Calcium Integrated Physiology and Disorders

Andrew Bland, MD, FACP, FAAP

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Introduction: The Calcium Axis

Calcium homeostasis is maintained through a tightly coordinated feedback loop involving three target organs (parathyroid glands, kidneys, intestine) and two hormones (parathyroid hormone [PTH] and active vitamin D [1,25-dihydroxyvitamin D]) [1]. A comprehensive understanding of this axis is essential for board-level nephrology practice.

> [!important] Key Point Serum calcium represents only 0.1% of total body calcium; 99% is stored in bone. However, the small extracellular pool maintains critical neuromuscular and cardiac function.

Calcium Distribution and Measurement

Total vs. Ionized Calcium

Calcium Fraction	Percentage	Pathophysiology
Ionized (free)	45–50%	Physiologically active; unaffected by albumin
Protein-bound	40–45%	Bound mostly to albumin; decreases in hypoalbuminemia
Complexed	5–10%	Bound to citrate, phosphate; increases in acidosis

Clinical Pearl: When albumin is low, measured total calcium falls 0.8 mg/dL per 1 g/dL albumin decrease, but ionized calcium (and symptoms) may be normal.

Corrected Calcium Formula [2]

Corrected Ca = Measured Ca + 0.8 × (4.0 − measured albumin [g/dL])

Example: Patient with measured Ca 7.2 mg/dL and albumin 2.0 g/dL - Corrected Ca = 7.2 + 0.8 × (4.0 − 2.0) = 7.2 + 1.6 = 8.8 mg/dL (likely normal ionized Ca)

> [!tip] Clinical Pearl When corrected calcium is normal but symptoms suggest hypocalcemia (paresthesias, tetany), measure ionized calcium directly. Acidosis or severe hypomagnesemia may lower ionized Ca despite normal total Ca.

Normal Calcium Homeostasis Physiology

The Negative Feedback Loop

Step 1: Serum calcium decreases (< 8.5 mg/dL) - Calcium-sensing receptor (CaSR) on parathyroid cells detects low Ca - PTH secretion increases immediately

Step 2: PTH acts on three target sites: - **Kidney (proximal tubule):** Activates 1α-hydroxylase $\rightarrow$ increases 1,25-(OH)2D (calcitriol) - **Kidney (distal tubule):** Increases calcium reabsorption via TRPV5 channels - **Bone:** Stimulates osteoclasts $\rightarrow$ releases Ca and phosphate

Step 3: Calcitriol increases intestinal calcium absorption (duodenum/jejunum)

Step 4: Serum calcium normalizes $\rightarrow$ CaSR senses high Ca $\rightarrow$ PTH suppressed

FGF-23 and Mineral Homeostasis

In chronic kidney disease, the axis becomes dysregulated: - **Early CKD:** Phosphate retention stimulates FGF-23 production - **FGF-23 suppresses:** 1α-hydroxylase (less calcitriol) and PTH (via Klotho co-receptor) - **Later CKD:** Secondary hyperparathyroidism develops as GFR < 45 and 1,25-D falls critically

Hypercalcemia: Differential Diagnosis and Approach [3]

PTH-Dependent Hypercalcemia (5–10% of cases)

Condition	PTH	1,25-D	Urine Ca	Mechanism
1° Hyperparathyroidism	High	Normal/↑	↑ (usually)	Adenoma/hyperplasia, loss of CaSR set point
Familial Hypocalciuric Hypercalcemia (FHH)	Normal/↑	Normal	↓ (< 150 mg/24h)	Gain-of-function CaSR mutation; kidney thinks Ca is low

FHH Pearl: Always check urine calcium; FHH presents with **hypercalcemia + hypocalciuria** (opposite of 1° hyperparathyroidism). PTH may be inappropriately high for calcium level.

PTH-Independent Hypercalcemia (90% of cases)

Non-PTH-Mediated Humoral Hypercalcemia (PTHrP-Mediated)

- **PTHrP-producing malignancies:** Squamous cell lung, renal, ovarian, breast cancers
- **PTHrP mimics PTH:** Increases renal Ca reabsorption, activates 1α-hydroxylase
- **Key finding:** High Ca, low PTH, elevated 1,25-D (because PTHrP stimulates activation)

Calcitriol-Producing Hypercalcemia (1,25-D-Mediated)

- **Granulomatous diseases:** Sarcoidosis, TB, histoplasmosis, coccidioidomycosis, berylliosis
- **Lymphomas:** Especially Hodgkin, non-Hodgkin with extragonadal germ cell origin

- **Mechanism:** Granuloma macrophages or malignant lymphocytes produce 1α-hydroxylase (unregulated)
- **Key finding:** High Ca, low PTH, **elevated 1,25-D** (unregulated activation)

Osteolytic Hypercalcemia (1,25-D-Mediated)

- **Metastatic bone disease:** Breast cancer with bone mets producing IL-6, TNF-α
- **Multiple myeloma:** Osteoclast activation via RANKL
- **Mechanism:** Direct bone resorption + calcitriol production
- **Key finding:** High Ca, low PTH, often elevated 1,25-D

Vitamin D Intoxication and Vitamin A Intoxication

- **Vitamin D:** Iatrogenic (over-supplementation), granulomatous production
- **Vitamin A:** Chronic excess from supplements, retinoids
- **Both:** Increase intestinal Ca absorption

Diagnostic Algorithm for Hypercalcemia

```
Hypercalcemia (Ca > 10.5 mg/dL)
    ↓
[Measure PTH]
    ├─→ PTH High or Normal–High → 1° Hyperparathyroidism or FHH
    │   └─→ Check urine Ca
    │       ├─→ Urine Ca low (< 150/24h) → FHH
    │       └─→ Urine Ca high → 1° Hyperparathyroidism
    │
    └─→ PTH Low (< 15) → PTH–Independent
        ├─→ [Check 1,25–Dihydroxyvitamin D and PTHrP]
      ├─→ 1,25–D High + PTHrP High → PTHrP–secreting malignancy or granulomatous disease
      ├─→ 1,25–D High + PTHrP Low → Granulomatous disease (sarcoidosis, TB) or lymphoma
      └─→ 1,25–D Normal/Low + PTHrP Low → Osteolytic hypercalcemia or vitamin D intoxication
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Hypocalcemia: Differential Diagnosis and Approach

PTH Response in Hypocalcemia

Category	PTH	1,25-D	Phosphate	Cause
PTH Deficiency	Low	Low	High	Post-surgical, autoimmune, infiltrative
PTH Resistance	High	Normal/Low	**High**	CKD, pseudo-hypoparathyroidism (PHP), hypomagnesemia

Category	PTH	1,25-D	Phosphate	Cause
1,25-D Deficiency	High	Low	Normal/High	CKD stage 3–5, vitamin D malabsorption, dietary lack

> [!warning] High-Yield Board Point Hypomagnesemia (< 1.5 mg/dL) suppresses both PTH secretion AND PTH action on kidneys. Always replete magnesium in patients with refractory hypocalcemia.

Common Causes of Hypocalcemia [4]

Acute Hypocalcemia (< 7.0 mg/dL)

- **Acute pancreatitis:** Saponification of fat; severe
- **Tumor lysis syndrome:** Phosphate released → Ca precipitates; acute, life-threatening
- **Sepsis/Critical illness:** Reduced 1,25-D production, increased FGF-23
- **Blood transfusion (massive):** Citrate binds Ca

Chronic Hypocalcemia

- **CKD stages 3–5:** Phosphate retention + loss of 1α-hydroxylase function
- **Vitamin D deficiency:** Malabsorption, insufficient sun exposure, dietary lack
- **Hypoparathyroidism:** Post-thyroidectomy/parathyroidectomy, autoimmune, infiltrative (infiltration granulomas, iron, amyloid)
- **Pseudohypoparathyroidism:** Tissue resistance to PTH; PTH high but ineffective

Hungry Bone Syndrome

- **Setting:** Post-parathyroidectomy, post-thyroidectomy, or after stopping PTH treatment
- **Mechanism:** Suppressed osteoclasts abruptly reactivate; bone ravenously takes up Ca and phosphate
- **Prevention:** Careful post-operative monitoring, IV calcium if severe

Symptoms and Emergency Management

Severity	Ca Level	Symptoms	Management
Mild	7.0–8.5	Paresthesias, muscle cramps	Oral supplementation
Moderate	6.5–7.0	Tetany, positive Chvostek/Trousseau	IV calcium + oral
Severe	< 6.5	Seizures, laryngeal spasm, arrhythmias	**Urgent IV calcium**

Acute IV Calcium Therapy: - **Calcium gluconate 10%:** 10 mL (1 g Ca) IV slowly over 2–5 min (can give peripherally; safer for extravasation) - **Calcium chloride 10%:** 10 mL (270 mg Ca)

IV slowly (central line preferred; tissue necrosis risk if peripheral) - **Repeat every 10–20 min** as needed to stop tetany; monitor QT interval

CKD-Mineral Bone Disease (CKD-MBD): The Integrated Picture [5]

The Vicious Cycle in CKD

GFR < 60 (CKD Stage 3b): - Phosphate retention → FGF-23 rises (first abnormality) - FGF-23 suppresses 1α-hydroxylase

GFR < 45 (CKD Stage 4): - Calcitriol falls → hypocalcemia develops - Hypocalcemia stimulates PTH (secondary hyperparathyroidism) - High PTH + high phosphate → vascular calcification

GFR < 15 (CKD Stage 5): - Severe hyperparathyroidism, bone disease, vascular calcification - Risk of cardiac arrhythmias, fracture, cardiovascular death

CKD-MBD Management Targets (KDIGO 2017)

Stage	Target PTH	Target Phosphate	Target Calcium
3b–4	IPTH 35–70 pg/mL	2.5–4.5 mg/dL	8.5–10.5 mg/dL
5D (dialysis)	IPTH 150–300 pg/mL	3.5–5.5 mg/dL	8.5–10.5 mg/dL

> [!tip] Clinical Pearl Early intervention in Stage 3 is critical. Starting phosphate binders and vitamin D analogs before PTH becomes severely elevated prevents secondary hyperparathyroidism progression.

Calcium-Phosphorus Product (CaxP)

CaxP = Serum Ca $\times$ **Serum PO4** (both in mg/dL)

Traditional target: < 55 mg²/dL² (though some newer guidelines are more liberal)

Clinical significance: Products > 70 associated with increased vascular and soft-tissue calcification

Treatment of Hypercalcemia: Board-Level Approach

Severity	Acute Management	Long-Term
Mild (10.5–12 mg/dL), Asymptomatic	Hydration if dehydrated; dietary Ca restriction	Treat underlying cause
Moderate (12–14 mg/dL), Symptomatic	IV hydration (saline 200–300 mL/h)	Thiazide (1° HPT), steroids (sarcoid), chemotherapy (malignancy)

Severity	Acute Management	Long-Term
Severe (> 14 mg/dL), Life-Threatening	IV hydration + calcitonin 4 IU/kg q6h + zoledronic acid 4 mg IV	Parathyroidectomy (1° HPT), definitive cancer treatment

Drug-Specific Interventions

Cause	First-Line	Alternative	Rationale
1° Hyperparathyroidism	Parathyroidectomy	Cinacalcet (CaSR agonist)	Definitive; partial in cinacalcet
Sarcoidosis	Corticosteroids	Hydroxychloroquine	Reduce granuloma macrophage 1α-hydroxylase
Vitamin D Intoxication	Corticosteroids	Monitor; restriction	Inhibit 1α-hydroxylase activity
Lymphoma/PTHrP malignancy	Chemotherapy	Bisphosphonates	Treat cancer; symptomatic relief
Immobilization	Mobilization	Hydration	Restore normal bone turnover

Treatment of Hypocalcemia: Board-Level Approach

Asymptomatic Hypocalcemia (> 7.0 mg/dL, no symptoms)

- **Oral supplements:** Calcium citrate 2–4 g/day divided TID (with meals for absorption)
- **Vitamin D:** 1,25-dihydroxyvitamin D (calcitriol) if deficient or in CKD
- **Monitor:** Ionized Ca, ECG, renal function

Symptomatic Hypocalcemia (< 7.0 mg/dL or paresthesias/tetany)

- **IV calcium gluconate:** 10 mL (1 g) in 50 mL saline over 2–5 min; repeat q10–20 min
- **After initial stabilization:** IV infusion (500 mg Ca in 250 mL saline over 2–4 h) or switch to oral
- **Magnesium:** Repleted to > 2.0 mg/dL (otherwise PTH secretion blocked)

Hypoparathyroidism Management

- **Active vitamin D (calcitriol):** 0.5–1 mcg TID–BID
- **Thiazide diuretic:** Paradoxically decreases urine Ca reabsorption (used to reduce hypercalciuria side effect)
- **Low phosphate diet:** Reduces PTH stimulus

CKD Hypocalcemia Management

- **Vitamin D analogues:** Cholecalciferol (vitamin D3) or calcitriol

- **Phosphate binders:** Non-calcium-based (sevelamer, lanthanum) preferred in later CKD
- **Monitor PTH:** Serial measurements guide intensity of therapy

[!warning] High-Yield Board Point In severe symptomatic hypocalcemia, give IV calcium even if total calcium is borderline normal—ionized Ca may be severely low. Never withhold treatment waiting for labs if tetany or seizures present.

Clinical Vignettes

Vignette 1: Asymptomatic Hypercalcemia

A 68-year-old woman is found to have Ca 11.2 mg/dL on routine labs. PTH 8 pg/mL (low), 1,25-D 22 pg/mL (low), albumin normal. 15-year history of sarcoidosis on chronic prednisone.

Diagnosis: Granulomatous (sarcoidosis) hypercalcemia **Key clues:** Low PTH + low 1,25-D + history of sarcoid = **unregulated 1α-hydroxylase from granuloma macrophages Management:** Increase prednisone dose; monitor Ca q1–2 weeks; hydroxychloroquine if refractory

Vignette 2: Severe Symptomatic Hypocalcemia

A 56-year-old man post-total thyroidectomy develops severe tetany (Trousseau sign positive). Ca 6.2 mg/dL (measured), Mg 1.2 mg/dL, PTH 2 pg/mL.

Diagnosis: Hypoparathyroidism (surgical) + hypomagnesemia **Key clues:** Undetectable PTH in setting of hypocalcemia = **post-surgical hypoparathyroidism Management:** 1. IV magnesium sulfate to Mg > 2.0 (allows PTH secretion) 2. IV calcium gluconate 1 g over 3–5 min, repeat q10–20 min until tetany stops 3. Start calcitriol 0.5 mcg BID + oral calcium 2 g TID 4. Serial ionized Ca, Mg, Ca-P product

Vignette 3: Tumor Lysis Syndrome

A 44-year-old with newly diagnosed Burkitt lymphoma (pre-treatment labs): Ca 6.8 mg/dL, PO4 8.2 mg/dL, uric acid 12.5 mg/dL, Cr 1.9 (baseline 0.9), K 6.8 mEq/L.

Diagnosis: Acute tumor lysis syndrome with incipient acute kidney injury **Key clues:** Hypocalcemia + **hyperphosphatemia + hyperkalemia + hyperuricemia** = massive cell lysis **Management:** 1. Aggressive IV hydration (target urine output > 200 mL/h) 2. Rasburicase 0.2 mg/kg IV to lower uric acid 3. Allopurinol 600 mg PO daily (or febuxostat) 4. Monitor Ca, K, PO4, Cr q4–6h initially 5. Loop diuretics if fluid overload develops 6. Prepare for possible dialysis

Vignette 4: CKD-MBD in Stage 4 CKD

A 72-year-old with CKD Stage 4 (GFR 18): Ca 8.2 mg/dL, PO4 5.1 mg/dL, Albumin 3.8 g/dL, PTH 412 pg/mL (markedly elevated), 1,25-D 18 pg/mL (low).

Diagnosis: Secondary hyperparathyroidism from CKD-MBD **Key clues:** Low 1,25-D (loss of 1α-hydroxylase) + **phosphate retention (despite low GFR) = FGF-23 suppression of calcitriol Management:** 1. **Phosphate binder:** Start sevelamer (non-calcium) or lanthanum given hypocalcemia already present 2. **Vitamin D:** Calcitriol 0.5 mcg BID to suppress PTH 3. **Dietary:** Restrict phosphate to < 1 g/day 4. **Monitor:** Repeat Ca, PO4, PTH q4–6 weeks; goal PTH 35–70 for Stage 4 5. **Goals:** Ca-P product < 55, maintain Ca 8.5–10.5, reduce PTH surge

References

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Related Resources

- BMP Pattern Recognition Master Guide
- Phosphorus Comprehensive Guide
- Urinalysis Master Diagnostic Algorithm
- CKD Mineral Bone Disease Overview
- Hyperparathyroidism Diagnostic Workup

Last updated: 2026-02-28 | Board-review quality reference. For acute symptomatic hypocalcemia, never delay IV calcium awaiting confirmatory labs.