DISORDER OF CALCIUM

Calcium is the most abundant mineral in the human body. It has many important functions in the body for instace, its effect on neuromuscular activity is of particular importance in the symptomatology of hypocalcaemia and hypercalcaemia.

Functions of the calcium

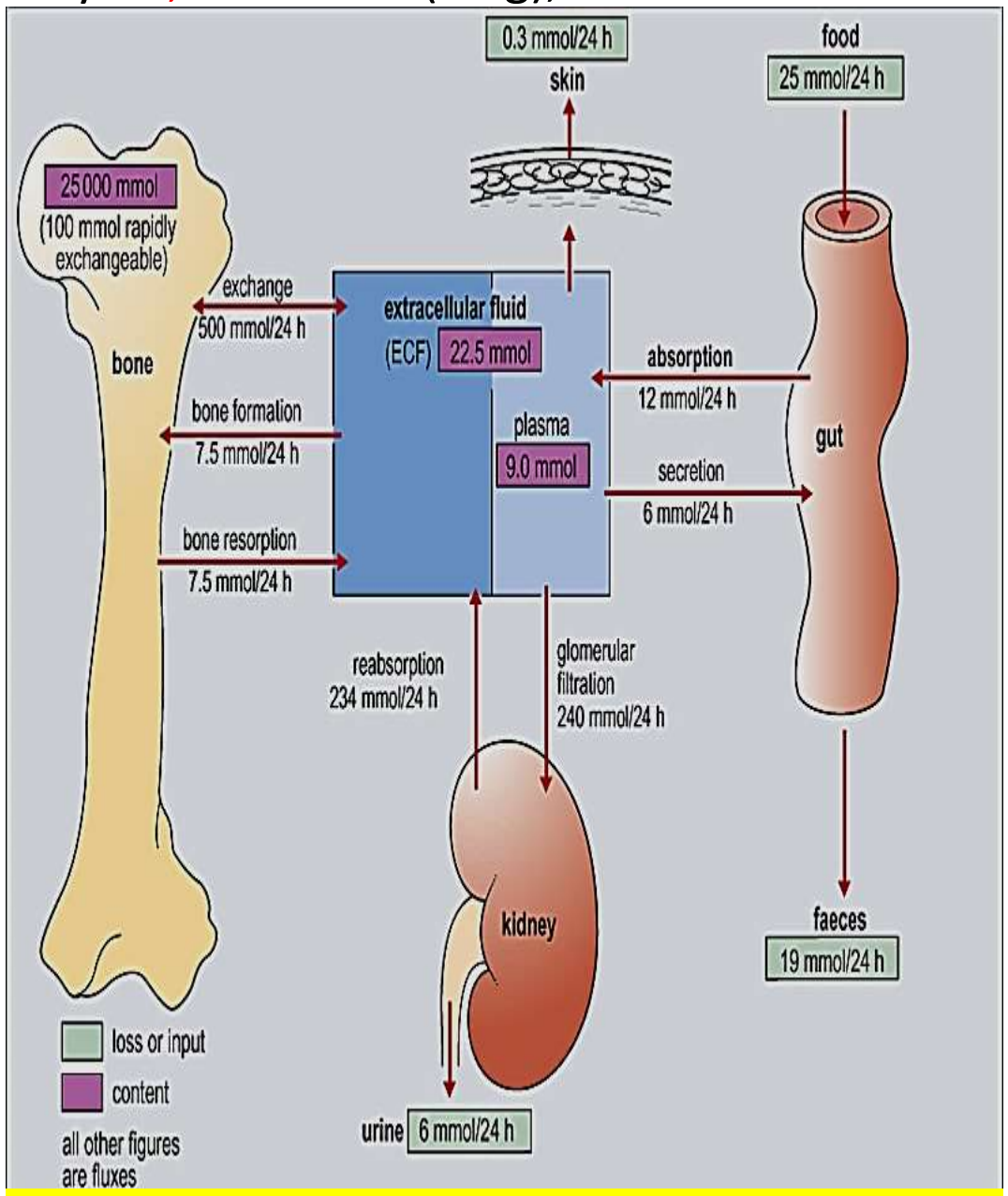
Function	Example
structural	bone teeth
neuromuscular	control of excitability release of neurotransmitters initiation of muscle contraction
enzymic	coenzyme for coagulation factors
signalling	intracellular second messenger

The average adult body contains nearly 25,000 mmol (1 kg), of which 99% is bound in the skeleton.

The total calcium content of ECF is only 22.5 mmol, of which about 9 mmol is in the plasma.

Bone is not metabolically inert. Most of the calcium in bone is stable but approximately 500 mmol/24 h moves between bone and the ECF to support calcium homoeostasis. about 7.5 mmol/24 h moves between the stable pool and the ECF in the course of bone remodeling.

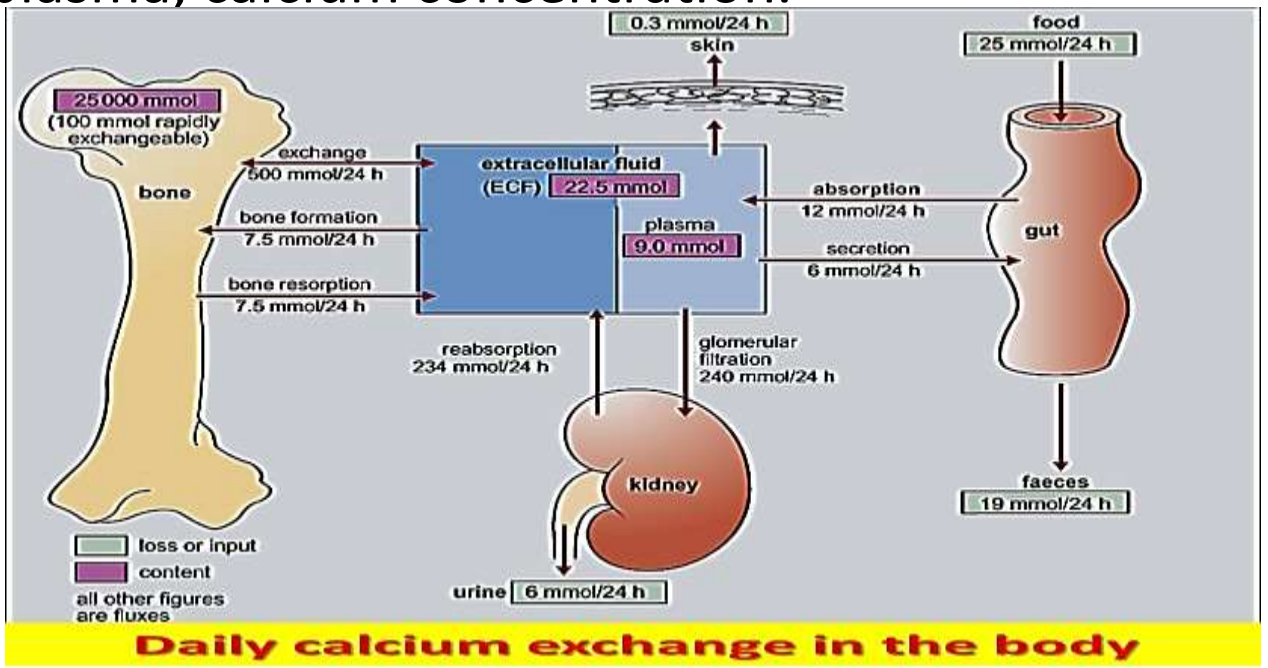
In the kidneys, ionized calcium is filtered by the glomeruli (240 mmol/24 h). Most of this is reabsorbed in the tubules and normal renal calcium excretion is 2.5-7.5 mmol/24 h.



Daily calcium exchange in the body

Because of the faecal loss, the minimum dietary requirement is about 12.5 mmol/24 h (though it is higher during growth, pregnancy and lactation).

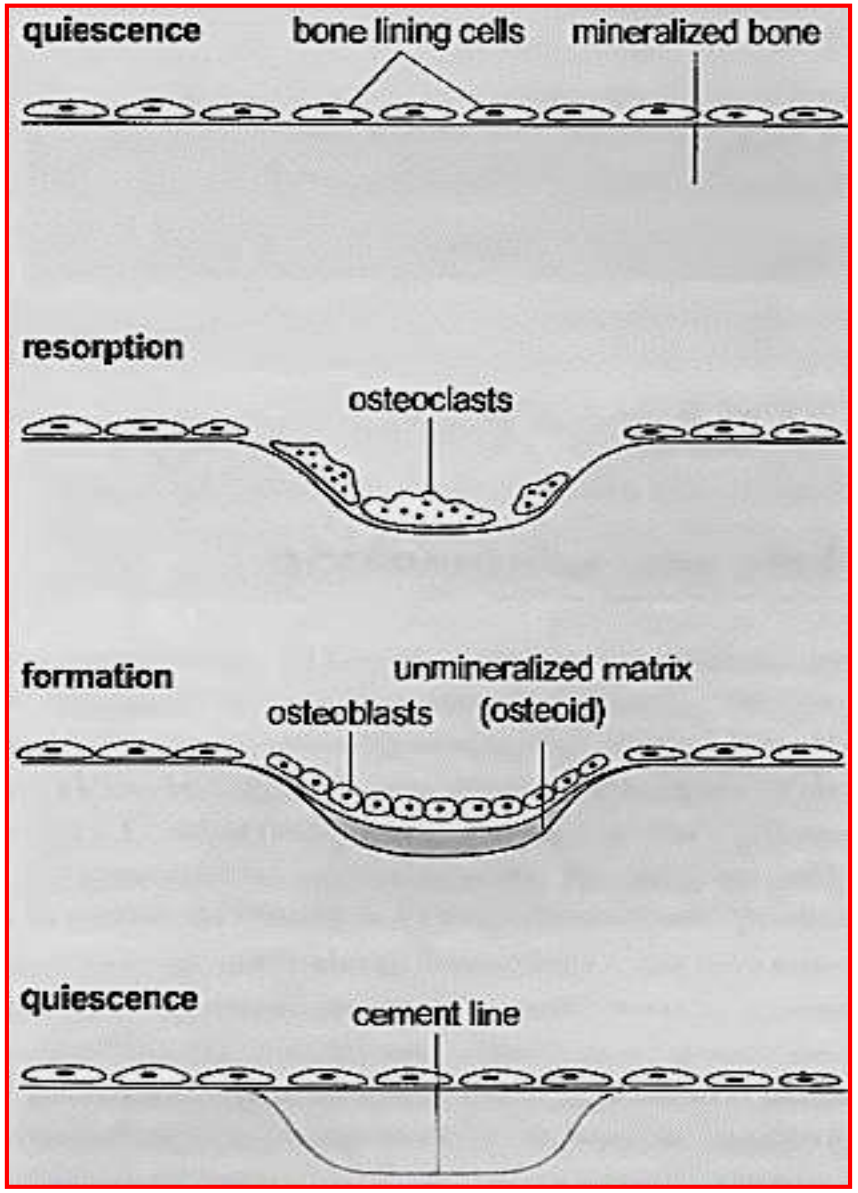
Gastrointestinal secretions contain calcium, some of which is reabsorbed together with dietary calcium. Since calcium in the ECF pool is effectively exchanged through the kidneys, gut and bone about 33 times every 24 hours, a small change in any of these fluxes can have a profound effect on ECF and hence plasma, calcium concentration.



Bone consists of osteoid, a collagenous organic matrix, on which is deposited complex inorganic hydrated calcium salts known as hydroxyapatites. These have the general formula: $Ca_{10}(PO_4)_6(OH)_2$

Bone remains biologically active when growth has ceased. Continuous remodeling occurs with bone resorption (mediated by osteoclasts) being followed by new bone formation {mediated by osteoblasts) At any one time, about 5% of bone mass in adults is subject to remodeling. This process is controlled and coordinated by hormones, growth factors and cytokines.

Bone formation requires osteoid synthesis and adequate calcium and phosphate. Alkaline phosphotase, secreted by osteoblasts, is essential to the process, probably acting by releasing phosphate from pyrophosphate. Bone provides an important reservoir of ca, p and lesser Mg and Na.

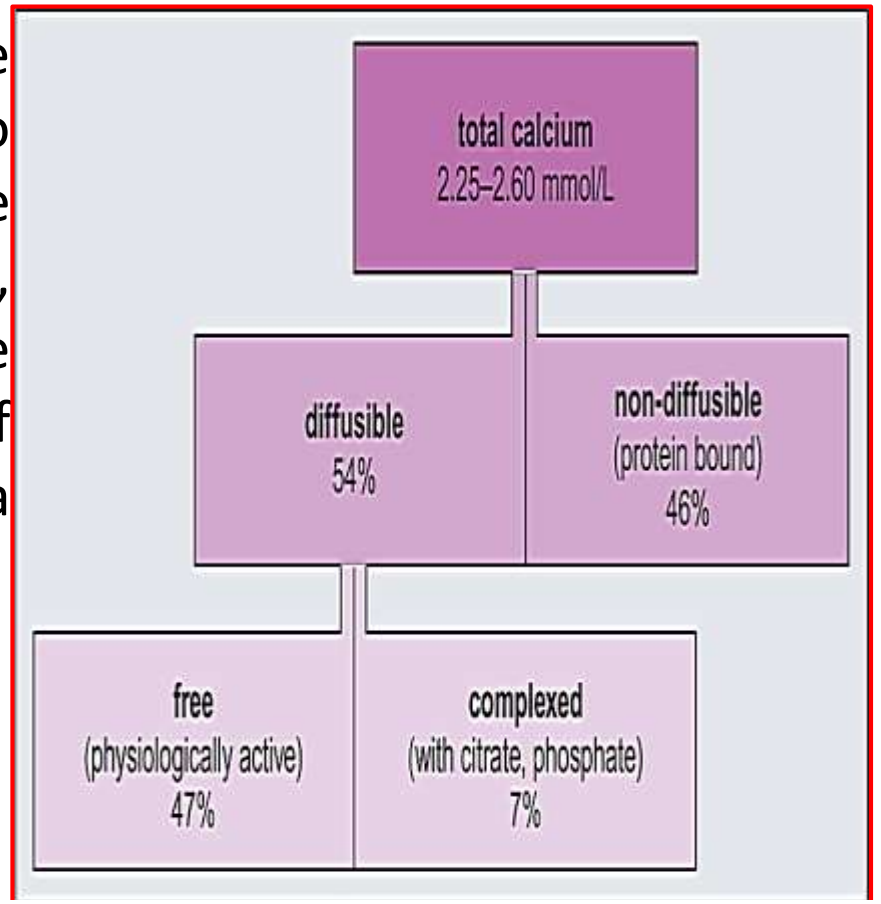


Plasma calcium

In the plasma, calcium is present in three forms: a-bound to protein, b-complexed with citrate and phosphate, and c-free ions. Only the latter form is physiologically active and it is the concentration of ionized calcium that is maintained by homoeostatic mechanisms.

In alkalosis, hydrogen ions dissociate from albumin, and calcium binding to albumin increases. As a result, the concentration of ionized calcium falls, and this may be sufficient to produce clinical symptoms and signs of hypocalcaemia although total plasma calcium concentration is uncharged.

In an acute acidosis, the reverse effect is observed (hypercalcaemia), that is the ionized calcium concentration is increased.



Distribution of Calcium in human plasma

The measurement of plasma calcium concentration be useful to monitor calcium in circumstances when rapid changes in concentration can occur, for example during exchange blood transfusion and during surgery with extracorporeal bypass.

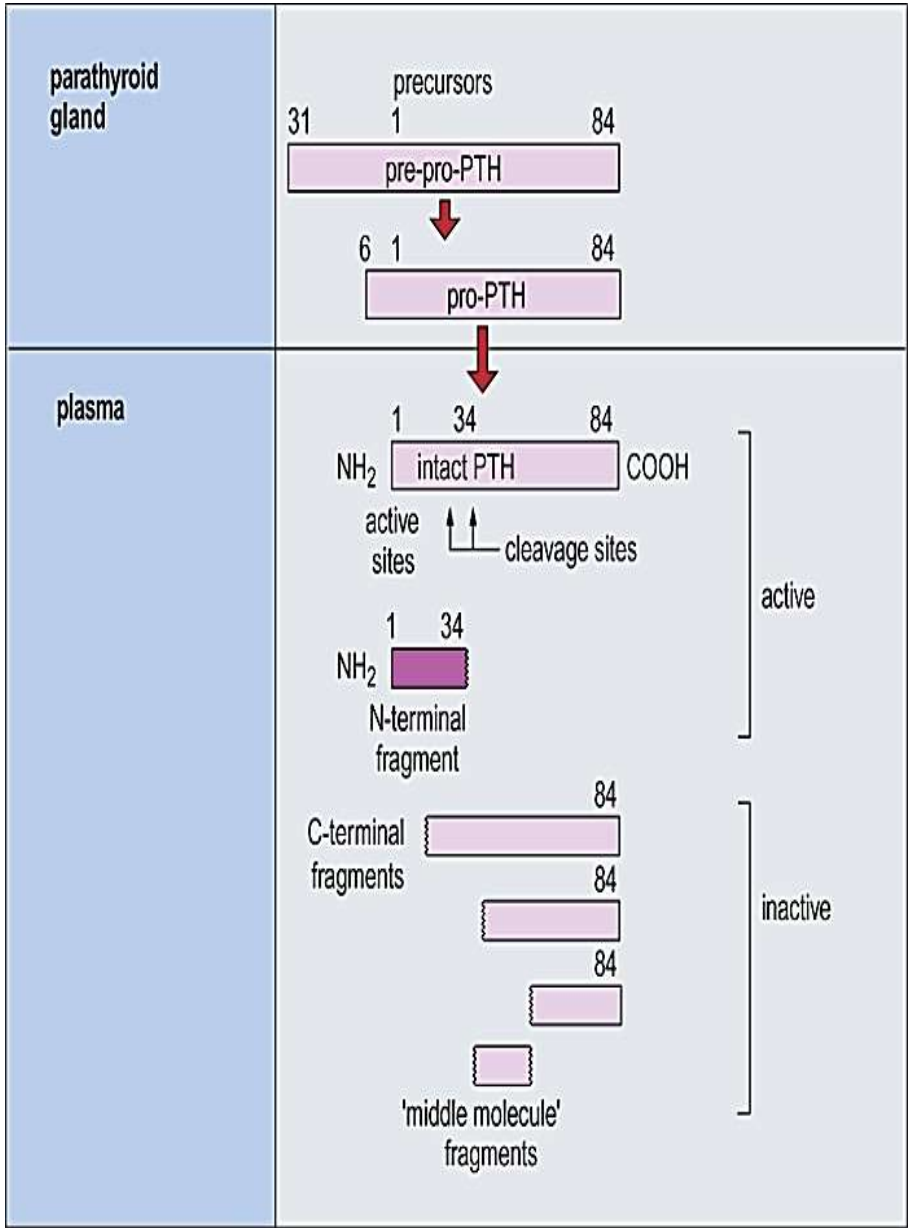
Calcium-regulating hormones

Calcium concentration in the ECF is controlled by two hormones: parathyroid hormone (PTH) and calcitriol (1,25 dihydroxycholecalciferol). These hormones also control the inorganic phosphate concentration of the ECF. Calcitonin probably has only a minor role in calcium homoeostasis.

Parathyroid hormone

This hormone is a polypeptide, comprising 84 amino Acids, it is synthesized as a larger precursor, pre-pro-PTH (115 amino acids). Prior to secretion, two amino acid sequences are lost; the removal of a 25 amino acid chain produces pro-PTH, a further 6 amino acids being removed to form PTH itself. The biological activity of PTH resides in the N-terminal 1-34 amino acid sequence of the hormone.

PTH is secreted by the parathyroid glands in response to a fall in plasma (ionized) calcium concentration. Hypercalcaemia and calcitriol inhibit PTH secretion and synthesis, respectively.



Parathyroid hormone; precursors and cleavage products

PTH acts on bone and the kidneys, tending to increase the plasma concentration of calcium and reduce that of phosphate. PTH mobilizes calcium from bone

Actions of parathyroid hormone

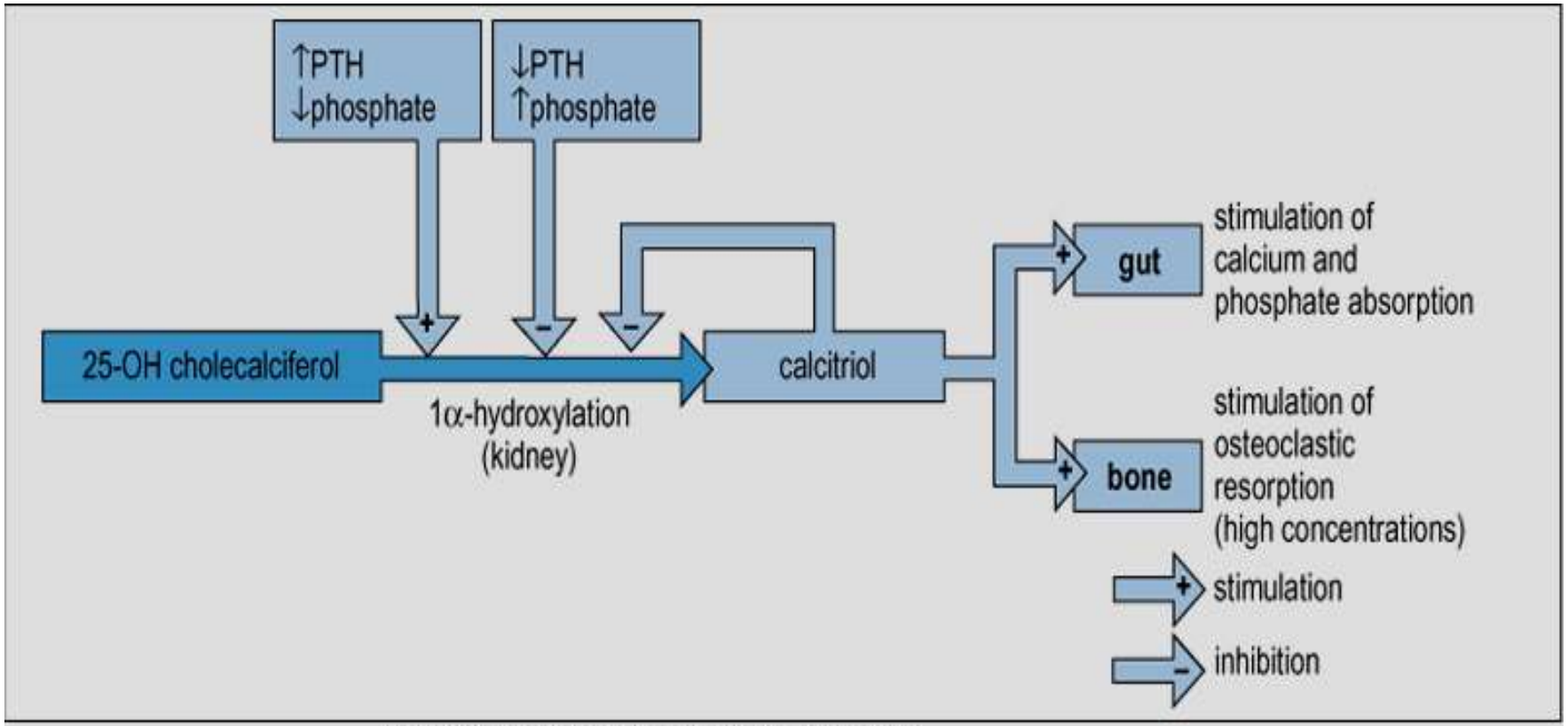
Target organ	Action	Effect
bone	rapid release of calcium ↑ osteoclastic resorption	↑ plasma [Ca^+]
kidney	↑ calcium reabsorption ↓ phosphate reabsorption ↑ 1α-hydroxylation of 25-hydroxycholecalciferol	↑ plasma [Ca^+] ↓ plasma [Pi] ↑ calcium and phosphate absorption from gut
	↓ bicarbonate reabsorption	acidosis

Action of parathyroid hormone in bone and kidney

In the kidneys, PTH increases the fraction of the filtered load that is reabsorbed. However, because increased resorption of bone increases the amount of calcium that is filtered, there is hypercalciuria despite the increased reabsorption.

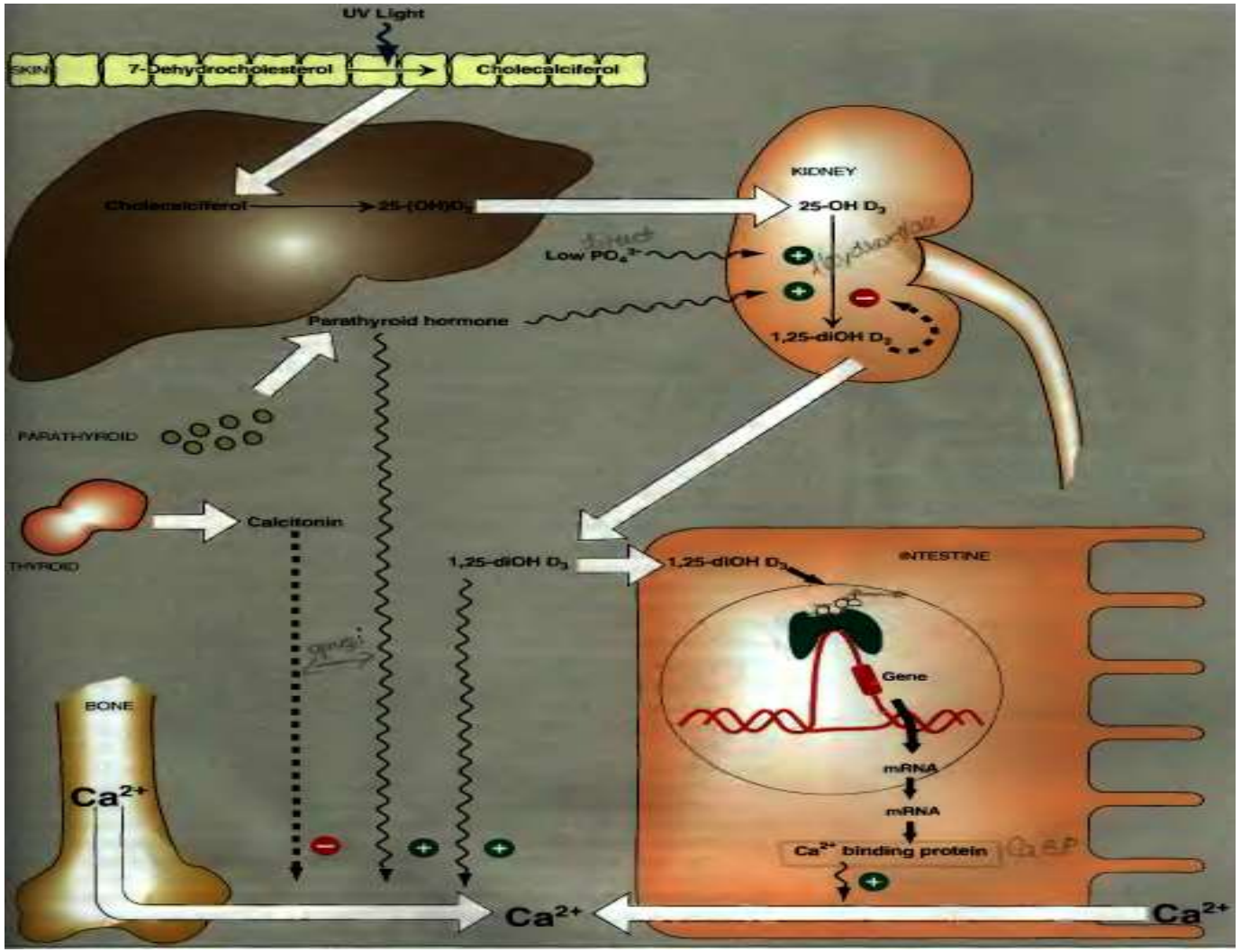
Also in the kidneys, PTH promotes phosphaturia by decreasing the reabsorption of filtered phosphate and stimulates the formation of calcitriol (see bellow Fig.), the calcium-regulating hormone derived from vitamin D.

Despite the importance of PTH in the control of phosphate excretion, changes in phosphate concentration do not directly affect secretion of the hormone. Mild hypomagnesaemia stimulates PTH secretion, but more severe hypomagnesaemia reduces it, as the secretion of PTH is magnesium-dependent.



Synthesis of calcitriol

This hormone is derived from vitamin D by successive hydroxylation in the liver (25-hydroxylation) and kidney (1α-hydroxylation) as in the below figure. When the 1α-hydroxylation of 25 hydroxycholecalciferol is inhibited, there is an increase in 24-hydroxylation. The product of this reaction, 24,25dihydroxycholecalciferol, has no known physiological function.

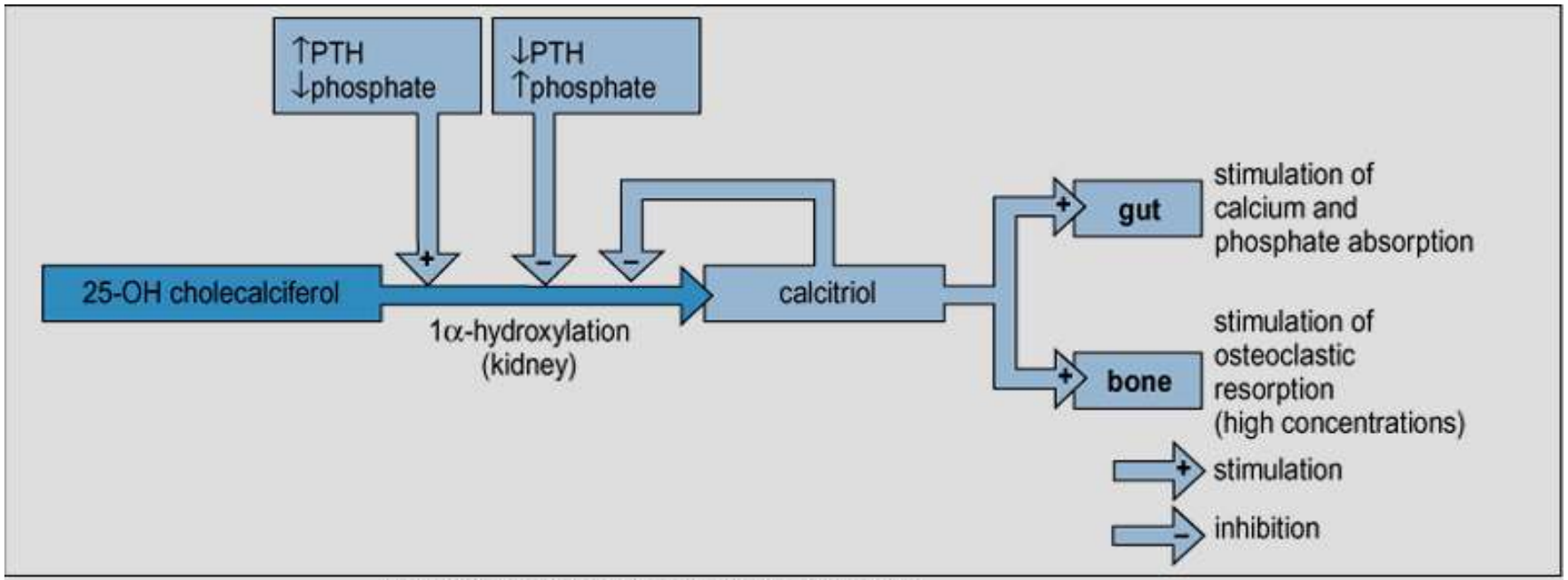


The principal actions of calcitriol are indicated in below Fig. In the gut, it stimulates absorption of dietary calcium and phosphate; this process involves the synthesis of a calcium-binding protein (calbindin D) in enterocytes. This protein is one of a widely distributed group of calcium-binding proteins that are present in many other tissues.

In bone, calcitriol promotes mineralization largely indirectly, through its role in the maintenance of ECF calcium and phosphate concentrations.

The binding of calcitriol to osteoblasts increases the production of alkaline phosphatase and of a calcium-binding protein. At high concentrations, calcitriol stimulates osteoclastic bone resorption, which releases calcium and phosphate into the ECF.

In the kidney, calcitriol inhibits its own synthesis. It may have a small stimulatory effect on calcium reabsorption, acting permissively with PTH.



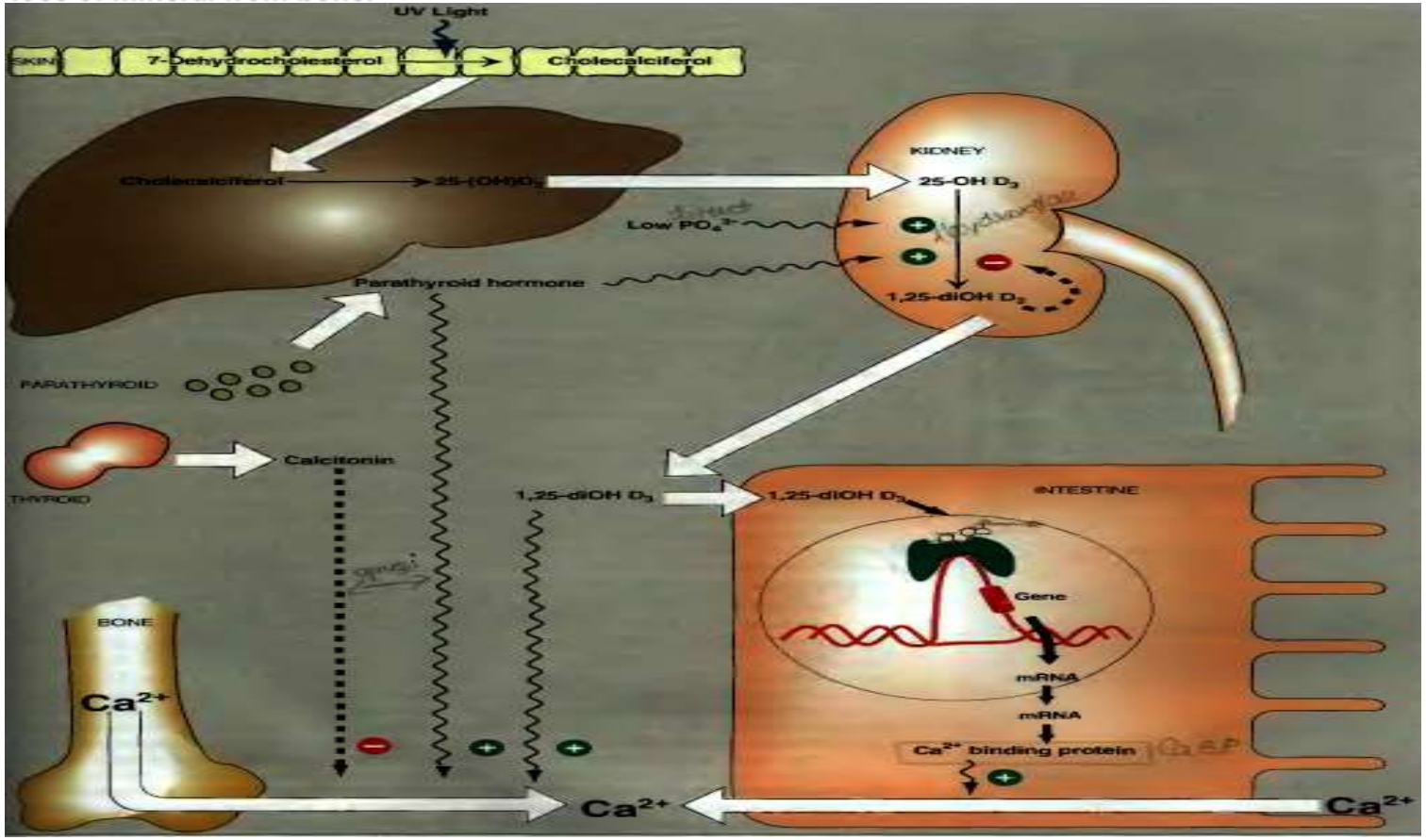
Calcitonin

This polypeptide hormone, produced by the C-cells of the thyroid, is secreted when plasma calcium concentration rised and also in response to certain gut hormone.

It can be shown experimentally to inhibit osteoclast activity, and thus bone resorption, but its physiological role is uncertain.

Subjects who have had a total thyroidectomy do not develop a clinical syndrome that can be ascribed to calcitonin deficiency. Also, calcium homoeostasis is normal in patients with medullary carcinoma of the thyroid, a tumour that secretes large quantities of calcitonin. Plasma calcitonin concentration is elevated during pregnancy and lactation.

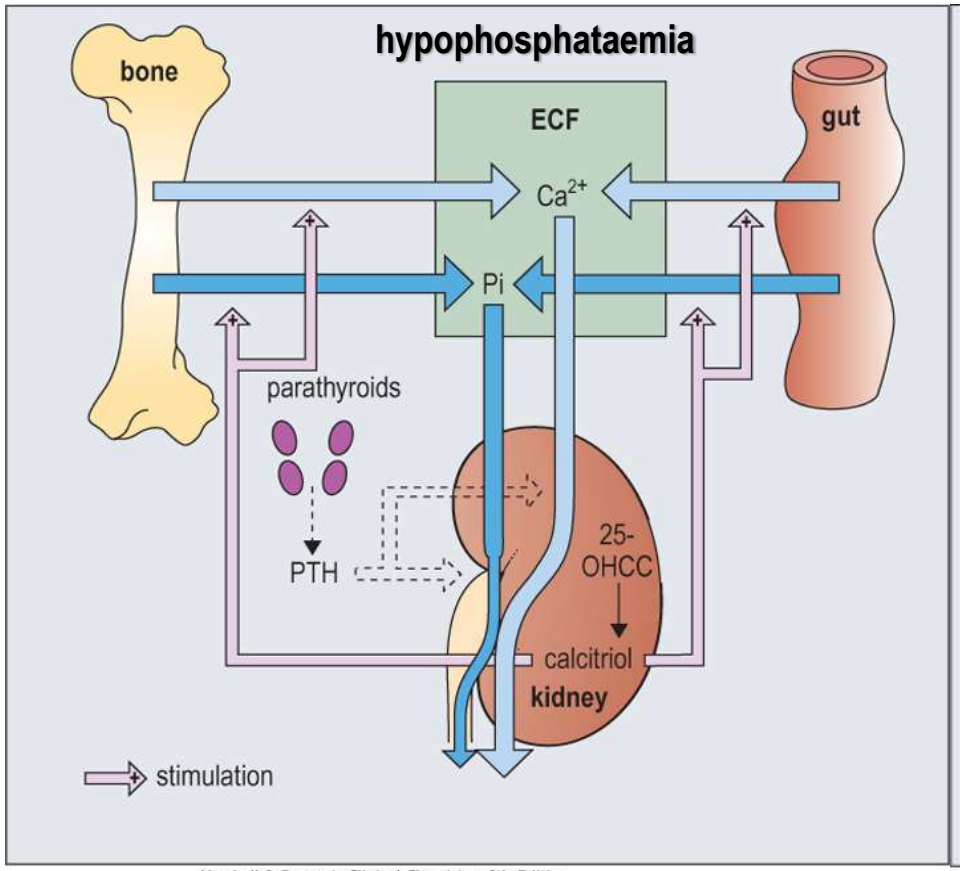
So, too, is calcitriol concentration, and calcitonin may block the action of calcitriol on bone and permit increased calcium uptake from the gut to take place to satisfy increased requirements without loss of mineral from bone.

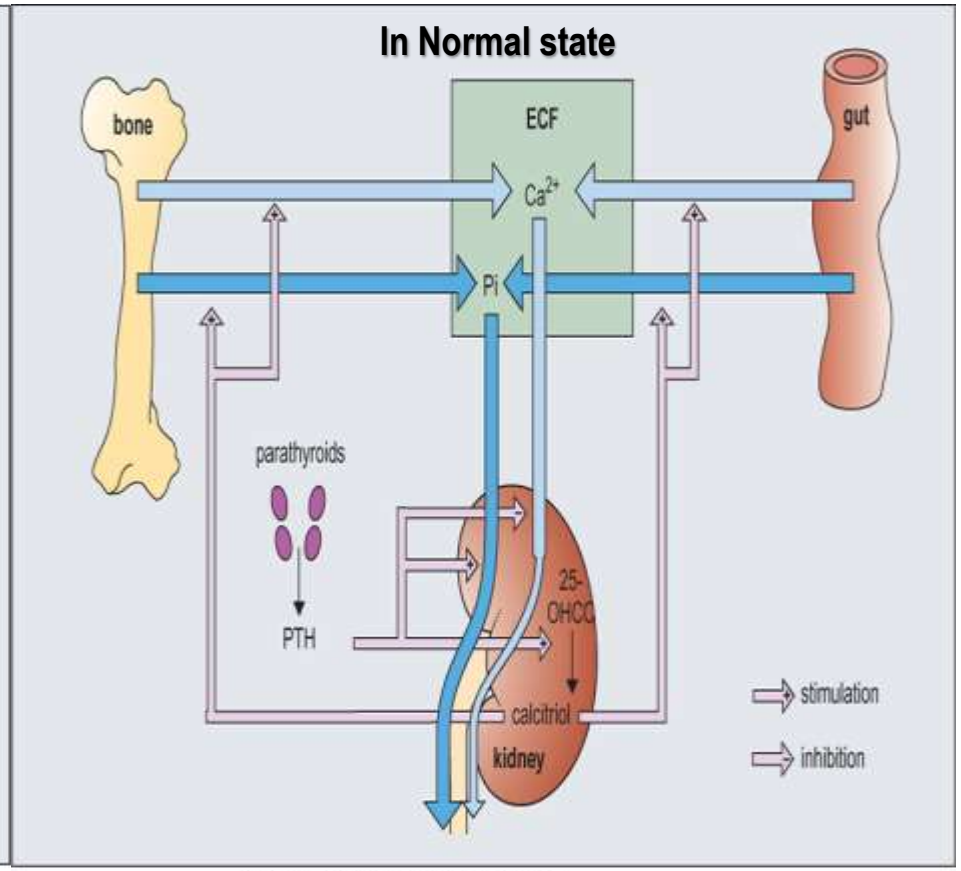


CALCIUM AND PHOSPHATE HOMOEOSTASIS

Hypocalcaemia stimulates the secretion of PTH and, through this, increases the production of calcitriol. there is an increase in the uptake of both calcium and phosphate from the gut and in their release from bone. PTH is phosphaturic, so the excess phosphate is excreted but the fractional reabsorption of calcium by the kidney is increased, some of the mobilized calcium is retained and the plasma calcium concentration tends to rise towards normal.

in **hypophosphataemia** calcitriol secretion is increased but PTH is not. Indeed, any tendency for calcitriol to increase the plasma calcium concentration should inhibit PTH secretion. in the absence of PTH, the excess calcium absorbed from the gut is excreted in the urine. The net outcome is the restoration of the phosphate concentration towards normal, independently of that of calcium.





DISORDERS OF CALCIUM, PHOSPHATE AND MAGNESIUM METABOLISM

Hypercalcaemia

The causes of hypercalcaemia are listed in bellow Fig. Two conditions account for up to 90% of cases: primary hyperparathyroidism and malignancy. However, hypercalcaemiais often clinically silent and discovered incidentally when calcium is measured as part of a biochemical profile.

Hypercalcaemia

Causes	Clinical features
Common	weakness, tiredness, lassitude, weight loss and muscle weakness
malignant disease, with or without metastasis to bone	mental changes (impaired concentration, drowsiness, personality changes, coma)
primary hyperparathyroidism	anorexia, nausea, vomiting and constipation
Less common	abdominal pain (rarely peptic ulceration and pancreatitis)
thyrotoxicosis	polyuria, dehydration and renal failure
vitamin D intoxication	renal calculi and nephrocalcinosis (mainly associated with primary hyperparathyroidism)
thiazide diuretics	short QT interval on ECG
sarcoidosis	cardiac arrhythmias and hypertension
familial hypocalciuric hypercalcaemia	corneal calcification and vascular calcification
renal transplantation (tertiary hyperparathyroidism)	there may also be features of the underlying disorder, such as bone pain in malignant disease and hyperparathyroidism
Uncommon	
milk–alkali syndrome	
lithium treatment	
tuberculosis	
immobilization (especially in Paget's disease)	
acute adrenal failure	
idiopathic hypercalcaemia of infancy	
diuretic phase of acute renal failure	

Malignant disease

This is a very common cause of hypercalcaemia, particularly in patients in hospital. There may or may not be obvious metastases in bone.

it is due to the secretion by the tumour of PTH-related peptide (PTHrP). This is a peptide having some N-terminal amino acid sequence homology with PTH. It acts as a growth factor in the fetus but is not detectable in significant amounts in adults except in the breast during lactation. It is secreted in breast milk but its function in this fluid is unknown.

In patients with metastases in bone there is often no relationship between the extent of metastasis and the severity of the hypercalcaemia, suggesting that humoral factors may be involved in the pathogenesis of hypercalcaemia in malignant disease whether or not osseous metastases are present.

Primary hyperparathyroidism

The prevalence of this condition is one case per thousand persons. It can occur at any age and affects both men and women but is most common in post-menopausal women.

It is usually due to a parathyroid adenoma, less often to diffuse hyperplasia of the glands, and only rarely to parathyroid carcinoma. Adenomas may be multiple and the condition is sometimes familial.

The definitive treatment for hyperparathyroidism is surgery. Patients with mild (<3.00 mmol/L) asymptomatic hypercalcaemia may stay healthy for many years without an operation, but are at increased risk of developing osteoporosis and renal impairment and should be reassessed regularly. A high fluid intake should be maintained to discourage renal calculus formation. Surgery is recommended even for asymptomatic patients if plasma calcium concentrations exceed 3.00 mmol/L.

Secondary and tertiary hyperparathyrodism ?

Hypocalcaemia

The causes of hypocalcaemia are listed in bellow Fig. deficiency or impaired metabolism of vitamin D, renal failure, hypoparathyroidism and hypomagnesaemia account for the majority of cases. The clinical features relate to increased neural and muscular excitability . Mild hypo- calcaemia may be asymptomatic.

Causes	Clinical features
Artefactual (blood collected into EDTA tube)	behavioural disturbance and stupor
	numbness and paraesthesiae
Associated with low PTH concentration	muscle cramps and spasms (tetany)
hypoparathyroidism	laryngeal stridor
hypomagnesaemia	convulsions
hungry bone syndrome (see *p. 232*)	cataracts (chronic hypocalcaemia)
neonatal hypocalcaemia	basal ganglia calcification (chronic hypocalcaemia)
	papilloedema
Associated with high PTH concentration	Trousseau's sign positive
vitamin D deficiency:	Chvostek's sign positive
dietary	prolonged QT interval on ECG
malabsorption	
inadequate exposure to ultraviolet light	
disordered vitamin D metabolism:	
renal failure	
anticonvulsant treatment	
1α-hydroxylase deficiency	
pseudohypoparathyroidism	
acute pancreatitis	
high phosphate intake (rare)	
massive transfusion with citrated blood	
acute rhabdomyolysis	

Hyperphosphataemia

By far the most common cause of hyperphosphataemia is renal insufficiency; other causes are listed in bellowFig,

Causes of hyperphosphataemia

- renal failure
- hypoparathyroidism
- pseudohypoparathyroidism
- acromegaly
- excessive phosphate intake/administration
- vitamin D intoxication
- catabolic states, e.g. tumour lysis syndrome

Hypophosphataemia

This is a common biochemical finding. When mild it is probably of little consequence, but severe hypo phosphataemia (<0.3 mmol/L) can have important consequences on the function of all cells, particularly muscle cells (causing muscle weakness or even rhabdomyolysis), red and white blood cells, and platelets, by limiting the formation of essential phosphate- containing compounds such as adenosine triphosphate (ATP) and 2,3-diphosphoglycerate (2,3-DPG). Chronic hypophosphataemia is a cause of rickets and osteomalacia. The bellow fig. clarify causes of hypophosphotaemia.

Causes of hypophosphataemia

- vitamin D deficiency
- primary hyperparathyroidism
- enteral/parenteral nutrition with inadequate phosphate (particularly in malnourished patients); intravenous glucose therapy
- diabetic ketoacidosis (recovery phase)
- alcohol withdrawal
- renal tubular disease
- phosphate binding agents, such as magnesium and aluminium salts (rare)
- respiratory alkalosis

magnesium status

Magnesium is an essential cofactor for many enzymes. Its concentration in the extracellular fluid is controlled primarily through regulation of its urinary excretion.

Hypomagnesaemia can cause clinical features similar to those of hypocalcaemia and indeed can cause hypocalcaemia, since the secretion of parathyroid hormone is magnesium- dependent. Deficiency of magnesium can occur with prolonged diarrhoea and malabsorption.

Hypermagnesaemia is common in renal failure, but it appears to be tolerated well by the body and increased concentrations rarely give rise to obvious clinical disturbances.