Bone and Mineral Metabolism in Health and Disease

Chapter 421 | Part 12: Endocrinology and Metabolism

KEY CLINICAL POINTS

1. Bone is a dynamic tissue where osteoclasts (resorption) and osteoblasts (formation) are coordinated by osteocytes.
2. Osteocytes act as master regulators, sensing mechanical stress and secreting FGF23 to regulate phosphate metabolism.
3. FGF23 is a 'phosphatonin' that inhibits renal phosphate reabsorption and reduces 1,25(OH)D synthesis.
4. Calcium homeostasis depends on intestinal absorption (active/passive), renal reabsorption, and bone flux, regulated by PTH and 1,25(OH)D.
5. Severe hypophosphatemia (<0.75 mmol/L) can lead to life-threatening complications like rhabdomyolysis, respiratory failure, and cardiac dysfunction.
6. Hungry bone syndrome occurs after parathyroidectomy or vitamin D treatment due to rapid bone uptake of calcium and phosphate.
7. Vitamin D requires two hydroxylations: 25-hydroxylation in the liver and 1α-hydroxylation in the kidney.
8. Renal calcium reabsorption is regulated by PTH, 1,25(OH)D, and the calcium-sensing receptor (CaSR) in the thick ascending limb.
9. Osteoclasts utilize a ruffled border with a proton pump ATPase and cathepsin K to resorb bone within Howship's lacunae.
10. Hypomagnesemia can be caused by renal wasting, intestinal loss, or rapid intracellular redistribution.

DEFINITION & OVERVIEW

- **Bone Nature:** Dynamic tissue providing structural support, mineral reservoir (Ca, Mg, P, Na), and a niche for hematopoiesis.
- **Structure:**
  - Compact/Cortical: Cylindrical shell of long bones.
  - Cancellous/Trabecular: Internal plate-like meshwork supporting the cortical shell.
- **Matrix Composition:**
  - Organic: 90–95% type I collagen; contains noncollagenous proteins (e.g., osteopontin, osteocalcin).
  - Mineral: Poorly crystalline hydroxyapatite (calcium and phosphate).
- **Cell Lineages:**
  - Osteoblasts: Mesenchymal origin; synthesize/secrete matrix; regulate mineralization.
  - Osteocytes: Long-lived cells embedded in matrix; master regulators of bone; secrete FGF23.

– Osteoclasts: Hematopoietic lineage (macrophage precursors); multinucleated; perform resorption via ruffled border and acid secretion.

Bone Structure & Matrix

- **Mineralization:** Requires osteoblast-derived alkaline phosphatase to hydrolyze inhibitors like pyrophosphate.
- **Collagen Integrity:** Mutations in COL1A1 or COL1A2 lead to osteogenesis imperfecta.

Osteoclast Function

- **Mechanism:** Osteoclasts form Howship's lacurae → create a tight seal → secrete protons (via proton pump ATPase) and proteases (cathepsin K).
- **Regulation:**
  - RANK ligand: Stimulates osteoclast differentiation.
  - OPG: Soluble decoy receptor that inhibits RANK ligand.
  - Calcitonin: Directly inhibits osteoclasts via basal surface receptors.

EPIDEMIOLOGY

- **Remodeling Dynamics:**
  - ~4% of trabecular surface is in active resorption.
  - 10–15% of trabecular surfaces covered by osteoid (unmineralized).
  - ~18% of total skeletal calcium is exchanged annually.
- **Mechanical Sensing:** Osteocytes sense mechanical stress → regulate bone formation/resorption; produce sclerostin to inhibit wnt signaling.

ETIOLOGY & PATHOPHYSIOLOGY

- **Calcium Homeostasis:**
  - Serum Range: 2.2–2.6 mM (8.5–10.5 mg/dL).
  - Ionized Fraction: ~50% of total serum calcium.
  - Correction for Protein: Adjust total calcium by +0.8 for each g/dL deficit in albumin or +0.5 for serum immunoglobulin.
- **Intestinal Absorption:**
  - Passive: Non-saturable.
  - Active: Transcellular (TRPV5/6); requires 1,25(OH)D and gastric acid.
- **Renal Reabsorption:**
  - Regulated by PTH, 1,25(OH)D, and the calcium-sensing receptor (CaSR) in the thick ascending limb.
- **Phosphorus Metabolism:**
  - Serum Range: 0.75–1.45 mmol/L (2.5–4.5 mg/dL).
  - Renal Regulation: Primarily in proximal tubule via NaPi-2a and NaPi-2c transporters.
  - FGF23 Role: Secreted by osteocytes → inhibits renal phosphate reabsorption → reduces 1,25(OH)D synthesis.

Vitamin D Metabolism

- **Synthesis:** Skin (UV radiation) or Gut (dietary intake).

- **Activation Pathway:**

1. Liver: 25-hydroxylation → 25(OH)D (major circulating form).
2. Kidney: 1α-hydroxylation → 1,25(OH)D (active hormone).

CLINICAL FEATURES

- **Hypophosphatemia Risks:**
  - Severe (<0.75 mmol/L) → rhabdomyolysis, respiratory failure, and cardiac dysfunction.

Neuromuscular & Respiratory Manifestations

- **Critical Threshold:** Serum phosphorus <0.75 mmol/L (2.5 mg/dL) is associated with high risk of acute complications.

Metabolic & Surgical Contexts

- **Hungry Bone Syndrome:** Occurs after parathyroidectomy or vitamin D treatment → rapid bone uptake of calcium and phosphate.

DIFFERENTIAL DIAGNOSIS

- **Mechanisms of Hypophosphatemia (Table 1):**

1. **Reduced Renal Reabsorption:**
   - PTH/PTHrP-dependent: Primary hyperparathyroidism, secondary hyperparathyroidism (Vitamin D deficiency/resistance, Calcium starvation/malabsorption, Bartter's syndrome, Autosomal recessive renal hypercalciuria with hypomagnesemia), PTHrP-dependent hypercalcemia of malignancy, Familial hypocalciuric hypercalcemia.
   - PTH/PTHrP-independent: Excess FGF23 or other "phosphatonins" (XLH, ARHP, ADHR [DMP1, ENPP1 deficiency], TIO, McCune-Albright syndrome, Epidermal nevus syndrome), intrinsic renal disease (Fanconi's syndrome(s), Cystinosis, Wilson's disease, NaPi-2a or NaPi-2c mutations), systemic disorders (Poorly controlled DM, Alcoholism, Hyperaldosteronism, Hypomagnesemia, Amyloidosis, Hemolytic-uremic syndrome, Renal transplantation/partial liver resection, Rewarming/induced hyperthermia), drugs/toxins (Ethanol, Acetazolamide, high-dose estrogens/glucocorticoids, heavy metals [lead, cadmium, saccharated ferric oxide], Toluene, N-methyl formamide, Cisplatin, ifosfamide, foscarnet, rapamycin).
2. **Impaired Intestinal Absorption:**
   - Aluminum-containing antacids, Sevalamer.
3. **Shift of Extracellular Phosphate into Cells:**
   - Intravenous glucose, Insulin therapy for prolonged hyperglycemia/DKA, Catecholamines (epinephrine, dopamine, albuterol), Acute respiratory alkalosis, Gram-negative sepsis, toxic shock syndrome, Recovery from starvation or acidosis, Rapid cellular proliferation (Leukemic blast crisis, intensive erythropoietin/growth factor therapy).
4. **Accelerated Net Bone Formation:**
   - After parathyroidectomy, Treatment of vitamin D deficiency, Paget's disease, Osteoblastic metastases.

Hyperphosphatemia & Hypomagnesemia

- **Hyperphosphatemia (Table 3):**

– Impaired renal excretion: Renal insufficiency, Hypoparathyroidism (Developmental, Autoimmune, post-surgery/radiation, CaSR mutations), Parathyroid suppression (Vitamin D/A intoxication, Sarcoidosis, Immobilization, Milk-alkali syndrome, severe hypermagnesemia/hypomagnesemia), Pseudohypoparathyroidism, Acromegaly, Tumoral calcinosis, Heparin therapy.

– Massive extracellular loads: Rapid administration of exogenous phosphate, Extensive cellular injury (Crush injuries, Rhabdomyolysis, Hyperthermia, Fulminant hepatitis, Cytotoxic therapy, Severe hemolytic anemia), Transcellular shifts (Metabolic acidosis, Respiratory acidosis).

- **Hypomagnesemia (Table 4):**

– Impaired intestinal absorption: TRPM6 mutations, Malabsorption syndromes, Vitamin D deficiency, Proton pump inhibitors.

– Increased intestinal losses: Protracted vomiting/diarrhea, Intestinal drainage, fistulas.

– Impaired renal tubular reabsorption: Genetic magnesium-wasting (Gitelman's, Bartter's, Claudin 16 or 19 mutations, Potassium channel mutations [Kv1.1, Kir4.1], Na+,K+-ATPase γ-subunit mutations [FXYD2]), Acquired renal disease (Tubulointerstitial, Postobstruction, ATN, Renal transplantation), Drugs/toxins (Ethanol, Diuretics, Cisplatin, Pentamidine, foscarnet, Cyclosporine, Aminoglycosides, amphotericin B, Cetuximab).

– Other: ECF volume expansion, Hyperaldosterosism, SIADH, Diabetes mellitus, Hypercalcemia, Phosphate depletion, Metabolic acidosis, Hyperthyroidism.

– Rapid shifts from extracellular fluid: Intracellular redistribution (Refeeding syndrome, Correction of respiratory alkalosis), Accelerated bone formation (Post-parathyroidectomy, Vitamin D treatment, Osteoblastic metastases).

DIAGNOSTIC APPROACH

1. **Assess Serum Phosphorus:** Identify if level is <0.8 mmol/L (2.5 mg/dL) or <0.3 mmol/L (1.0 mg/dL).
2. **Evaluate Clinical Stability:** Check for signs of rhabdomyolysis, respiratory distress, or cardiac dysfunction.
3. **Identify Mechanism of Hypophosphatemia:**
   - Assess PTH and 1,25(OH)D to differentiate between PTH-dependent (e.g., hyperparathyroidism) and PTH-independent (e.g., FGF23 excess) renal loss.
   - Evaluate for intestinal malabsorption or drug interference.
   - Identify rapid cellular shifts (e.g., during insulin therapy or respiratory alkalosis).
4. **Assess Renal Function:** Measure serum creatinine; if >220 µmol/L (>2.5 mg/dL), reduce phosphate dose by 50%.
5. **Evaluate Calcium Status:** Determine if hypocalcemia needs correction before treating hypercalcemia.

Vitamin D Action Assessment

- **Identify Cause of Impaired Vitamin D Action (Table 6):**

– Vitamin D Deficiency: Cutaneous production, Dietary absence, Malabsorption, Accelerated loss, Increased metabolism (barbiturates, phenytoin, rifampin), Impaired enterohepatic circulation, Nephrotic syndrome, CYP3A4 mutation.

– Impaired 1α-hydroxylation: Hypoparathyroidism, Ketoconazole, 1α-Hydroxylase mutation, FGF23 excess, Oncogenic osteomalacia, Hypophosphatemic rickets, Fibrous dysplasia, Chronic kidney disease.

– Target organ resistance: Vitamin D receptor mutation, Phenytoin, Obesity.

MANAGEMENT & TREATMENT

1. **Initial Assessment:**
   - Evaluate severity of phosphate depletion and presence of complications (neuromuscular, cardiopulmonary, or hematologic).
2. **Pre-treatment Adjustments:**
   - If serum creatinine >220 µmol/L (>2.5 mg/dL) → reduce phosphate dose by 50%.
   - If hypercalcemia is present → reduce dose by 50% (correct hypocalcemia first).
3. **Intravenous Phosphate Administration (Table 2):**
   - **For Serum Phosphorus <0.8 mmol/L (<2.5 mg/dL):**
   - Option A: 2 mmol/h for 6 hours (Total 12 mmol).
   - Option B: 4 mmol/h for 6 hours.
   - **For Serum Phosphorus <0.3 mmol/L (<1.0 mg/dL):**
   - Dose: 8 mmol/h for 6 hours (Total 48 mmol).
4. **Monitoring:**
   - Monitor for signs of hypercalcemia or renal failure during aggressive correction.

Clinical Decision Pathway

1. Identify Serum Phosphorus Level → 2. Assess Renal Function & Calcium Status → 3. Adjust Dose (Reduce by 50% if renal failure or hypercalcemia) → 4. Administer Phosphate based on severity (<0.8 vs <0.3 mmol/L).

COMPLICATIONS & PROGNOSIS

- **Severe Hypophosphatemia:**
- Risk of rhabdomyolysis, respiratory failure, and cardiac dysfunction when levels are critically low.
- **Hypercalcemia Risks:**
- Potential for nephrocalcinosis and renal failure if calcium intake is excessively high (e.g., milk-alkali syndrome).

SPECIAL CONSIDERATIONS

- **Renal Failure Patients:** Require reduced phosphate doses due to impaired excretion.
- **Patients with FGF23 Mutations:** Suffer from ADHR or XLH; characterized by low 1,25(OH)D and high FGF23.
- **Post-Surgical/Vitamin D Treatment:** Risk of 'Hungry Bone Syndrome' (rapid calcium/phosphate depletion).

KEY PEARLS & CLINICAL TRAPS

- **FGF23 as a Phosphatonin:** It is the primary hormone inhibiting renal phosphate reabsorption and 1,25(OH)D synthesis.

- **Calcium Sensing:** The CaSR in the cTAL allows calcium to regulate its own excretion independently of PTH/Vitamin D.
- **Vitamin D Activation:** 25-hydroxylation (Liver) → 1α-hydroxylation (Kidney).
- **Acute Hypophosphatemia:** Often caused by rapid cellular shifts (e.g., insulin, glucose, respiratory alkalosis).
- **Management Rule:** Always correct hypocalcemia before treating hypercalcemia in the setting of phosphate replacement.

REFERENCE TABLES

TABLE 421-1

Causes of Hypophosphatemia I. Reduced renal tubular phosphate reabsorption

- I. Reduced renal tubular phosphate reabsorption A. PTH/PTHrP-dependent 1. Primary hyperparathyroidism 2. Secondary hyperparathyroidism a. Vitamin D deficiency/resistance b. Calcium starvation/malabsorption c. Bartter's syndrome d. Autosomal recessive renal hypercalciuria with hypomagnesemia 3. PTHrP-dependent hypercalcemia of malignancy 4. Familial hypocalciuric hypercalcemia B. PTH/PTHrP-independent 1. Excess FGF23 or other "phosphatonins" a. X-linked hypophosphatemic rickets (XLH) b. Autosomal recessive hypophosphatemia (ARHP) c. Autosomal dominant hypophosphatemic rickets (ADHR) (DMP1, ENPP1 deficiency) d. Tumor-induced osteomalacia syndrome (TIO) e. McCune-Albright syndrome (fibrous dysplasia) f. Epidermal nevus syndrome 2. Intrinsic renal disease a. Fanconi's syndrome(s) b. Cystinosis c. Wilson's disease d. NaPi-2a or NaPi-2c mutations 3. Other systemic disorders a. Poorly controlled diabetes mellitus b. Alcoholism c. Hyperaldosteronism d. Hypomagnesemia e. Amyloidosis f. Hemolytic-uremic syndrome g. Renal transplantation or partial liver resection h. Rewarming or induced hyperthermia 4. Drugs or toxins a. Ethanol b. Acetazolamide, other diuretics c. High-dose estrogens or glucocorticoids d. Heavy metals (lead, cadmium, saccharated ferric oxide) e. Toluene, N-methyl formamide f. Cisplatin, ifosfamide, foscarnet, rapamycin II. Impaired intestinal phosphate absorption A. Aluminum-containing antacids B. Sevalamer III. Shifts of extracellular phosphate into cells A. Intravenous glucose B. Insulin therapy for prolonged hyperglycemia or diabetic ketoacidosis C. Catecholamines (epinephrine, dopamine, albuterol) D. Acute respiratory alkalosis E. Gram-negative sepsis, toxic shock syndrome F. Recovery from starvation or acidosis G. Rapid cellular proliferation 1. Leukemic blast crisis 2. Intensive erythropoietin, other growth factor therapy IV. Accelerated net bone formation A. After parathyroidectomy B. Treatment of vitamin D deficiency, Paget's disease C. Osteoblastic metastases

TABLE 421-2

Intravenous Therapy for Hypophosphatemia CONSIDER Likely severity of underlying phosphate depletion Concurrent…

CONSIDER
Likely severity of underlying phosphate depletion
Concurrent parenteral glucose administration
Presence of neuromuscular, cardiopulmonary, or hematologic complications of hypophosphatemia
Renal function (reduce dose by 50% if serum creatinine >220 µmol/L [>2.5 mg/dL])

Serum calcium level (correct hypocalcemia first; reduce dose by 50% in hypercalcemia)			
Guidelines			
SERUM PHOSPHORUS, MM (MG/DL)	RATE OF INFUSION, MMOL/H	DURATION, H	TOTAL ADMINISTERED, MMOL
<0.8 (<2.5)	2	6	12
	4	6	
<0.3 (<1)	8	6	48

TABLE 421-3

Causes of Hyperphosphatemia

- I. Impaired renal phosphate excretion A. Renal insufficiency B. Hypoparathyroidism 1. Developmental 2. Autoimmune 3. After neck surgery or radiation 4. Activating mutations of the calcium-sensing receptor C. Parathyroid suppression 1. Parathyroid-independent hypercalcemia a. Vitamin D or vitamin A intoxication b. Sarcoidosis, other granulomatous diseases c. Immobilization, osteolytic metastases d. Milk-alkali syndrome 2. Severe hypermagnesemia or hypomagnesemia D. Pseudohypoparathyroidism E. Acromegaly F. Tumoral calcinosis G. Heparin therapy II. Massive extracellular fluid phosphate loads A. Rapid administration of exogenous phosphate (intravenous, oral, rectal) B. Extensive cellular injury or necrosis 1. Crush injuries 2. Rhabdomyolysis 3. Hyperthermia 4. Fulminant hepatitis 5. Cytotoxic therapy 6. Severe hemolytic anemia C. Transcellular phosphate shifts 1. Metabolic acidosis 2. Respiratory acidosis

TABLE 421-4

Causes of Hypomagnesemia I. Impaired intestinal absorption

- I. Impaired intestinal absorption A. Hypomagnesemia with secondary hypocalcemia (TRPM6 mutations) B. Malabsorption syndromes C. Vitamin D deficiency D. Proton pump inhibitors II. Increased intestinal losses A. Protracted vomiting/diarrhea B. Intestinal drainage, fistulas III. Impaired renal tubular reabsorption A. Genetic magnesium-wasting syndromes 1. Gitelman's syndrome 2. Bartter's syndrome 3. Claudin 16 or 19 mutations 4. Potassium channel mutations (Kv1.1, Kir4.1) 5. Na+,K+-ATPase γ-subunit mutations (FXYD2) B. Acquired renal disease 1. Tubulointerstitial disease 2. Postobstruction, ATN (diuretic phase) 3. Renal transplantation C. Drugs and toxins 1. Ethanol 2. Diuretics (loop, thiazide, osmotic) 3. Cisplatin 4. Pentamidine, foscarnet 5. Cyclosporine 6. Aminoglycosides, amphotericin B 7. Cetuximab D. Other 1. Extracellular fluid volume expansion 2. Hyperaldosteronism 3. SIADH 4. Diabetes mellitus 5. Hypercalcemia 6. Phosphate depletion 7. Metabolic acidosis 8. Hyperthyroidism IV. Rapid shifts from extracellular fluid A. Intracellular redistribution 1. Recovery from diabetic ketoacidosis 2. Refeeding syndrome 3. Correction of respiratory acidosis 4. Catecholamines B. Accelerated bone formation 1. Post-parathyroidectomy 2. Treatment of vitamin D deficiency 3. Osteoblastic metastases C. Other 1. Pancreatitis, burns, excessive sweating 2. Pregnancy (third trimester) and lactation

TABLE 421-5

Causes of Hypermagnesemia I. Excessive magnesium intake

- I. Excessive magnesium intake A. Cathartics, urologic irrigants B. Parenteral magnesium administration II. Rapid mobilization from soft tissues A. Trauma, shock, sepsis B. Cardiac arrest C. Burns III. Impaired magnesium excretion A. Renal failure B. Familial hypocalciuric hypercalcemia IV. Other A. Adrenal insufficiency B. Hypothyroidism C. Hypothermia

TABLE 421-6

Causes of Impaired Vitamin D Action Vitamin D deficiency

Vitamin D deficiency	Impaired 1α-hydroxylation
Impaired cutaneous production	Hypoparathyroidism
Dietary absence	Ketoconazole
Malabsorption (short gut syndrome, gastric bypass)	1α-Hydroxylase mutation
	FGF23 excess
Accelerated loss of vitamin D	Oncogenic osteomalacia
Increased metabolism (barbiturates, phenytoin, rifampin)	Hypophosphatemic rickets
	Fibrous dysplasia
Impaired enterohepatic circulation	Chronic kidney disease
Nephrotic syndrome	Target organ resistance
CYP3A4 mutation	Vitamin D receptor mutation
Impaired 25-hydroxylation	Phenytoin
Liver disease, isoniazid	Other
25-Hydroxylase mutation	Obesity