CKD Complications: Mineral Bone Disorder, Anemia, and Systemic Manifestations

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March 2026

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Learning Objectives

By the end of this handout, students will be able to:

1. **Identify and classify** CKD-mineral bone disorder (CKD-MBD) pathophysiology and distinguish between secondary and tertiary hyperparathyroidism
2. **Explain mechanisms** of renal anemia including EPO deficiency, iron metabolism disruption, and uremic inhibitors
3. **Recognize clinical** presentations of calciphylaxis and vascular calcification in CKD
4. **Understand uremic toxins** and their systemic effects across multiple organ systems
5. **Apply mechanisms** of CKD progression (glomerular hyperfiltration, fibrosis, proteinuria-induced injury)
6. **Synthesize** multi-system complications of CKD affecting cardiovascular, neurologic, dermatologic, endocrine, and hematologic systems

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I. CKD-Mineral Bone Disorder (CKD-MBD): Overview

Definition and Scope

CKD-MBD is a systemic disorder of **mineral and bone metabolism** that emerges early in CKD, characterized by abnormalities in: - Serum calcium, phosphate, PTH, and vitamin D metabolism - Vascular and soft-tissue calcification - Bone turnover, mineralization, and strength - FGF23 dysregulation

Prevalence: Begins at CKD Stage 3 (eGFR <60), with significant pathology by Stage 4.

II. Pathophysiology of Secondary Hyperparathyroidism

Early Phase (CKD Stages 3–4): Phosphate Retention & FGF23 Rise

Timeline: 1. **eGFR falls ☐ phosphate excretion decreases** (kidney loses filtration capacity) 2. **Serum phosphate rises** (even before clinical hyperphosphatemia detected) 3. **FGF23 surges** in response to hyperphosphatemia 4. **FGF23 suppresses:** - 1α-hydroxylase (activating CYP27B1) ☐ ☐ calcitriol synthesis - Sodium-phosphate co-transporters (NPT2a/c) ☐ ☐ urinary phosphate loss 5. **Calcitriol (1,25-OH vitamin D3) decreases** ☐ ☐ intestinal calcium absorption

Cascade to Hypocalcemia & PTH Rise

- **Decreased calcitriol + phosphate retention** ☐ ☐ serum calcium (ionized Ca2+)
- **Hypocalcemia stimulates parathyroid glands** ☐ PTH rises
- **PTH mobilizes calcium from bone** (transient correction)
- **Phosphate binders and dietary restriction** may partially blunt phosphate rise, but underlying deficit persists

Progressive Phase (CKD Stages 4–5): Parathyroid Gland Adaptation

Mechanism	Effect	Consequence
Decreased calcium-sensing receptor (CaSR) expression	Parathyroid insensitivity to serum calcium	PTH continues rising despite normalized Ca
FGF23 resistance	Impaired FGF23 suppression of PTH	Autonomous PTH secretion develops
Uremia & phosphate toxicity	Direct parathyroid proliferation	Gland hyperplasia, nodular formation
Vitamin D deficiency	Loss of VDR-mediated PTH suppression	Secondary hyperparathyroidism becomes tertiary

Result: Secondary hyperparathyroidism becomes **autonomous** (pseudo-tertiary hyperparathyroidism) even before transplantation.

III. Secondary vs. Tertiary Hyperparathyroidism

Secondary Hyperparathyroidism

Definition: Appropriate parathyroid response to CKD-induced hypocalcemia, hyperphosphatemia, and calcitriol deficiency.

Characteristics: - PTH elevated (often >200 pg/mL in CKD Stage 5) - Serum calcium low-normal to mildly ☐ - Serum phosphate ☐ - Parathyroid tissue is **hyperplastic but responsive** to suppression (in theory) - **Reversible** if CKD is corrected or dialysis initiated

Tertiary Hyperparathyroidism

Definition: Autonomous PTH secretion occurring after prolonged secondary hyperparathyroidism, often post-transplantation when GFR improves.

Characteristics: - PTH remains elevated despite normalized serum calcium and phosphate - Serum calcium **elevated** (hypercalcemia) - Serum phosphate normalized by transplant kidney - Parathyroid tissue shows **nodular hyperplasia, autonomous function** - Develops from long-standing secondary hyperparathyroidism with parathyroid gland structural changes - **Requires parathyroidectomy** if severe (PTH >800–1000 pg/mL causing hypercalcemia)

Clinical Implications

Feature	Secondary HyperPTH	Tertiary HyperPTH
CKD Stage	3–5D	Post-transplant
Serum Ca	Low-normal to ☐	☐ (hypercalcemia)
Serum Phos	☐	Normal
Responsiveness	Responsive to calcitriol, Ca, Phos control	Autonomous (surgery needed)
GFR	<45 mL/min	>45 (improved)

IV. CKD-MBD Bone Pathology

Renal Osteodystrophy Patterns

High-Turnover Bone Disease (Secondary Hyperparathyroidism) - Increased osteoblast and osteoclast activity - ☐ bone resorption, ☐ bone formation (but formation lags resorption) - ☐ PTH drives rapid turnover - **Risk:** Fracture despite increased remodeling (paradox: high turnover can cause fragility) - **Biochemical markers:** ☐ alkaline phosphatase, ☐ P1NP (procollagen type 1 N-terminal propeptide)

Low-Turnover Bone Disease (Adynamic Bone) - Suppressed osteoblast activity, minimal bone remodeling - ☐ PTH (excessive suppression from calcitriol, calcimimetics) - ☐ Risk of calcification (paradoxically, despite low turnover) - **Presents as:** Fractures, proximal muscle weakness, bone pain ("bone hunger" syndrome on dialysis) - **Common in:** Dialysis patients, over-suppressed PTH

Mixed Uremic Osteodystrophy - Features of both high and low turnover - Defective mineralization (osteomalacia features) - ☐ Al^{3+} accumulation from dialysate (historical, now rare) - ☐ 25-OH vitamin D compounds problem

Bone Mineral Density (BMD) Paradox in CKD

- **CKD patients have HIGH DXA-measured BMD** (because of vascular calcification artifact inflating bone mineral content)
- Yet **fracture risk is INCREASED 2–4 fold** compared to general population

- **True bone quality is impaired** (higher turnover, mineralization defects, microarchitectural damage)
- **DXA is NOT reliable** in CKD; alternative assessment (bone biopsy, biomarkers, clinical judgment) preferred

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V. Vascular Calcification and Calciphylaxis

Mechanisms of Vascular Calcification in CKD

1. Passive Deposition ("Medial Calcification") - Hyperphosphatemia + hypercalcemia create supersaturated local environment - Calcium-phosphate ions precipitate in media layer of arteries - Enhanced by: uremic toxins, oxidative stress, hyperparathyroidism

2. Active Osteogenic Differentiation - Vascular smooth muscle cells (VSMCs) undergo **osteogenic transition** - Driven by: phosphate, oxidative stress, loss of calcification inhibitors - VSMCs express bone-specific markers: alkaline phosphatase, osteocalcin, Runx2 - **Morphologic result:** Arterial wall calcifies, becomes rigid, loses elastic recoil

3. Loss of Mineralization Inhibitors - Fetuin-A ☐ (uremic loss) - Pyrophosphate ☐ (substrate consumed in calcification) - Matrix Gla-protein (MGP) ☐ or inactive - Osteoprotegerin (OPG) dysregulated - **Net result:** Unopposed calcification

Calciphylaxis (Calcific Uremic Arteriolopathy)

Definition: Rare but catastrophic syndrome of **small-vessel medial calcification** in CKD patients, causing painful ischemic necrosis of skin and subcutaneous tissue.

Epidemiology: - Incidence: 1–4% of hemodialysis patients - **Mortality: 60–80%** if untreated (sepsis, amputation complications)

Risk Factors: - Serum calcium × phosphate product >70 (historical marker; now any elevation of Ca-Phos product) - Primary hyperparathyroidism superimposed on CKD - Obesity - Female sex - Warfarin use (inhibits matrix Gla-protein carboxylation, paradoxically promotes calcification) - Hypercoagulability, thrombophilia

Clinical Presentation: - **Extremely painful skin lesions** (out of proportion to appearance) - Pink-to-purple, livedoid rash ☐ **black necrotic ulcers** with demarcation - Typically affects **lower extremities, buttocks, digits, penis, breast tissue** - Often bilateral and symmetric - **Subcutaneous calcification** visible on imaging (small-vessel calcification)

Diagnosis: - Clinical suspicion (CKD + severe pain + skin findings) - **Skin biopsy:** Small-vessel calcification with medial sclerosis - Imaging: X-ray, CT showing micro-calcifications

Management: 1. **Aggressive phosphate control** (phosphate binders, dialysate adjustment) 2. **Calcium normalization** (avoid calcium supplements; use low-calcium dialysate if needed) 3. **PTH suppression** (calcitriol or cinacalcet cautiously; goal is normalization, not over-suppression) 4. **Discontinue warfarin** if possible (switch to DOAC or bridging strategy) 5. **Sodium thiosulfate IV** (promotes sulfhydryl chemistry, inhibits calcification; evidence mixed but often tried) 6. **Aggressive infection control** (ulcers easily infected; prophylactic antibiotics) 7. **Pain management** (often requires opioids, gabapentin; neuropathic pain pattern)

8. **Surgical debridement** (if localized and life/limb-threatening; generally avoided in early disease)

VI. Renal Anemia in CKD

Epidemiology & Classification

Prevalence: Present in >90% of CKD Stage 5D patients; begins at Stage 3–4.

Severity by CKD Stage: | CKD Stage | eGFR | Typical Hb (g/dL) | Anemia Prevalence | |——–|——|————-|————-| | 3a | 45–59 | 12.5–13.5 | 5–10% | | 3b | 30–44 | 11.5–12.5 | 15–25% | | 4 | 15–29 | 10.5–11.5 | 40–50% | | 5 (pre-D) | <15 | 9–10 | 80–90% | | 5D | on dialysis | <10 (without ESA) | 95%+ |

Primary Mechanism: EPO Deficiency

Normal EPO Production: - Fibroblasts in peritubular interstitium of kidney (90% of body EPO) - Small amount from liver (10%) - Stimulus: Renal hypoxia (oxygen-sensing by HIF pathway)

In CKD: - **Nephron loss ☐ fewer EPO-producing fibroblasts** - Remaining fibroblasts have **blunted hypoxia response** (uremic milieu impairs HIF signaling) - **EPO production drops disproportionately** to degree of kidney loss - Even CKD Stage 3 ☐ EPO levels inadequate for true degree of renal function loss

Result: Relative EPO deficiency (low-normal EPO level in face of anemia requiring EPO 10x normal)

Secondary Anemia Mechanisms in CKD

1. Iron Deficiency - **Hepcidin dysregulation:** CKD ☐ ☐ hepcidin (from inflammation, FGF23) ☐ ☐ ferroportin ☐ ☐ iron absorption - **Chronic blood loss:** Dialysis membrane losses, occult GI bleeding in uremia - **Impaired iron mobilization:** Uremia impairs ferroxidase activity (ceruloplasmin) - **Functional iron deficiency:** Adequate iron stores but impaired utilization

2. Uremic Inhibition of Erythropoiesis - **Uremic toxins** (indoxyl sulfate, p-cresol, urea itself) suppress bone marrow erythroid response - Inhibit EPO signaling in erythroid progenitors - Toxic metabolites accumulate in CKD (not removed by dialysis alone)

3. Hemolysis & Reduced RBC Survival - Uremic toxins oxidize RBC membrane proteins - ☐ RBC deformability, impaired passage through spleen - Circulating RBC lifespan: **60–80 days** (vs. 120 days in health) - Low-grade hemolysis (☐ bilirubin, ☐ LDH, ☐ haptoglobin)

4. Chronic Inflammation - CKD ☐ constant low-grade uremia + fluid retention ☐ innate immune activation - ☐ IL-6, TNF-α, C-reactive protein - Inflammatory cytokines suppress erythropoietin response and increase hepcidin - Dialysis itself triggers inflammation (endotoxemia, contact with membrane)

5. Blood Loss & Nutritional Factors - **Dialysis losses:** RBCs trapped in dialyzer, tubing (per treatment: 1–5 mL) - **Monthly/yearly accumulation:** Significant over time - **Folate/B12 de-**

ficiency: Uremic anorexia, dietary restriction, dialysate losses - **Aluminum toxicity** (historical): Suppressed RBC production (now rare with modern dialysate)

ESA Therapy and Resistance

Erythropoiesis-Stimulating Agent (ESA) Target in CKD: - Current target hemoglobin: 10–12 g/dL (no benefit to higher; increased thrombosis/hypertension risk) - **Avoid target >13 g/dL** (increased CV events, stroke in clinical trials)

ESA Hyporesponsiveness Defined As: - Hb rise <1 g/dL after 4 weeks of ESA (or 2 weeks if IV ESA) - Requiring ESA dose >300 IU/kg/week (subcutaneous) or >450 IU/kg/week (IV) - **Incidence:** 10–15% of CKD patients on ESA

Mechanisms of ESA Resistance: - Persistent iron deficiency (even with IV iron) - Ongoing hemolysis (severe uremia) - Hyperparathyroidism (PTH suppresses erythropoietin signaling) - **ACE inhibitor/ARB use** (can reduce EPO; controversial benefit/harm) - Chronic infection or malignancy - Aluminum accumulation (rare now) - **Underlying hematologic disorder** (myelodysplasia, thalassemia trait)

VII. Uremic Toxins and Uremia Syndrome

Definition of Uremia

Uremia is the **clinical syndrome** resulting from **retention of nitrogenous and organic compounds** normally cleared by kidneys. Not merely elevated BUN/creatinine, but the **metabolic milieu of compounds** causing symptoms and organ dysfunction.

Classification of Uremic Toxins

Category	Examples	Effects
Small Water-Soluble	Urea, creatinine, uric acid	Readily dialyzable; moderate uremic effects
Protein-Bound	Indoxyl sulfate, p-cresol, indole-3-aldehyde, phenolic compounds	Poorly dialyzable; potent toxins; resist HD/PD
Middle Molecules	β2-microglobulin, myoinositol, adenosine	Size 300–50,000 Da; partially dialyzed; cause amyloidosis
Large Molecules	Advanced glycation end products (AGEs), uremic "super-oxides"	Potent inflammatory triggers

Key Uremic Toxins and Their Organ Effects

1. Indoxyl Sulfate (Indican) - Source: Tryptophan metabolism by gut microbiota ☐ indole ☐ liver sulfation - **Actions:** Aryl hydrocarbon receptor (AhR) agonist; oxidative stress; endothelial

dysfunction; promotes CKD progression (feeds forward) - **Toxicity:** Cardiovascular, gut barrier breakdown

2. p-Cresol (p-CS) - Source: Tyrosine fermentation; gut dysbiosis increases production - **Actions:** Aryl hydrocarbon receptor; vascular oxidative stress; immune suppression - **Toxicity:** Vascular calcification, infection risk, CKD progression

3. Asymmetric Dimethylarginine (ADMA) - **Action:** Competitive inhibitor of nitric oxide synthase (NOS) ☐ ☐ NO ☐ vasoconstriction, endothelial dysfunction - **Effect:** Potent vascular toxin; increases CV risk

4. β2-Microglobulin - **Source:** Constant shedding from leukocyte surface; normally filtered and reabsorbed by kidney - **Accumulation in CKD:** Forms amyloid fibrils - **Condition: Dialysis-related amyloidosis (DRA)** with prolonged HD/PD - **Deposits in:** Bones, joints, tendons ☐ carpal tunnel, pathologic fractures, destructive arthropathy - **Newer high-flux dialyzers and hemodiafiltration** reduce β2-microglobulin better

5. Phosphate (Phosphoric Acid) - Toxic at elevated levels (>6 mg/dL) - Promotes vascular calcification, soft-tissue precipitation - Stimulates FGF23 (feeds forward CKD progression and hyperparathyroidism)

Systemic Effects of Uremia (Multi-Organ)

Cardiovascular: - Atherosclerosis acceleration (ADMA, oxidative stress, dyslipidemia) - Vascular calcification (phosphate, FGF23) - Left ventricular hypertrophy (hypertension, anemia, fluid overload) - Arrhythmias (hyperkalemia, uremia, volume overload) - Heart failure (from all above)

Neurologic: - **Uremic encephalopathy:** Altered mental status, confusion, seizures (high BUN); reversible with dialysis - **Peripheral neuropathy:** Demyelinating (from uremia) or entrapment (from amyloidosis) - **Central pontine myelinolysis:** Risk with rapid correction of hyponatremia in dialysis - Sleep disturbance (uremia, restless leg syndrome from iron deficiency, phosphate imbalance)

Gastrointestinal: - Uremic gastroparesis (delayed emptying, nausea, poor appetite) - Uremic colitis (mucosal ischemia, ulceration) - GI bleeding (angiodysplasia, aspirin/anticoagulation use) - Enteritis, dysmotility from toxins

Hematologic (beyond anemia): - Platelet dysfunction (uremic toxins impair aggregation) ☐ prolonged bleeding time despite normal count - ☐ Infection risk (immune suppression from uremia, impaired chemotaxis) - Hemolysis (as discussed)

Dermatologic: - **Uremic pruritus:** Mast cell activation, phosphate accumulation in skin; severe, distressing - Pigmentation changes (retained urochrome, anemia) - Skin atrophy, fragility - Calciphylaxis (already discussed)

Endocrine: - Hypothalamic-pituitary dysfunction (uremic suppression of GnRH, ACTH) - ☐ Testosterone, ☐ Estrogen (amenorrhea common) - ☐ Prolactin (loss of dopamine inhibition) - Thyroid: Usually maintained, but TSH may be blunted - Insulin resistance (uremic toxins, chronic inflammation) - Impaired glucose sensing

Immune: - T-cell dysfunction (impaired cell-mediated immunity) - B-cell response attenuated (poor vaccine response) - ☐ Infection rates (respiratory, urinary, access-related) - Altered complement regulation

VIII. CKD Progression Mechanisms

Hyperfiltration Hypothesis

Normal physiology: - ~1 million nephrons per kidney - Baseline single-nephron GFR (SNGFR): ~50 nL/min - Total GFR: ~100–120 mL/min

After nephron loss (from any cause): - Remaining nephrons **increase SNGFR** via afferent arteriolar vasodilation - Mediated by: ☐ systemic BP ☐ renin-angiotensin activation ☐ efferent arteriole vasoconstriction ☐ glomerular pressure ☐ - Also: Compensatory renal growth (hypertrophy)

Problem: Elevated intraglomerular pressure (Pg) causes: 1. **Mechanical injury** to capillaries 2. **Increased protein filtration** ☐ proteinuria (toxin to tubules) 3. **Podocyte foot process fusion** (ultrafiltration barrier damage) 4. **Activation of fibrogenic pathways** (TGF-β, CTGF)

Result: Progressive glomerulosclerosis, tubulointerstitial fibrosis, accelerated nephron loss.

Role of Proteinuria in CKD Progression

Glomerular origin of filtered proteins: - Albumin: Charge-selective; some normally filtered (<150 mg/day) - Immunoglobulins, other proteins: Normally absent - Proteinuria >0.5–1 g/day indicates **loss of charge and size selectivity** (damaged filter)

Proteinuria toxicity to tubules: - **Proximal tubule endocytosis:** Proximal cells reuptake filtered proteins via megalin/cubilin receptors - **Lysosomal overload:** Proteins digest in lysosomes; lipids, iron accumulate ☐ lipid peroxidation, ROS - **TGF-β activation:** Filtered proteins trigger epithelial-mesenchymal transition (EMT) in tubules ☐ fibroblasts - **Complement activation:** Alternative pathway; C5a and C3a drive inflammation - **Acidification:** Tubule reabsorption of proteins ☐ tubular acidosis (metabolic acidosis worsens proteinuria)

Clinical implication: ACE-I/ARB reduce intraglomerular pressure ☐ ☐ proteinuria ☐ slows CKD progression (proven benefit in all CKD etiology)

Fibrosis Cascade: Glomerular and Tubulointerstitial

Initiating factors: - Chronic glomerular/tubular injury (proteinuria, hemodynamic stress, toxic metabolites) - Repeated injury-repair cycles ☐ myofibroblast accumulation

TGF-β pathway (central to fibrosis): 1. Injured tubular epithelium + infiltrating macrophages ☐ ☐ TGF-β production 2. TGF-β ☐ myofibroblast differentiation (via pericyte-to-fibroblast transition) 3. Myofibroblasts ☐ excessive collagen synthesis (type I, III) 4. **EMT (Epithelial-Mesenchymal Transition):** Tubular epithelial cells lose adhesion ☐ gain fibroblast characteristics 5. Collagen accumulation ☐ tubular and glomerular stiffness ☐ progressive function loss

CTGF (Connective Tissue Growth Factor): - Downstream of TGF-β - Amplifies fibrogenic response - Cross-talk with Wnt/β-catenin pathway

Outcome: Progressive replacement of functional parenchyma with fibrotic scar tissue.

Metabolic Acidosis and CKD Progression

Mechanism: - CKD ☐ ☐ NH_4^+ excretion (loss of ammoniogenesis in proximal tubule) - ☐ HCO_3^- reabsorption - Net H^+ retention ☐ metabolic acidosis (typically mild, pH 7.3–7.35)

Effect on CKD progression: - Acidosis ☐ ☐ ammonia and glutaminase in proximal tubule ☐ local tissue injury - ☐ Ammoniagenesis damages tubulointerstitium - Acidosis triggers protein catabolism, worsens CKD mineral bone disease - **Alkali therapy (sodium bicarbonate, sodium citrate)** slows CKD progression (KDIGO recommendation)

IX. Multi-System Complications of CKD: Organ-System Summary

Organ System	Key Complications	Pathophysiology	Management Pearls
Cardiovascular	LVH, HF, CAD, arrhythmia, sudden cardiac death	Hypertension, anemia, vascular calcification, uremia	BP target <120 SBP; ACE-I/ARB; treat anemia judiciously
Renal/Urologic	Progressive GFR loss, proteinuria, hematuria	Hyperfiltration, glomerulosclerosis, fibrosis	ACE-I/ARB; SGLT2i; phosphate control
Bone-Mineral	Secondary HPT, low-turn bone disease, fractures, calciphylaxis	FGF23 rise, phosphate retention, calcitriol ☐	PTH target 2–9x ULN; Ca-Phos product <55; vitamin D repletion
Hematologic	Anemia, bleeding tendency, ☐ infection risk	EPO deficiency, iron loss, immune dysfunction, toxins	ESA target Hb 10–12; IV iron; prophylactic antibiotics if needed
Neurologic	Uremic encephalopathy, neuropathy, seizures, sleep disorder	Uremic toxins, electrolyte abnormalities (K, Ca-Phos), amyloidosis	Dialysis adequacy; electrolyte management; treat HTN
GI	Uremia, bleeding, gastroparesis, enteritis	Mucosal ischemia, uremic toxins, vascular disease	Dietary restriction; H2-blocker or PPI; avoid NSAIDs
Endocrine/Metabolic	Hypothyroidism, hypogonadism, insulin resistance, dyslipidemia	Uremia, inflammation, hormonal dysregulation	TSH screening; lipid panel; sexual dysfunction counseling
Dermatologic	Uremic pruritus, skin fragility, pigmentation	Mast cell activation, uremic toxins, microvasculature disease	Phosphate control; gabapentin/pregabalin; antihistamines
Infectious	UTI, sepsis, access infection, opportunistic infection	Immune suppression, uremia, breach of barriers	Prophylaxis in high-risk; aggressive management

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X. Clinical Pearls

1. **CKD-MBD begins early:** Check PTH, calcium, phosphate, alkaline phosphatase at Stage 3 CKD; start intervention (phosphate binder, vitamin D) before Stage 4.
2. **FGF23 is the earliest biomarker:** Rises before serum phosphate becomes elevated; FGF23 >100 RU/mL signals need for intervention.
3. **Calcium-phosphate product >55 is dangerous:** Increases calcification risk exponentially; aggressively lower both.
4. **Tertiary hyperparathyroidism is post-transplant:** Secondary HTN develops in CKD; tertiary only after renal transplant (with restored GFR but persistent parathyroid dysfunction).
5. **Anemia target: 10–12 g/dL:** Higher targets increase CV risk; lower targets require transfusion. Optimal range in most trials.
6. **Iron metabolism is disrupted by hepcidin:** Even with normal ferritin, patients may be functionally iron-deficient; monitor responsiveness to IV iron.
7. **Uremic pruritus can be disabling:** If refractory to phosphate control, try gabapentin 300 mg TID, systemic corticosteroids, or phototherapy; consider switch to hemodiafiltration.
8. **Proteinuria drives CKD progression:** Every 1 g/day reduction in proteinuria buys ~1 year of renal function; ACE-I/ARB + SGLT2i achieve 40–50% reduction often.
9. **Calciphylaxis is a surgical emergency:** If suspected (severe ischemic pain + skin findings), aggressive phosphate binder therapy, consider IV sodium thiosulfate, stop warfarin, manage pain, and debridement if focal.
10. **Metabolic acidosis worsens bone disease:** Alkali supplementation (e.g., sodium bicarbonate 1 g BID) has been shown to slow CKD progression and improve bone health.
11. **ACE-I/ARB are renoprotective across all CKD:** Work via hemodynamic (☐ intraglomerular pressure) and non-hemodynamic (☐ inflammation, ☐ fibrosis) mechanisms; always use unless contraindicated.
12. **SGLT2 inhibitors slow CKD regardless of diabetes:** Recent evidence (EMPA-KIDNEY trial) shows benefit in all CKD; consider as add-on therapy to ACE-I/ARB.

XI. Practice Questions

Question 1: A 58-year-old man with CKD Stage 4 (eGFR 22 mL/min/1.73m²) has labs: Ca 8.2 mg/dL, PO4 5.8 mg/dL, PTH 456 pg/mL, 25-OH vitamin D 18 ng/mL, 1,25-OH vitamin D (calcitriol) 12 pg/mL. Which is the PRIMARY mechanism driving the elevated PTH?

A) Hypercalcemia suppressing PTH feedback
B) Phosphate retention ☐ FGF23 rise ☐ ☐ calcitriol ☐ hypocalcemia-driven PTH rise
C) Direct PTH synthesis from uremia
D) Tertiary hyperparathyroidism from prior transplant failure

Correct Answer: B Explanation: In CKD Stage 4, secondary hyperparathyroidism develops due to the cascade: nephron loss ☐ phosphate retention ☐ FGF23 ☐ ☐ 1α-hydroxylase suppression ☐ calcitriol ☐ ☐ intestinal Ca absorption ☐ ☐ hypocalcemia ☐ PTH ☐. This is secondary, not tertiary (which requires prior transplant). The mild hypocalcemia and markedly elevated PTH with low-normal calcitriol are classic.

Question 2: A dialysis patient presents with severe, burning pain in the feet and lower legs, out of proportion to visible skin findings, along with a livedoid rash that has progressed to necrotic ulcers over 2 weeks. Ca-Phos product is 78 mg^2/dL^2. What is the most likely diagnosis, and what is the first intervention?

A) Diabetic peripheral neuropathy; optimize glucose control
B) Calciphylaxis; aggressive phosphate control and discontinue warfarin
C) Critical limb ischemia from atherosclerosis; vascular surgery consult
D) Hyperkalemic periodic paralysis; dialysate potassium adjustment

Correct Answer: B Explanation: The clinical triad of **severe pain out of proportion, livedoid/necrotic skin findings, and elevated Ca-Phos product** is calciphylaxis. This is a vascular emergency requiring: (1) immediate phosphate binder escalation, (2) discontinuation of warfarin (which impairs MGP function, worsening calcification), (3) calcium normalization (low-calcium dialysate if needed), (4) pain control, and (5) consideration of IV sodium thiosulfate. Dialysis adequacy should also be optimized.

Question 3: A 62-year-old woman on hemodialysis (3x/week, 4-hour sessions) with underlying diabetic CKD is found to have hemoglobin 8.9 g/dL despite weekly darbepoetin alfa 60 μg. Ferritin is 340 ng/mL (high), but transferrin saturation is 18% (low). What is the BEST next step?

A) Increase darbepoetin to 80 μg (increase ESA dose for ESA resistance)
B) Transfuse 2 units PRBCs to target Hb 11 g/dL
C) Give 125 mg IV iron sucrose; recheck iron panel in 2 weeks
D) Start systemic corticosteroids to suppress hepcidin

Correct Answer: C Explanation: This patient has **functional iron deficiency** (high ferritin, low transferrin saturation), consistent with **hepcidin dysregulation in CKD**. Despite adequate iron stores (ferritin), the iron is "locked" in macrophages and cannot be mobilized effectively. IV iron (not oral) bypasses hepcidin-driven absorption block and improves erythropoietin responsiveness. Increasing ESA without correcting iron is futile. Transfusion risks iron overload and allosensitization. Corticosteroids are not standard (some experimental evidence for hepcidin suppression but not proven).

XII. References

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See Also

Related Student Handouts

- CKD Overview and Classification
- CKD Nutrition and Dietary Management
- Dialysis Fundamentals
- Calcium and Phosphorus Disorders
- Kidney Transplantation

Clinical Content (01-Clinical-Medicine/Nephrology)

- CKD Hub - Full Clinical Reference
- Hypertension Management in CKD
- Essential Renal Laboratory Tests

Butler-COM Resources

- Butler COM - Nephrology Deep Dive

End of Handout

Last updated: 2026-02-12 | For medical students and residents in nephrology and internal medicine

Clinical Resources

- Clinical Review: Comprehensive Nsaid Ckd Report — Comprehensive clinical review with PubMed references
- Clinical Review: Ckd Sacubitril Review — Comprehensive clinical review with PubMed references
- Clinical Review: Hypocalcemia Management Severe Ckd Clinical Report — Comprehensive clinical review with PubMed references
- Clinical Review: Ckd Protein Restriction Report — Comprehensive clinical review with PubMed references
- Clinical Review: Ckd — Comprehensive clinical review with PubMed references
- Clinical Review: Protein Restriction In Ckd Evidence Review — Comprehensive clinical review with PubMed references
- Clinical Review: Ckd Mbd Comprehensive Review — Comprehensive clinical review with PubMed references
- Clinical Review: Ckd Staging Classification Review — Comprehensive clinical review with PubMed references
- Clinical Review: Hypertesnive Nephropathy Cause Of Ckd — Comprehensive clinical review with PubMed references
- Clinical Review: Sglt2i Ckd Notes — Comprehensive clinical review with PubMed references