27 ■ CALCIUM METABOLISM ESSENTIALS

Chad D. Sagnella, MD and Pam Taxel, MD

MAINTENANCE OF OVERALL CALCIUM BALANCE

- Calcium is an essential dietary element with critical roles in normal physiology
  - Extracellular calcium functions in bone mineralization, blood coagulation, membrane excitability, enzyme kinetics
  - Intracellular calcium functions in neuronal activation, muscle contraction, hormone secretion
- Human body contains about 1000 g of calcium, the majority of which (99%) resides in bone and teeth as calcium hydroxyapatite
- Dietary intake of calcium
  - 75% lost in feces
  - 25% absorbed in the proximal small intestine
    - By passive diffusion
    - By hormonally regulated active transport (stimulated by vitamin D)
- Renal excretion normally results in 100–250 mg of calcium loss per day (with adequate intake)
- Plasma calcium divided into three fractions
  - 50% ionized calcium
  - 40% protein-bound calcium (albumin, globulins)
  - 10% complexed to anions (including citrate, phosphate, sulfate, bicarbonate)
- Calcium-sensing receptor (CaSR)
  - Located in the parathyroid glands and kidney
    - Regulates PTH secretion
    - Regulates renal excretion of calcium
  - Responds to fluctuations in ionized calcium on minute-to-minute basis
- Approximately 1 g of calcium is recommended per day (**Table 27.1**)
  - Dietary sources of calcium (1 dairy serving size = 250–300 mg calcium)
    - Dairy products including milk, cheeses, yogurts, calcium-fortified soy milk, and calcium-fortified tofu
    - Canned salmon with bones
    - Green vegetables such as turnips, collard greens, kale, and broccoli
  - Supplemental calcium intake (i.e., multivitamin and calcium supplements)

TABLE 27.1 Recommended Intakes for Calcium

	Estimated Average Requirement (mg/day)	Recommended Dietary Allowance* (mg/day)	Upper Level Intake (mg/day)
9–18 years old	1100	1300	3000
19–50 years old	800	1000	2500
51–70-year-old males	800	1000	2000
51–70-year-old females	1000	1200	2000
>70 years old	1000	1200	2000

*RDA includes total dietary + supplemental calcium intake.

PTH

- Parathyroid gland anatomy
  - 4 small ovoid glands located on the dorsal aspect of left and right lobes of the thyroid
    - Inferior parathyroid glands derived from third branchial pouches
    - Superior parathyroid glands derived from fourth branchial pouches
    - Approximately 10–20% of humans have fifth parathyroid gland, often located in mediastinum
  - 2 cell types
    - Chief (or principal) cells: predominant epithelial cell type with clear cytoplasm
    - Oxyphil cells: larger, mitochondria-rich cell type with granular eosinophilic cytoplasm
- Structure and synthesis of PTH
  - 84-amino acid polypeptide synthesized as a pre-prohormone by the chief cells of the parathyroid
  - PTH proteolytically cleaved by liver and kidney (half-life of circulating PTH <5 minutes)
  - Normal range for serum intact PTH is approximately 10–65 pg/mL
- Secretion of PTH
  - Regulated by serum ionized calcium (iCa^{2+})
    - ↑ iCa^{2+} can activate CaSR and suppress PTH secretion
    - ↓ iCa^{2+} stimulates PTH secretion
  - Regulated by serum magnesium Mg^{2+}
    - ↓ Mg^{2+} can inhibit PTH secretion and action
    - ↑ Mg^{2+} can activate CaSR and thus suppress PTH secretion
- PTH 1-receptor (PTH-1R)
  - 7-transmembrane G-protein–coupled receptor (Gs/Gq) expressed on osteoblasts and proximal and distal tubules of the kidney
  - PTH-1R binds PTH and PTH-related protein (PTHrP) with equal affinity

- Actions of PTH
  - Bone
    - ↑ bone resorption of calcium by directly stimulating osteoblasts and indirectly stimulating osteoclasts via Macrophage-Colony Stinulatin Factor (M-CSF), receptor activator of nuclear factor kappa-B ligand (RANKL), Osteoprotegrin (OPG) (decoy receptor for RANKL)
  - Kidney
    - ↑ renal reabsorption of calcium by ↑ insertion of apical Ca^{2+} channels in the distal tubule
    - ↑ renal 1α-hydroxylase activity to ↑ 1,25-$(OH)_2$ vitamin D production in the proximal tubule, to increase both calcium and phosphate absorption in gut

VITAMIN D

- Structure and synthesis of vitamin D
  - Inactive prohormones
    - Vitamin D_2: ergocalciferol
      - Produced by photolysis (UVB) from ergosterol (in plants)
    - Vitamin D_3: cholecalciferol
      - Produced by UVB from 7-dehydrocholesterol
      - Formed in the skin, mainly in the deepest layers of the epidermis
    - 25-hydroxyvitamin D: calcidiol (or calcifediol)
      - Vitamin D_2/D_3 rapidly converted in the liver to 25-hydroxyvitamin D by hepatic 25-hydroxylase (constitutively active)
      - >85% of vitamin D metabolites carried in the blood bound to vitamin D–binding protein (VDBP)
  - Regulation of vitamin D
    - Activation to 1,25-$(OH)_2$ vitamin D_3 (calcitriol) occurs via 1α-hydroxylase cytochrome P-450 1-alpha (CYP1α) in the mitochondria of renal proximal tubule
      - ↓ [iCa^{2+}] stimulates 1,25-$(OH)_2$ vitamin D via CaSR to ↑ 1α-hydroxylase production
      - ↑ PTH stimulates 1,25-$(OH)_2$ vitamin D via PTH-1R to ↑ 1α-hydroxylase production
      - ↑ 1,25-$(OH)_2$ vitamin D causes ↓ 1α-hydroxylase activity (feedback inhibition)
      - ↓ [phosphate] stimulates 1,25-$(OH)_2$ vitamin D generation