Summary

- Calcium homeostasis is dependent on three major organs (intestine, kidney, bone) and three major hormones: parathyroid hormone (PTH), 1,25-(OH)₂-D₃, and calcitonin.
- Bone composition is complex and contains matrix with minerals and proteins (collagen and others).
- Bone is continuously turned over by osteoclasts and osteoblasts, during growth by modeling and during adulthood by remodeling.
- The receptor activator for the nuclear factor κB (RANK) ligand and its decoy receptor osteoprotegerin (OPG) are key regulatory factors of bone resorption produced by osteoblastic stromal cells, which respectively stimulate and inhibit osteoclast differentiation via interaction with the RANK receptor of osteoclast precursors.

Normal Calcium Homeostasis

Plasma-ionized calcium (normal concentration 8.3–10.3 mg/dl) is regulated within narrow limits. Only 43% of total plasma calcium is ionized; another 10% is complexed to anions and the majority is bound to protein (90% to albumin). Normal concentrations of plasma-ionized calcium therefore range between 1.8 and 3.0 mg/dl.

Calcium in plasma and extracellular fluid (the central pool of calcium) is less than 2% of total body calcium. The bulk of total body calcium (as for magnesium and phosphate) is present in the skeleton. The endoskeleton is composed of crystalline molecules such as hydroxyapatite, Ca₁₀(PO₄)₆(OH)₂, which provides mechanical support and serves as a reservoir for the central pool of calcium.

This central pool of calcium has large fluxes across three epithelia (bone, kidney, intestine), which are regulated and modulated by the calcitropic hormones (Figure 2.1).

Adults in zero net calcium balance do not have net daily flux between the central calcium pool and bone. Thus, urinary (plus sweat) calcium equals the daily net calcium absorption from the intestine. Major deviations from zero calcium balance occur during skeletal growth, bone senescence, lactation, and disease.
Figure 2.1 The central pool of calcium has large fluxes across the kidney, intestine, and bone. The figure shows daily fluxes in balance for a diet of 900 mg.

Calciotropic Hormones

Parathyroid Hormone

PTH is the major hormone of calcium homeostasis. PTH is secreted by the parathyroid gland, which serves as the central detector of plasma calcium via a specific membrane-bound G-protein-coupled calcium receptor.

The principal storage form in parathyroid secretory vesicles is the native hormone, which consists of 84 amino acids. Although for full biological activity (binding to PTH receptor) only the 34 amino terminal acids are needed, PTH circulates in its 1–84 form together with carboxy-terminal fragments that lack any relevant biological activity. Plasma calcium is the major modulator of PTH secretion. When plasma calcium increases, PTH secretion is inhibited within seconds. PTH gene transcription and replication of parathyroid cell mass are also decreased by both calcium and 1,25-(OH)₂-D₃, respectively, in a scale of hours and weeks.

PTH acts to increase plasma Ca²⁺ concentration in three ways:

- In the presence of permissive amounts of active vitamin D, it stimulates bone resorption, resulting in release of calcium and phosphate.
- It enhances intestinal Ca²⁺ and phosphate absorption indirectly by promoting the production of calcitriol in the kidney.
- It augments active renal Ca²⁺ reabsorption in the distal tubule.

PTH also reduces proximal tubular reabsorption of phosphate. PTH also tends to increase phosphate entry in the extracellular fluid by its effect on bone and intestinal absorption. However, the urinary effect of PTH on phosphate usually predominates; therefore, it tends to mostly lower serum phosphate.