CKD Mineral-Bone Disorder (CKD-MBD): Pathophysiology & Management

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Definition & Scope

CKD-MBD is a systemic disorder of mineral homeostasis characterized by: 1. **Abnormalities in calcium, phosphate, PTH, vitamin D metabolism** 2. **Bone disease** (abnormal turnover, mineralization, or volume) 3. **Vascular and soft-tissue calcification**

Present in ~80% of CKD G3b–G5; major driver of cardiovascular mortality in ESRD.

> [!important] **CKD-MBD is NOT just "renal osteodystrophy"** — includes vascular calcification, myocardial calcification, and systemic effects of abnormal mineral metabolism.

Pathophysiology: The Phosphate-FGF23-PTH-Vitamin D Axis

Phase 1: Early CKD (G3a, eGFR 45–59)

Trigger: Nephron loss → ↓ filtered load of phosphate

Compensatory response: 1. **FGF23** ↑↑ (fibroblast growth factor 23) - Secreted by osteoblasts/osteocytes in response to ↓ GFR + ↑ phosphate - **Early marker** of dysregulation; may ↑ before serum PO4 rises - Suppresses PTH, ↑ FGF23-mediated phosphate excretion - Inhibits 1,25-(OH)2 vitamin D (active vitamin D) synthesis

2. **PTH rises slightly** (phosphate retention drives PTH)
   - ↑ Serum PTH → ↑ phosphate excretion per remaining nephron
   - Net effect: Serum PO4 stays NORMAL for longer
3. **Serum phosphate remains NORMAL** (~3.5–4.5 mg/dL)

> [!tip] **Clinical pearl — Early CKD:** FGF23 is HIGH, PTH is mildly ↑, but serum PO4 is NORMAL. This is the "compensation window" — recognizing this allows early intervention before overt hyperphosphatemia.

Phase 2: Moderate-to-Advanced CKD (G3b–G4, eGFR 15–44)

Worsening phosphate retention: - More nephrons lost → even with ↑↑ FGF23, phosphate accumulates - **Serum phosphate begins to rise** (>4.5 mg/dL)

PTH escalation: - Combines effects of: hyperphosphatemia + ↓ 1,25(OH)2 vitamin D (low calcium) + persistent FGF23 - PTH ↑↑↑ (may exceed 100 pg/mL)

Vitamin D metabolism disrupted: - ↓ **1,25-(OH)2 vitamin D** (active form) - Normally produced by proximal tubule with FGF23 suppression - FGF23 ↑↑ → ↓↓ 1,25(OH)2D synthesis - ↓ 1,25(OH)2D → ↓ intestinal calcium absorption → ↓ serum Ca → ↑ PTH (vicious cycle)

- ↑ **25-OH vitamin D may be normal** — stored form less affected (but may be low from poor nutrition/sun exposure)

Result: Secondary hyperparathyroidism (2° HPT) — PTH elevated due to CKD-induced stimuli

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Phase 3: Advanced CKD & ESRD (G5, eGFR <15)

Overt hyperphosphatemia: PO_4 >5 mg/dL

Tertiary hyperparathyroidism: PTH becomes autonomous - Even if phosphate, calcium normalize, PTH remains ↑ (from years of stimulation + parathyroid gland hyperplasia)

Calcification cascade: - **Ca-PO_4 product > 55** (risk zone for precipitation) - Calcification occurs in: coronary arteries, aorta, cardiac valves, soft tissues - **Vascular calcification** → arterial stiffness → ↑ pulse pressure → LVH → HF

Bone disease spectrum: 1. **High-turnover bone disease** (secondary HPT) - Excessive PTH → osteoblast & osteoclast activity ↑ - Rapid remodeling, loss of cortical bone, trabecular preservation 2. **Low-turnover bone disease** (adynamic bone) - Suppressed PTH (over-treatment with vitamin D, calcimimetics) - Minimal bone remodeling → impaired fracture healing 3. **Mixed uremic osteodystrophy** — elements of both

> [!warning] **Fragility fractures in dialysis patients are common** and cause significant morbidity/mortality despite good Ca/PO_4 control. Paradox: high PTH → high turnover → weak bone.

Diagnostic Approach: CKD-MBD Screening

When to Start Monitoring

Stage	Serum Ca/PO_4	PTH	25-OH VitD	Interval
G1–G2	No	No	No	—
G3a	Yearly	No	Once	Yearly
G3b	Yearly	Q12 months	Once	Q6–12 months
G4	Q6 months	Q3–6 months	Once	Q3–6 months
G5	Monthly–Q6 weeks	Q3 months	Q6–12 months	Every month

Key Lab Parameters

Test	Normal	Concern in CKD
Serum Ca	8.5–10.5 mg/dL	<8.5 (hypocalcemia) or >10.5 (risk if PO4 also ↑)
Serum PO4	2.5–4.5 mg/dL	>4.5 (hyperphosphatemia); target <5.5 in G4–G5
PTH	15–65 pg/mL	G3: <110; G3b–4: <110–165; G5: 150–300 (wide range)
25-OH VitD	30–100 ng/mL	<30 (insufficient); <20 (deficiency)
Ca-PO4 product	~35	>55 (risk of metastatic calcification)
Alkaline phosphatase	30–120 U/L	↑ in high-turnover; ↓ in adynamic
FGF23	<100 RU/mL	↑ (research marker; not routine but predictive)

> [!tip] **FGF23 as early warning:** Rising FGF23 (>100 RU/mL) at G3a predicts future progression to secondary HPT and bone disease. Not routine but valuable in research settings.

Management Strategy by Stage

CKD G3a–G3b (eGFR 30–59)

Goal: Prevent secondary HPT development

1. **Phosphate restriction**
   - Diet: <1,000 mg/day (limit dairy, nuts, processed foods)
   - **No binders needed yet** if serum PO4 normal
2. **Vitamin D repletion** (if 25-OH VitD <30)
   - Ergocalciferol (Vitamin D2) 50,000 IU weekly × 12 weeks, then monthly
   - OR Cholecalciferol (Vitamin D3) 1,000–2,000 IU daily
   - Goal: 25-OH VitD 30–100 ng/mL
3. **Monitor PTH trend**
   - If PTH ↑ into 65–110 range → consider active vitamin D
4. **Calcium neutral approach** — avoid hypercalcemia

CKD G4 (eGFR 15–29)

Goal: Control PTH, phosphate; prevent vascular calcification

1. **Phosphate binders** (if PO4 >4.5 mg/dL)
   - **Calcium-based:** Calcium carbonate, calcium acetate
     - Pro: Inexpensive, help with acidosis
     - Con: ↑ Calcium load → vascular calcification risk if Ca-PO4 product >55
   - **Non-calcium:** Sevelamer, lanthanum, sucroferric oxyhydroxide
     - Pro: Don't ↑ Ca; may ↓ phosphate absorption better

- Con: Expensive, GI tolerability, multiple daily doses

[!important] **Modern trend:** Avoid calcium-based binders in late CKD; prefer non-calcium agents to minimize Ca load and vascular calcification risk.

2. **Active vitamin D** (if PTH >110 AND Ca-PO4 product <55)
   - Calcitriol (1,25-(OH)2D3): Start 0.25–0.5 mcg daily–BID (potent; monitor Ca/PO4)
   - Paricalcitol (1,25-(OH)2D analogue): 1–2 mcg daily (selectivity for VDR in parathyroid)
   - Goal: Suppress PTH while maintaining Ca/PO4 balance
3. **Calcimimetics** (if PTH severely ↑ or hypercalcemia)
   - Cinacalcet: Allosteric activator of CaSR → ↓ PTH secretion
   - Doesn't ↑ serum Ca or PO4 (advantage over vitamin D)
   - Use if PTH >300 despite binders + vitamin D, or if hypercalcemia
4. **Monitor:** Ca, PO4, PTH monthly

CKD G5 (eGFR <15, Dialysis)

Goal: PTH in target range (150–300 pg/mL); prevent hyperphosphatemia, calcification

1. **Dialysis phosphate removal**
   - Depends on GFR, urine output, residual kidney function
   - ~70–80% of phosphate removed by dialysis
2. **Aggressive phosphate management**
   - Binders with meals: Non-calcium preferred (sevelamer, lanthanum)
   - Dietary PO4 restriction <1,000 mg/day
   - Avoid high-phosphate foods (colas, processed meats, dairy)
3. **PTH target range: 150–300 pg/mL** (KDIGO 2009)
   - Some argue 200–400 acceptable (more physiologic; prevents adynamic bone)
   - Avoid over-suppression (adynamic bone, vascular stiffness)
4. **Calcium balance**
   - Avoid hypercalcemia (Ca >10 mg/dL)
   - Consider low-Ca dialysate if hypercalcemia
5. **Bone biopsy** (if unexplained bone pain, fractures, or concern for adynamic bone)
   - Tetracycline labeling → assess turnover, mineralization
   - Guides intensity of therapy

Newer Agents (Emerging in CKD G3b–G4)

FGF23 Antagonists (Research phase)

- Pegpamorelin, others in development
- Target upstream: Block FGF23 directly
- May prevent secondary HPT earlier
- Not yet routine but promising

Phosphate Binders (Newer generation)

- **Sucroferric oxyhydroxide** — once-daily dosing (better adherence)

- **Patiromer (potassium binders):** Also binds phosphate; dual benefit if hyperkalemia

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Bone Health: Fracture Prevention

Screening for Osteoporosis in CKD

- DEXA (dual-energy x-ray absorptiometry) often **NOT useful** in CKD
  - May underestimate fracture risk (vascular calcification mimics high bone density)
  - Dynamic processes override static density measure
- **Better approach:** Clinical assessment
  - Age >70, female, steroid use, fracture history
  - Consider high-turnover vs low-turnover bone disease
  - PTH >300 → likely high turnover (less osteoporosis, more fracture from remodeling)

Management

1. **Exercise & nutrition:** Weight-bearing activity, adequate protein (1.0–1.2 g/kg)
2. **Calcium balance:** Avoid both hypo- and hypercalcemia
3. **Vitamin D:** Maintain 25-OH VitD >30 ng/mL
4. **Avoid bisphosphonates in CKD G4–G5** — risk of low-turnover bone, impaired fracture healing
5. **Consider anabolic agents** (PTH analogues) if documented low-turnover bone on biopsy (rare, specialized)

Vascular Calcification & Cardiovascular Risk

> [!warning] **Coronary artery calcification in ESRD:** Present in 40–80% of dialysis patients; major predictor of CV death (more predictive than Framingham risk).

Mechanisms of Vascular Calcification in CKD

1. **Passive precipitation:** Ca-PO4 product >55 → hydroxyapatite crystal formation in vessel walls
2. **Active osteogenic conversion:** Vascular smooth muscle cells transdifferentiate → osteoblast-like → produce mineralization matrix
3. **Loss of calcification inhibitors:** ↓ Fetuin-A, matrix Gla protein (MGP)
4. **Oxidative stress & inflammation** from uremia

Prevention

- Tight phosphate control (target <5.5 mg/dL at G5)
- Minimize Ca-PO4 product <55
- Avoid excess calcium supplementation
- Use non-calcium binders
- Manage inflammation (dialysis adequacy)

[!tip] **Clinical pearl:** Vascular calcification is IRREVERSIBLE once established. Prevention is key — tight mineral control at G3b–G4 prevents future calcification.

Related Resources

- Detailed CKD-MBD Pathophysiology
- CKD Staging & Classification
- Dialysis & Mineral Management
- Post-Transplant Bone Management

Self-Test Questions

1. **50M, GFR 40, serum Ca 8.2, PO4 4.6, PTH 95, 25-OH VitD 28**
   - CKD-MBD stage: Mild 2° HPT (early)
   - Intervention: Vitamin D2 to target >30; dietary PO4 reduction; recheck PTH Q3 months
   - Agent if PTH ↑ further: Active vitamin D (calcitriol)
2. **72F, GFR 18, Ca 9.8, PO4 6.2, PTH 450, Ca-PO4 product 61**
   - CKD-MBD stage: Advanced 2° HPT with calcification risk
   - Intervention: Start binder (non-calcium), phosphate diet <1,000 mg/day, active vitamin D if tolerated
   - If Ca >10: Lower binder dose, avoid vitamin D, consider cinacalcet
3. **Dialysis patient, PTH 120 (LOW)**
   - Risk: Adynamic bone disease (suppressed turnover)
   - Intervention: Reduce vitamin D, consider bone biopsy, hold calcimimetics
   - Goal: Titrate toward PTH 150–300 range

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References: KDIGO 2009 Clinical Practice Guideline for CKD–Mineral and Bone Disorder. Kidney Disease: Improving Global Outcomes. Am J Kidney Dis. 2009;53(3 Suppl).