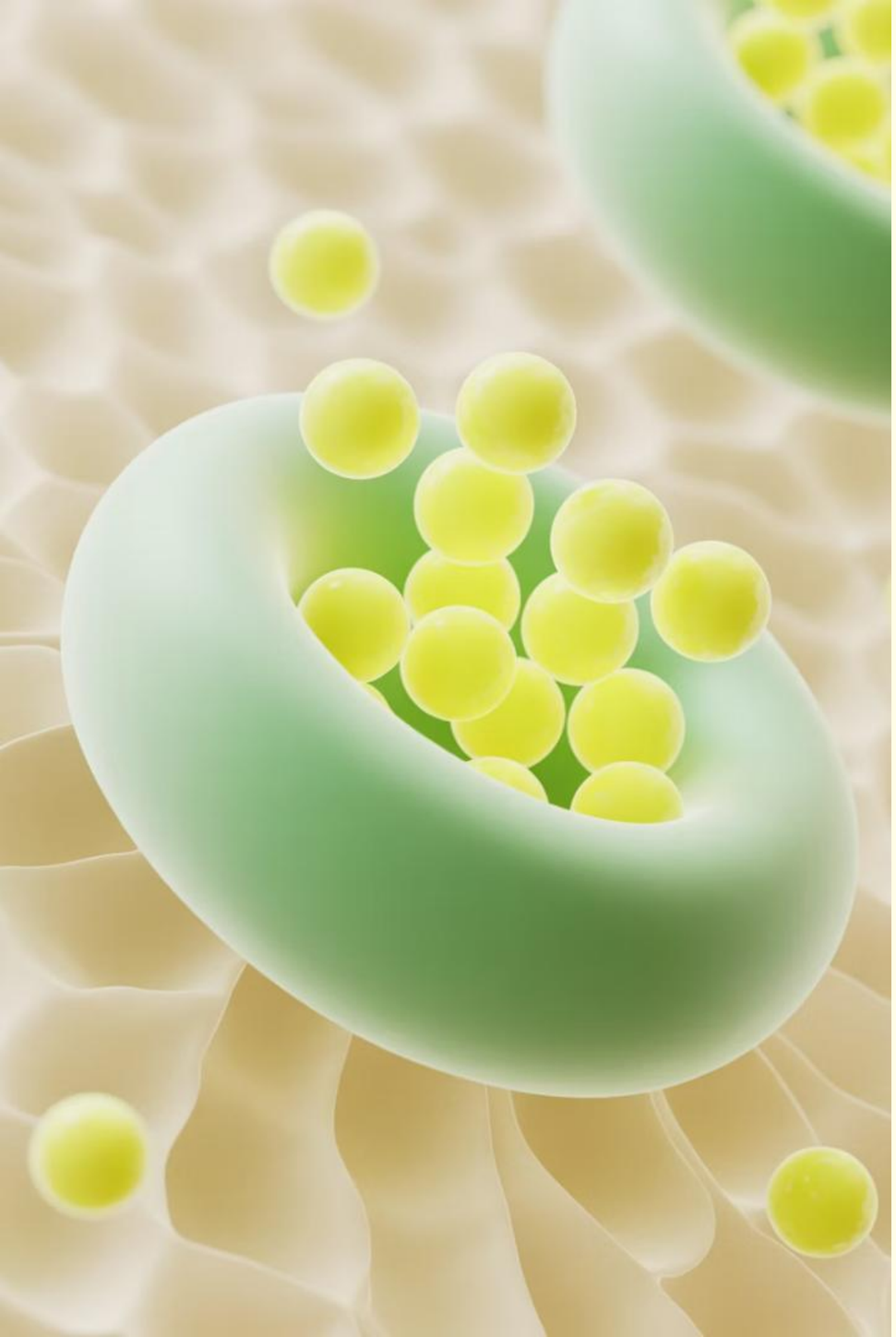
3

Intestinal Effects

1,25-(OH)2 D3 increases calcium absorption by intestinal mucosal cells.

Vitamin D Receptor (VDR)

The VDR is found in almost all cell nuclei. Calcitriol activates the receptor, which forms a heterodimer with the retinoid-X receptor and binds to hormone response elements on DNA, affecting gene expression.



Calcium-Sensing Receptor

Function

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.

Genetic Disorders

Defects in the CaSR gene are responsible for various rare defects of calcium homeostasis:

- Inactivating mutations: familial benign hypocalciuric hypercalcaemia and neonatal severe hyperparathyroidism
- Activating mutations: autosomal dominant hypocalcaemia with hypercalciuria

Therapeutic Applications

Calcimimetic agents have been devised that bind and activate the CaSR, resulting in decreased PTH release and reduced plasma calcium concentrations.

Other Mechanisms of Calcium Control

Thyroid Hormone

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.

Sex Hormones

Other hormones influencing calcium metabolism include oestrogens, prolactin and growth hormone. These may increase 1,25-(OH)2 D3 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.

1

Normal Relationship

Calcium and phosphate usually vary in the same direction

2

Exception 1

Renal glomerular dysfunction severe enough to impair the phosphaturic effect of PTH or PTHRP

3

Exception 2

Inappropriate excess or deficiency of PTH due to a primary disorder of the parathyroid gland or secretion of PTHRP

Clinical Effects of Hypercalcaemia

Renal Effects

Renal damage, polyuria, renal calculi, and hypokalaemia often with metabolic alkalosis

Neurological Effects

Depression, anorexia, nausea, vomiting, and muscular hypotonia

Gastrointestinal Effects

Increased gastrin secretion, peptic ulceration, constipation, and abdominal pain

Cardiovascular Effects

Hypertension, shortened Q-T interval, broadened T waves, and risk of cardiac arrest

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

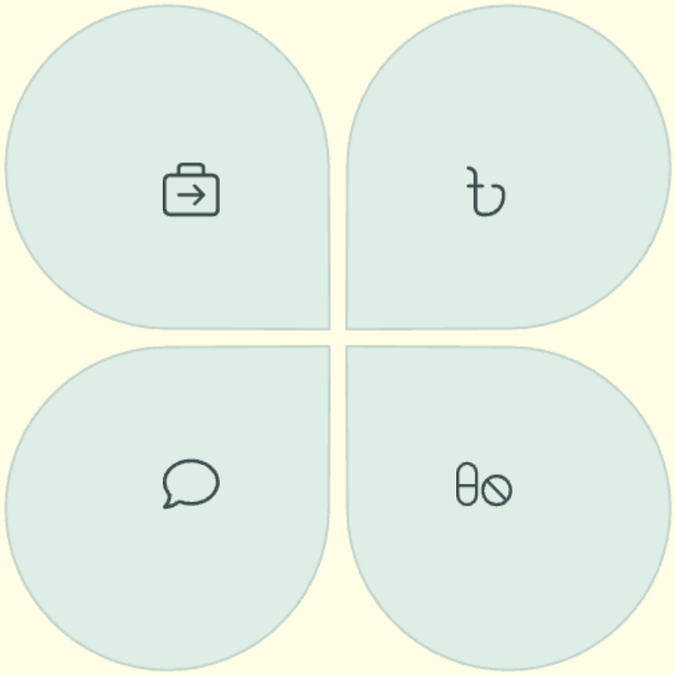
Causes of Hypercalcaemia

Malignancy

- Bony metastases (breast, lung, prostate, kidney, thyroid)
- Solid tumors with humoral effects
- Haematological tumors (multiple myeloma)

Vitamin D Related

- Vitamin D toxicity
- Granulomatous disease (sarcoidosis, TB)



Parathyroid Disorders

- Primary hyperparathyroidism
- Tertiary hyperparathyroidism
- Lithium-induced hyperparathyroidism

Drugs

- Thiazides
- Vitamin A toxicity
- Milk-alkali syndrome

Case 2: Primary Hyperparathyroidism

Test	Result	Reference Range
Albumin-adjusted calcium	2.96 mmol/L	2.15-2.55 mmol/L
Phosphate	0.62 mmol/L	0.80-1.35 mmol/L
Parathyroid hormone	157 ng/L	20-65 ng/L

A 53-year-old man saw his general practitioner because of bone pain and constipation. The patient has hypercalcaemia with 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.

Primary Hyperparathyroidism

Etiology

Primary hyperparathyroidism 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.

Demographics

The incidence of primary hyperparathyroidism increases with age, being most common in elderly females. The majority of cases are diagnosed after the chance finding of high plasma calcium, usually with low plasma phosphate concentrations.

Clinical Presentation

Symptoms include generalized ill health, depression, nausea, anorexia, abdominal pain, polyuria, renal calculi, bone pain, and rarely acute pancreatitis presenting as an "acute abdomen."

Treatment

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

Initial Hypocalcaemia

Long-standing low calcium levels (secondary hyperparathyroidism)

1

2

Parathyroid Hypertrophy

Glands enlarge due to chronic stimulation

Autonomous Function

PTH secretion becomes partly autonomous

3

4

Hypercalcaemia

When original cause of hypocalcaemia is removed (e.g., by renal transplantation)

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.

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.

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.

In humoral hypercalcaemia of malignancy, the plasma calcium concentration may rise from normal to dangerously high very rapidly, in contrast to primary hyperparathyroidism.

Case 3: Hypercalcaemia in Malignancy

Test	Result	Reference Range
Albumin-adjusted calcium	3.96 mmol/L	2.15-2.55 mmol/L
Phosphate	1.12 mmol/L	0.80-1.35 mmol/L
Parathyroid hormone	less than 10 ng/L	20-65 ng/L

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

Other Causes of Hypercalcaemia

Drugs/Medications

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

Milk-Alkali Syndrome

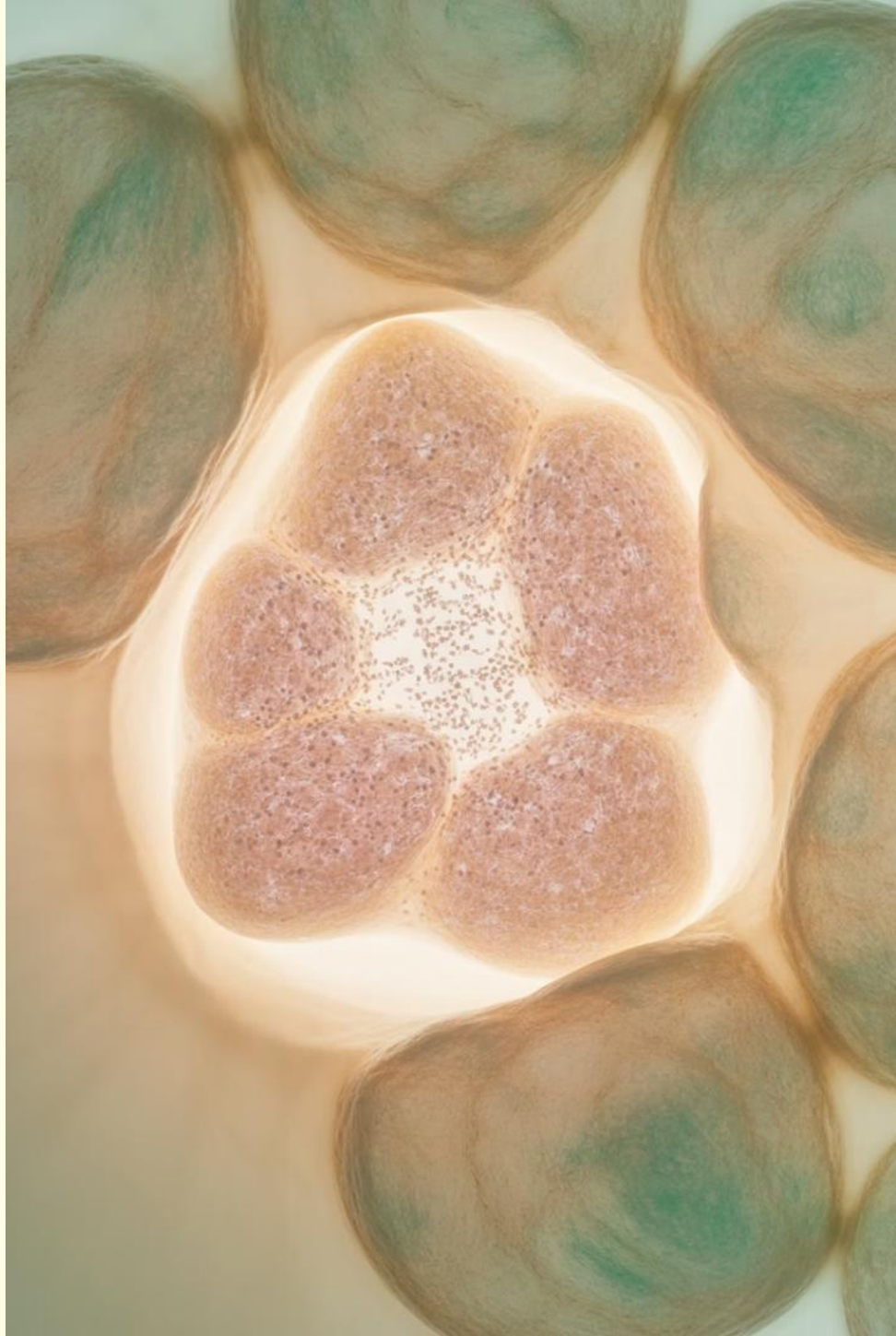
This rare condition occurs with the excessive use of calcium-containing antacids for dyspepsia. It is also associated with a metabolic alkalosis. Milk-alkali syndrome is now rarely seen, since the advent of proton pump inhibitors and H2 receptor antagonists for the treatment of dyspepsia.

Vitamin D Excess

Vitamin D excess may be caused by overvigorous treatment of hypocalcaemia. Increased intestinal calcium absorption may cause dangerous hypercalcaemia.

Granulomatous Diseases

Sarcoidosis, chronic beryllium poisoning, tuberculosis, histoplasmosis and leprosy can cause hypercalcaemia through granuloma tissue synthesizing 1,25-dihydroxycholecalciferol.



Familial Hypocalciuric Hypercalcaemia

Clinical Features

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.

Genetic Basis

The condition is inherited as an autosomal dominant trait. The aetiology of the condition is thought to be due a defect on the calcium-sensing receptor (CaSR).

Diagnostic Test

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). 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 but does not require surgical intervention.

Investigation of Hypercalcaemia

1

Confirm True Hypercalcaemia

Establish the plasma albumin concentration and check the albumin-adjusted calcium. Take a specimen without venous stasis to eliminate artefactual haemoconcentration.

2

Assess PTH Status

Measure plasma PTH. Elevated or inappropriately normal PTH suggests primary hyperparathyroidism, while suppressed PTH suggests other causes.

3

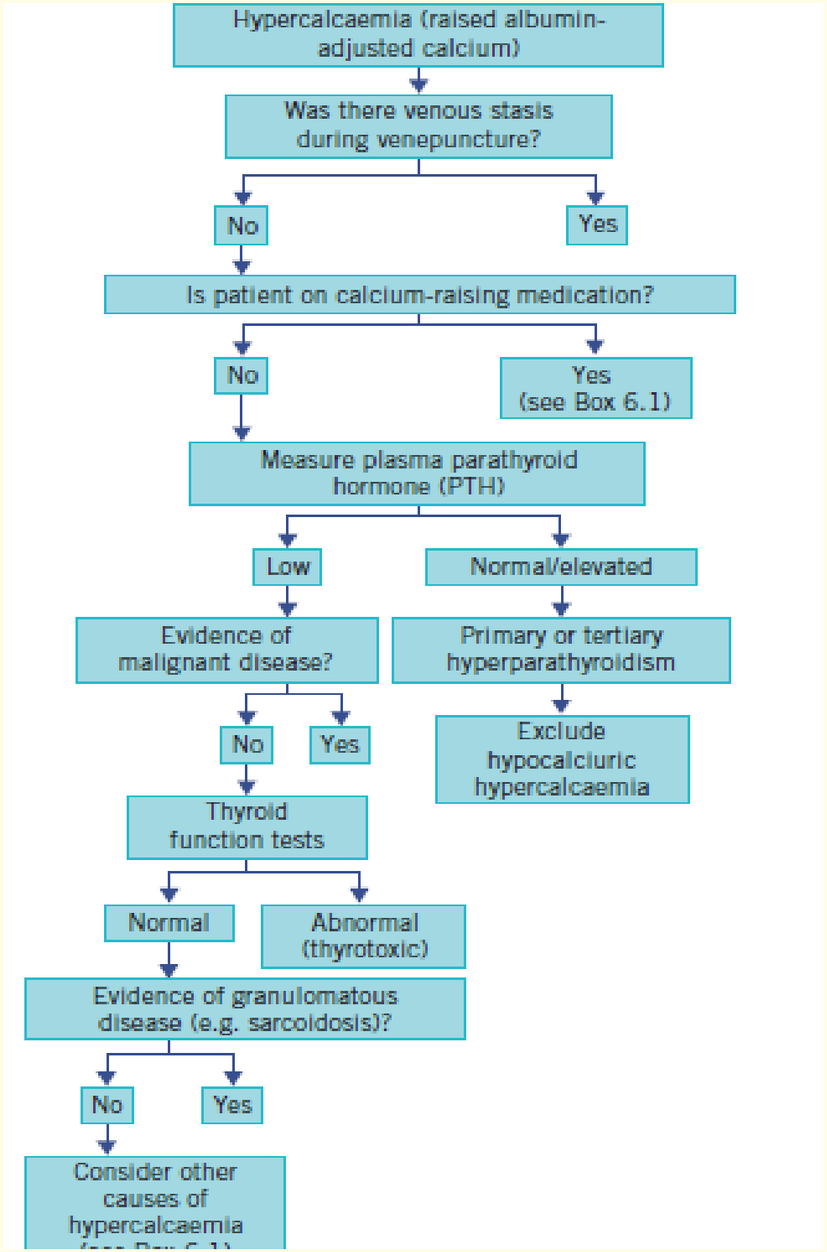
Check Phosphate

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

4

Consider Other Tests

Depending on clinical suspicion: check for malignancy, measure urinary calcium (CaE), look for evidence of sarcoidosis, check for other endocrine disorders.



Treatment of Hypercalcaemia

Mild to Moderate Hypercalcaemia

- Fluid volume repletion, if necessary by intravenous infusion of saline
- Bisphosphonates - first-line agents that bind to hydroxyapatite in bone, inhibiting bone turnover
- Treatment of the underlying cause

The management of apparently asymptomatic mild hypercalcaemia due to primary hyperparathyroidism is controversial. The decision whether to operate must be made on clinical grounds.

Severe Hypercalcaemia

- Rehydration with intravenous saline; furosemide may be given to increase urinary calcium clearance
- Bisphosphonates such as pamidronate after rehydration
- Steroids may lower calcium in malignancy, sarcoidosis and vitamin D intoxication
- Calcitonin sometimes used for severe hypercalcaemia

The aim of emergency treatment should be to lower the plasma concentration to one that is not immediately dangerous. Too rapid a reduction may cause tetany.

Clinical Effects of Hypocalcaemia

Neuromuscular Effects

Increased neuromuscular activity, tetany, carpopedal spasm, generalized seizures, laryngospasm, hyper-reflexia, and paraesthesiae

Ocular Effects

Prolonged hypocalcaemia may interfere with lens metabolism and cause cataracts

Psychiatric Effects

Depression and other psychiatric symptoms

Cardiac Effects

Cardiac arrhythmias, including prolonged Q-T interval on ECG

Case 4: Osteomalacia

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

A 72-year-old woman presented with tiredness, muscle aches and difficulty in standing up. 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.

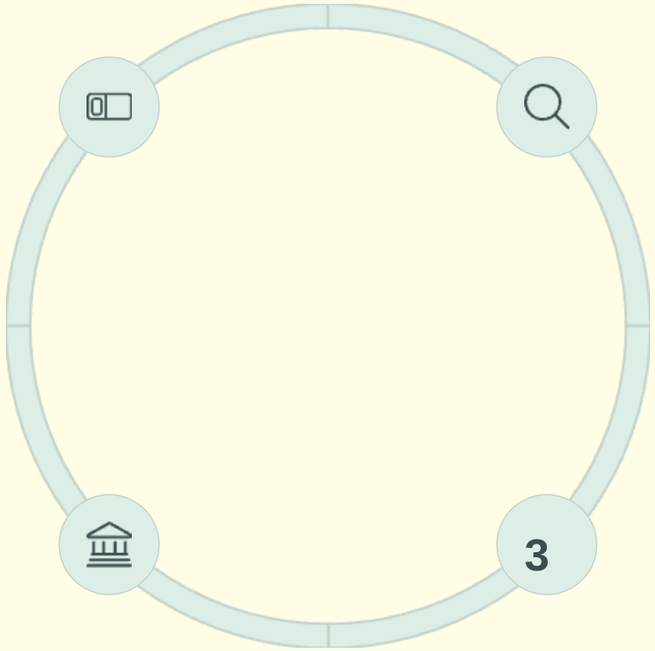
Causes of Hypocalcaemia

Drugs and Chemicals

- Furosemide
- Enzyme-inducing drugs (phenytoin)
- Ethylene glycol poisoning (rare)

Parathyroid Disorders

- Hypoparathyroidism
- Pseudohypoparathyroidism



Vitamin D Deficiency

- Rickets
- Osteomalacia
- Malabsorption states

Renal Causes

- Chronic kidney disease

Hypocalcaemia with Hypophosphataemia

Reduced Intake and Absorption

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.

Impaired Metabolism of Vitamin D

Chronic liver disease may occasionally be associated with mild osteomalacia, especially if there is cholestasis causing malabsorption. Prolonged anticonvulsant therapy may induce hepatic enzymes which catalyse the conversion of vitamin D to inactive metabolites.

Genetic Disorders

Type 1 vitamin-D-dependent rickets is due to 1-α-hydroxylase deficiency. Type 2 vitamin-D-dependent rickets causes vitamin D resistance due to a defect of the vitamin D receptor.

Hypocalcaemia with Hyperphosphataemia

Renal Dysfunction

The most common causes of hyperphosphataemia include acute kidney injury and chronic kidney disease. Renal disease causes relative resistance to vitamin D because of the direct effect on functioning renal tubular cells and inhibition of 1-α-hydroxylation by hyperphosphataemia.

Hypocalcaemia may develop within a few days of the onset of renal damage. Tetany is rare in renal disease, probably because the accompanying acidosis increases the plasma free ionized calcium concentration above tetanic concentrations.

Primary Hypoparathyroidism

Hypoparathyroidism is usually caused by surgical damage to the parathyroid glands during thyroid or neck surgery. Postthyroidectomy hypocalcaemia is not always due to damage to the glands and may be transient.

Other causes include:

- Autoimmune hypoparathyroidism (rare)
- Congenital absence of the parathyroid glands (DiGeorge's syndrome)

Pseudohypoparathyroidism

Definition

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.

Types

- Type 1: defect proximal to cyclic adenosine monophosphate (cAMP) tissue generation; urinary cAMP is low
- Type 2: defect distal to cAMP production; urinary cAMP levels are normal

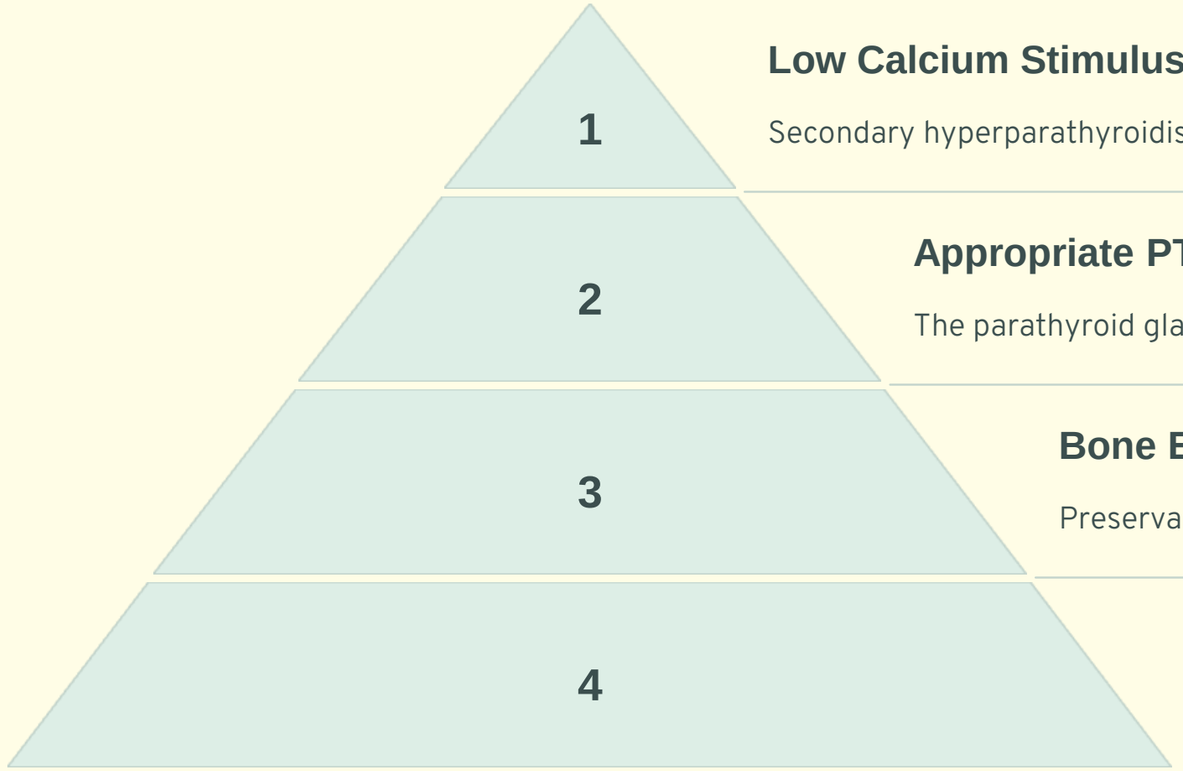
Clinical Features

The associated phenotype may show short stature, obesity, mental retardation and short third and fourth metacarpals.

Related Condition

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

Secondary Hyperparathyroidism



Low Calcium Stimulus

Secondary hyperparathyroidism occurs in response to a low plasma free ionized calcium concentration

Appropriate PTH Response

The parathyroid glands respond with appropriate secretion of PTH

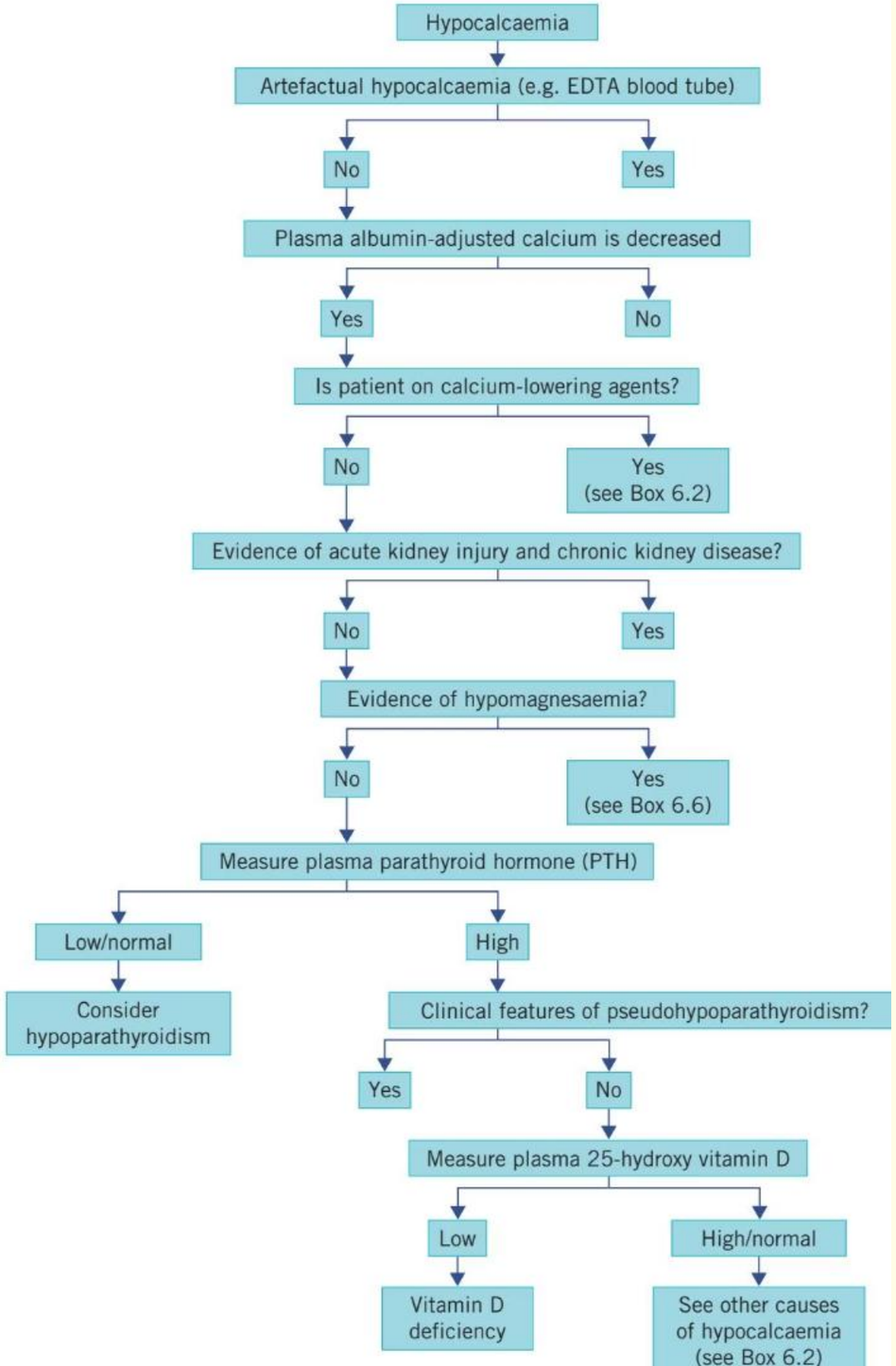
Bone Effects

Preservation of plasma calcium occurs at the expense of bone mineralization

Vitamin D Requirement

PTH cannot act effectively on bone in the absence of 1,25-(OH)2 D3

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.



Investigation of Hypocalcaemia

1

Confirm True Hypocalcaemia

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

2

Check Phosphate Status

Is the plasma phosphate concentration high (suggesting renal dysfunction or hypoparathyroidism) or low (suggesting calcium deficiency with normal PTH response)?

3

Measure PTH

A plasma PTH assay helps distinguish between primary hypoparathyroidism (low PTH) and secondary hyperparathyroidism (high PTH).

4

Additional Tests

Check plasma alkaline phosphatase, vitamin D levels, and consider bone radiographs if osteomalacia is suspected.

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 can usually be treated with oral calcium supplements and vitamin D supplements. 1,25-Dihydroxycholecalciferol and alfacalcidol are most commonly used if there is hypoparathyroidism or a defect in vitamin D metabolism.

Symptomatic Hypocalcaemia

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.

Hypocalcaemia during the first week after thyroidectomy or parathyroidectomy should be treated only if there is tetany, and usually with calcium replacement, which has a rapid effect and a short half-life.

Disorders of Bone Not Affecting Calcium

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.

Common causes include:

- Low sex hormones (post-menopausal, hypogonadism)
- Aging
- Endocrine disorders (hypercortisolism, hyperthyroidism)
- Medications (glucocorticoids, anticonvulsants)

Paget's Disease of Bone

Paget's disease is more common in the elderly, with increased bone turnover and remodelling due to increased osteoclastic and osteoblastic function.

It may present with:

- Bone pain
- Pathological fractures
- Deafness
- High-output cardiac failure

Plasma calcium and phosphate concentrations are rarely affected unless the patient is immobilized. Plasma alkaline phosphatase activity is typically very high.