Minerals

bone & mineral metabolism

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Skeletal Metabolism

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Skeletal Metabolism

- Bone is composed primarily of an extracellular mineralized matrix with a smaller cellular fraction
- It is a dynamic tissue that is under continuous turnover or **remodeling**, which enables bone to repair damage and adjust strength
- ***Osteoclasts*** resorb bone, ***osteoblasts*** lay down new bone at a site of previous bone resorption, and ***osteocytes*** nourish the skeleton and regulate bone cell activity

Skeletal Metabolism

- An estimated 10% to 30% of the skeleton is remodeled each year, with wide variation among individuals
- Bone growth and turnover are influenced by the metabolism of calcium, phosphate, and magnesium, and several hormones
- Also, numerous cytokines alter bone remodeling, primarily by stimulating resorption
- Exercise is a major factor in maintaining bone mass, and immobilization leads to rapid bone loss

Skeletal Metabolism

Osteoporosis is a disease resulting from remodeling imbalance, with loss of bone
Rickets and osteomalacia are diseases caused by abnormal mineralization of bone

primarily [illegible] ating resorption

- Exercise is a major factor in maintaining bone mass, and immobilization leads to rapid bone loss

Skeletal Metabolism

- The organic matrix of bone is primarily type I collagen (90%)
- The organic matrix is mineralized by the deposition of inorganic calcium and phosphate in small crystals with lesser amounts of carbonate, magnesium, sodium, potassium, and various other ions

Bone contains nearly all of the calcium (≈99%), most of the phosphate (85%), and much of the magnesium (55%) of the body

Minerals

and Calcium homeostasis

Calcium (Ca^{+2})

- Calcium is the most abundant mineral in the body, there being about 1 kg in a 70 kg man
- Approximately 99% of the body's calcium is present in the bone, mainly as the mineral hydroxyapatite, where it is combined with phosphate
- Calcium in the bone also acts as a reservoir that helps to stabilize ECF Ca^{+2}

Calcium (Ca^{+2})

- Serum calcium level is maintained at a constant level with a narrow range for:
  - nerve impulse transmission
  - muscular contraction
  - blood coagulation
  - hormone secretion
  - intercellular adhesion

Calcium (Ca^{+2})

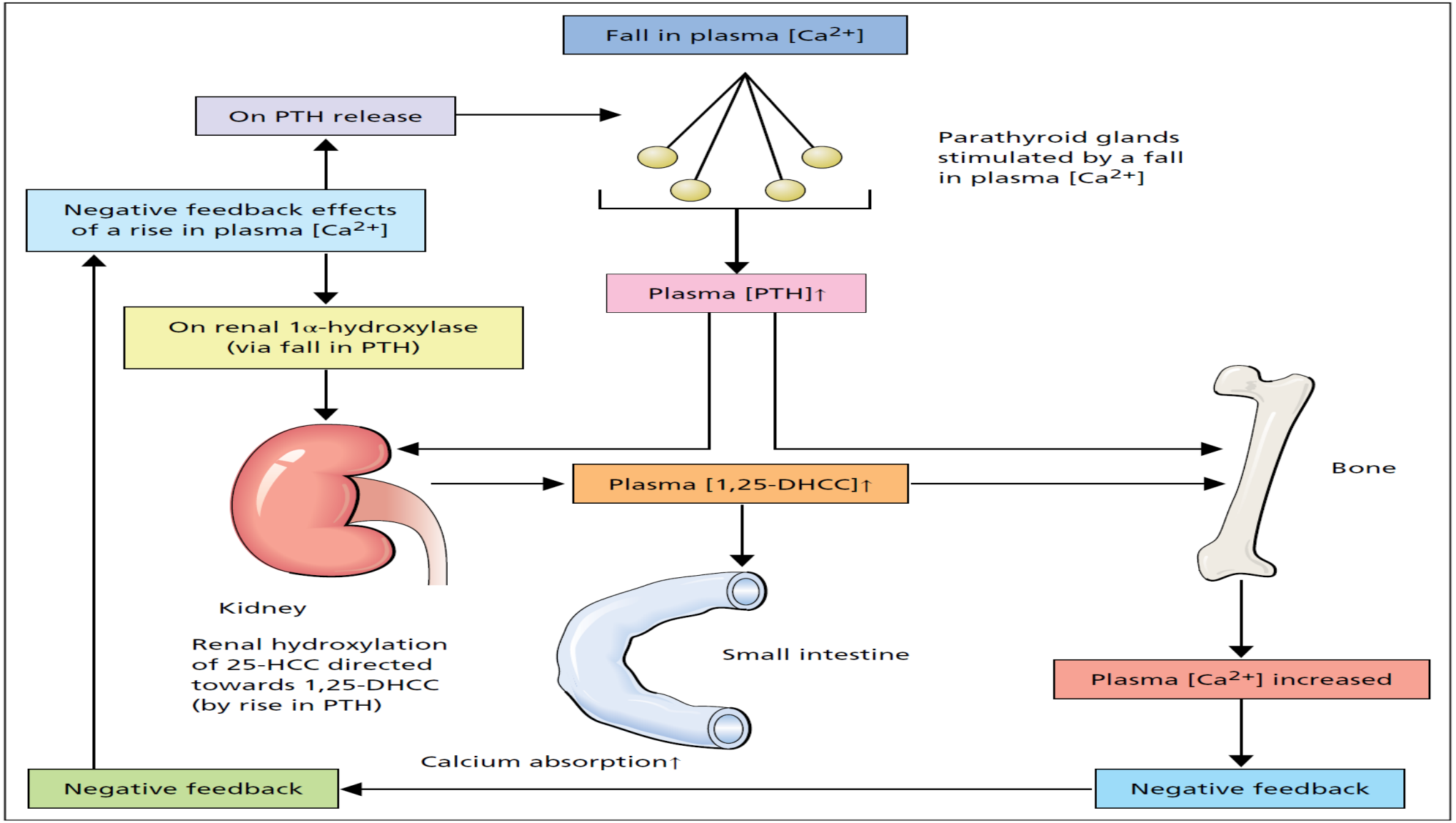
- Calcium is present in plasma in three forms in equilibrium with one another
- Free ionized Ca^{+2} comprises about 50%. Another 40% of serum calcium is bound to proteins in a non-diffusible state while 10% is complexed to salts

Only free, **ionized Ca^{+2}** is biologically active

Calcium (Ca^{+2})

- Plasma Ca^{+2} is closely regulated in humans by parathyroid hormone (PTH) and 1,25-dihydroxycholecalciferol (DHCC): both act to increase plasma Ca^{+2} and hence plasma calcium

Normal plasma Calcium =8.5-10 mg/dL
Normal plasma Ca^{+2} =4.6-5.3 mg/dL


Fall in plasma [Ca2+]
On PTH release
Parathyroid glands stimulated by a fall in plasma [Ca2+]
Negative feedback effects of a rise in plasma [Ca2+]
Plasma [PTH]↑
On renal 1α-hydroxylase (via fall in PTH)
Bone
Plasma [1,25-DHCC]↑
Kidney
Renal hydroxylation of 25-HCC directed towards 1,25-DHCC (by rise in PTH)
Small intestine
Plasma [Ca2+] increased
Calcium absorption↑
Negative feedback
Negative feedback

Calcium (Ca^{+2})

- Because albumin is the principal binding protein for calcium, a fall in serum albumin will lead to a fall in bound calcium and a decrease in total calcium (and vice versa)
- Under these circumstances, the unbound plasma Ca^{+2}, (the physiologically important fraction) will be maintained at normal levels by PTH
- Hypocalcemia: increases excitability, causes muscle tetany
- Hypercalcemia: inhibits neurons and muscle cells, may cause heart arrhythmias

Table 5.5 The causes of hypocalcaemia.

Category	Examples
Artefact	EDTA contamination of sample
Hypoproteinaemia	Low serum albumin
Renal disease	Hydroxylation of 25-HCC impaired
Inadequate intake of calcium	Deficiency of calcium or vitamin D, or of both; intestinal malabsorption
Magnesium depletion	See below
Hypoparathyroidism	Autoimmune, post-surgical, magnesium deficiency, infiltrative disease
Pseudohypoparathyroidism	Target organ resistance to PTH
Neonatal hypocalcaemia	
Acute pancreatitis	Calcium soaps in the abdominal cavity?
Critical illness	Mixed pathology – not clearly defined

Table 5.3 The causes of hypercalcaemia.

Category	Examples
Common	
• Parathyroid disease	Hyperparathyroidism, primary and tertiary; multiple endocrine neoplasia syndromes, MEN I and MEN IIa
• Malignant disease	Lytic lesions in bone: myeloma, breast carcinoma PTHrP: carcinoma of lung, oesophagus, head and neck, renal cell, ovary and bladder Ectopic production of 1,25-DHCC by lymphomas
Uncommon	
• Endogenous production of 1,25-DHCC	Sarcoidosis and other granulomatous diseases
• Excessive absorption of calcium	Vitamin D overdose (including self-medication); milk–alkali syndrome
• Bone disease	Immobilisation
• Drug induced	Thiazide diuretics, lithium
Miscellaneous (mostly rare)	Familial hypocalciuric hypercalcaemia Hypercalcaemia in childhood Thyrotoxicosis Addison's disease
• Artefact	Poor venepuncture technique (excessive venous stasis)

PTHrP = PTH-related protein.

Phosphate

- An adult has about 600g of phosphorus in inorganic and organic phosphates, of which about 85% is in the skeleton, and the rest is principally in soft tissue
- Approximately 10% of the phosphate in serum is protein-bound; 35% is complexed with sodium, calcium, and magnesium; and 55%, is free

Normal serum phosphate =2.6-4.5 mg/dL

Phosphate

- Inorganic phosphate is a major component of hydroxyapatite in bone; thus it plays an important role in the structural support of the body and provides phosphate for the extracellular and intracellular pool
- Although both inorganic and organic phosphate is present in cells, most is organic and is incorporated into nucleic acids, phospholipids, phosphoproteins, and high-energy compounds involved in metabolism (such as ATP & creatine phosphate)

Phosphate

- Phosphate and calcium homeostasis are inextricably linked
- Phosphate is absorbed in the intestine through diet, and regulated by renal excretion or reabsorption
- Renal regulation is effected by factors such as Vit. D, calcitonin, growth hormone, acid-base balance and PTH

Table 5.10 Causes of hyperphosphataemia and hypophosphataemia.

Hyperphosphataemia		Hypophosphataemia	
Increased intake	IV therapy	Decreased intake/absorption	Vitamin D deficiency
	Phosphate enemas		Malabsorption
	Oral (laxatives)		Oral phosphate binders
Reduced excretion	Acute/chronic renal failure	Increased excretion	Primary PTH excess
	Low PTH or resistance to PTH		Secondary PTH excess (e.g. vitamin D deficiency)
	Vitamin D toxicity		Post-renal transplant
Redistribution	Tumour lysis	Redistribution	Re-feeding starved patients
	Rhabdomyolysis		Hyperalimentation
			Recovery from diabetic ketoacidosis
	Heat stroke		Alkalosis (respiratory)
Genetic causes	X-linked hypophosphataemic rickets	Genetic causes	Pseudohypoparathyroidism

Magnesium (Mg^{+2})

- Magnesium is the second most abundant intracellular cation
- It is essential for the activity of many enzymes (cofactor), including the phosphotransferases
- Bone contains about 50% of the body's magnesium
- Factors concerned with the control of magnesium absorption have not been defined, but may involve active transport across the intestinal mucosa by a process involving vitamin D

Magnesium (Mg^{+2})

- Plasma magnesium is normally kept within narrow limits. Marked alterations in the body's content can occur with little or no change detectable in serum magnesium

Normal serum magnesium =1.7-2.4 mg/dL

- Serum magnesium may not reflect the true state of the body's reserves, particularly in chronic disorders

Magnesium (Mg^{+2})

- **Magnesium deficiency** rarely occurs as an isolated phenomenon. Usually it is accompanied by disorders of potassium, calcium and phosphorus metabolism
- Muscular weakness, sometimes accompanied by tetany, cardiac arrhythmias and CNS abnormalities, may all be due to magnesium deficiency
- Hypermagnesaemia is less frequently seen, and is most often due to acute renal failure or the advanced stages of chronic renal failure

Bone contains nearly all of the calcium, most of the phosphate, and much of the magnesium of the body

Serum calcium level is maintained at a constant level with a narrow range

Plasma Ca+2 is closely regulated by PTH and 1,25-dihydroxycholecalciferol (Vit. D)

Phosphate and calcium homeostasis are inextricably linked

Magnesium is essential for the activity of many enzymes