AJKD
Core Curriculum in Nephrology

CKD–Mineral and Bone Disorder: Core Curriculum 2011

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INTRODUCTION

Chronic kidney disease (CKD)–mineral and bone disorder (CKD-MBD) is a term that encompasses a constellation of abnormalities seen in progressive kidney disease that include altered levels of calcium, phosphorus, parathyroid hormone (PTH), and vitamin D; disturbances in bone modeling and remodeling, with the associated development of fractures or impaired linear bone growth (in children); and extraskeletal calcification in soft tissues and arteries. The kidney is responsible for maintenance of serum calcium and phosphorus levels within the normal range in people without kidney disease. In those with CKD stages 2 and 3, compensatory mechanisms in the form of elevated PTH, elevated fibroblast growth factor 23 (FGF-23), and decreased calcitriol levels result in normal to near-normal blood calcium and phosphorus levels. These compensatory mechanisms become overwhelmed in later stages of CKD, eventually failing and resulting in the group of abnormalities encompassed by CKD-MBD (Box 1).

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Box 1. Definition of CKD-MBD

A systemic disorder of mineral and bone metabolism due to CKD manifested by either one or a combination of the following:
- Abnormalities of calcium, phosphorus, PTH, or vitamin D metabolism
- Abnormalities in bone turnover, mineralization, volume, linear growth, or strength
- Vascular or other soft-tissue calcification

Abbreviations: CKD, chronic kidney disease; CKD-MBD, chronic kidney disease–mineral and bone disorder; PTH, parathyroid hormone.

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BIOCHEMICAL ABNORMALITIES OF CKD-MBD

Phosphorus

Physiologic Levels and Dietary Sources

- Serum phosphorus concentration reference range is 2.5-4.5 mg/dL; total-body stores of phosphorus equal 700 g
- Of total-body stores, 85% is in bone as hydroxyapatite; 14%, intracellular; and 1%, extracellular
  - Of extracellular phosphorus, 70% is within phospholipids (organic), 30% is inorganic
    - 15% of inorganic fraction is 15% protein bound
    - 85% of inorganic fraction is complexed with cations or circulating in free monohydrogen or dihydrogen forms
    - This 85% is the fraction measured in phosphorus assays and therefore not a reliable estimate of total-body phosphorus, especially in CKD
- Typical American diet contains about 1,000-1,400 mg/d of phosphorus; two-thirds excreted in urine, one-third excreted in stool
- Processed foods and foods rich in animal-based protein are high in phosphorus and thus it is difficult for patients with CKD to control serum phosphorus levels by diet alone while also eating the recommended amounts of protein
- 60%-70% of dietary phosphorus is absorbed in all intestinal segments
  - Dependent on luminal concentration

- Absorbed through sodium/phosphate cotransporter 2b (Npt2b)
- Stimulated by calcitriol

Renal Handling

- Inorganic phosphorus is filtered by glomeruli, then 70%-80% is reabsorbed in proximal tubule through the Npt2a cotransporter
- Npt2a is moved to or removed from the brush border to facilitate phosphorus reabsorption or excretion, respectively
- 20%-30% of filtered phosphorus is reabsorbed in distal tubule
- Renal phosphorus excretion is sensitive to serum phosphorus levels; PTH and FGF-23 increase phosphorus excretion
- Phosphorus depletion decreases its own excretion

Fibroblast Growth Factor 23

- Belongs to a group of molecules called phosphatonins
  - Phosphatonins are hormones that regulate phosphorus excretion
  - Three phosphatonins have been identified: sFRP-4, MEPE, and FGF-23 (the most studied)
- Produced almost exclusively in osteocytes and bone-lining cells, but also found in heart, liver, thyroid/parathyroid, intestine, and skeletal muscle
- FGF-23 receptor on the proximal tubule requires a coreceptor (klotho) for signal transduction
  - Klotho is found in the distal renal tubule and parathyroid gland
  - Klotho is downregulated in aging and CKD
- FGF-23 has the following actions
  - Downregulates luminal sodium/phosphate cotransporters in the proximal tubule, decreasing phosphorus reabsorption and therefore increasing its excretion
  - Inhibits 1α-hydroxylase (*CYP27B1*), decreasing the conversion of 25-hydroxyvitamin D (25[OH]D) to 1,25-dihydoxyvitamin D (1,25$[OH]_2D_3$; calcitriol)
  - Stimulates 24-hydroxylase (*CYP24*), leading to vitamin D degradation
  - Inhibits PTH secretion
- FGF-23 gene expression in bone is stimulated by elevated phosphorus, PTH, and calcitriol levels, even in uremic animals
- Local bone proteins also regulate synthesis
- Figure 1 shows the regulation of serum phosphorus levels by PTH and FGF-23
  - Both FGF-23 and PTH lead to increased phosphorus excretion
  - Regulatory feedback loops for both PTH and FGF-23 are dependent on calcitriol

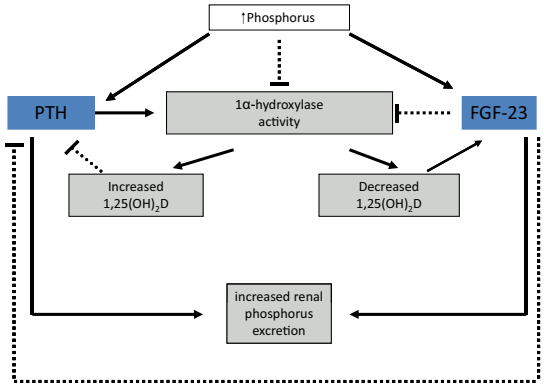

Figure 1. Regulation of serum phosphorus. A solid line indicates stimulation; a dashed line indicates inhibition. Abbreviations: 1,25$(OH)_2D_3$, calcitrol; FGF-23, fibroblast growth factor 23; PTH, parathyroid hormone. Adapted with permission of Elsevier from Moe SM, Sprague SM. Mineral bone disorders in chronic kidney disease. In: *Brenner and Rector's The Kidney.* 8th ed. Philadelphia, PA: WB Saunders Company; 2007:1784-1807.

  - PTH increases 1α-hydroxylase and therefore production of calcitriol, which in turn inhibits further PTH release
  - In contrast, FGF-23 inhibits 1α-hydroxylase and decreases calcitriol production, which will inhibit FGF-23 secretion
  - Hypocalcemia stimulates PTH and therefore in low-calcium high-phosphorus states, the action of PTH predominates
  - In high-calcium high-phosphorus states, the action of FGF-23 predominates

Phosphorus, FGF-23, and PTH in CKD

CKD and Phosphorus

- Phosphorus homeostatic control is impaired at a glomerular filtration rate (GFR) as high as 60 mL/min (well before frank hyperphosphatemia develops)
- As GFR decreases to <60 mL/min, there is a gradual increase in serum phosphorus levels
- During this period, "normal" phosphorus levels are maintained by continual increases in FGF-23 and PTH levels
- Eventually, this compensatory mechanism is overwhelmed when GFR decreases to <30 mL/min, and measured serum phosphorus levels may increase to higher than the reference range
- Hyperphosphatemia also leads to inhibition of calcitriol synthesis, which stimulates further PTH production; together, these processes trigger secondary hyperparathyroidism in CKD to develop
- Observational data suggest that hyperphosphatemia is connected to increased morbidity and mortality (all cause and cardiovascular) in CKD

- In different analyses of patients with CKD stage 5D, the phosphorus level associated with increased mortality varies from >5.5->7 mg/dL
- Even in the non-CKD population, serum phosphorus level in the high-normal ranges is associated with increased risk of cardiovascular and all-cause mortality
- No interventional study has shown that decreasing phosphorus to a certain "target" level is associated with better outcomes

CKD, FGF-23, and PTH

- In early CKD, FGF-23 levels start increasing
- This coincides with its effects on increasing phosphorus excretion, decreasing calcitriol synthesis (thereby stimulating PTH), and facilitating the development of secondary hyperparathyroidism
- In humans, FGF-23 and PTH levels appear to increase as GFR decreases
- Dialysis patients have FGF-23 levels that may be up to 1,000-fold greater than in non-CKD populations
- In dialysis patients, serum FGF-23 levels are associated with mortality even when adjusted for serum phosphorus levels and can predict the development of secondary hyperparathyroidism and responsiveness to calcitriol therapy

Calcium

Physiologic Levels and Dietary Sources

- Serum calcium levels are controlled tightly in the range of 8.5-10.5 mg/dL
- Total-body stores are ~1,000 g (99% in bone, 0.9% intracellular, and 0.1% extracellular)
- Extracellular calcium is measured as total calcium: 50% is free (the measured part), 10% is bound to anions, and 40% is bound to albumin
- Average dietary intake of calcium: 500-1,000 mg/d
- Calcium absorption occurs across intestinal epithelium through vitamin D–dependent TRPV5 and TRPV6 transporters, as well as paracellular pathways
- Bioavailability of calcium from foods is altered by phytate and oxalate
- Absorbed calcium enters 3 compartments: blood, soft tissue, and bone

Renal Handling

- Reabsorption
  - 60%-70% is reabsorbed passively in proximal tubules with sodium and water reabsorption
  - 10% is reabsorbed in the thick ascending limb by the paracellular route
  - The rest is reabsorbed through transcellular pathways in the distal convoluted tubule, connecting tubule, and cortical collecting duct through TRPV5 and TRPV6 calcium channels
  - TRPV6 predominates in the intestine, whereas TRPV5 predominates in the kidney
- Calcium-sensing receptor (CaSR)
  - G-protein–coupled protein that binds calcium to sense small changes in ionized calcium levels; decreased ionized calcium stimulates PTH secretion
  - CaSR is expressed in parathyroid cells, thyroid C cells, intestine, kidney, and likely bone
  - In the kidney, CaSR is in mesangial cells and throughout tubules
    - Activation of CaSR on the thick ascending limb decreases paracellular calcium reabsorption
    - Upregulation of CaSR in hypercalcemia inhibits antidiuretic hormone (ADH)-induced free water reabsorption, leading to urinary dilution
    - Renal effects of CaSR are both dependent and independent of PTH

Calcium Abnormalities in CKD

- In CKD stages 2-3, serum calcium levels are maintained in the reference range at the cost of secondary elevations in PTH levels
- Intestinal calcium absorption is impaired in CKD due to decreased calcitriol levels, but still proportional to calcium intake
- Urinary calcium excretion decreases as CKD progresses due to PTH-associated increased reabsorption and decreased filtered fraction of calcium
- In CKD, intestinal absorption is not equal to urinary excretion
- In CKD, the ability of bone to take up calcium depends on bone turnover
- Patients with lower bone turnover (adynamic bone and mixed uremic osteodystrophy) are less able to take up calcium
- When tubular excretion of calcium is decreased, these patients have a net positive calcium balance
- Given a net positive calcium balance in late CKD, KDOQI (Kidney Disease Outcomes Quality Initiative) guidelines recommend maximum total elemental calcium intake of 2 g/d (1.5 g from phosphate binder + 500 mg of dietary calcium)
- In patients with adynamic bone in whom calcium may be deposited in extracellular sites instead of being taken up by bone, it may be prudent to avoid calcium-based phosphate binders altogether, although there is no definitive evidence for this
- KDIGO (Kidney Disease: Improving Global Outcomes) guidelines also recommend limiting calcium-

Box 2. Vitamin D Nomenclature Used by the KDIGO Work Group

Vitamin D: cholecalciferol and/or ergocalciferol
25-Hydroxyvitamin D: the 25-hydroxylated metabolites of vitamin D; also known as ercalcidiol or calcidiol; abbreviated as 25(OH)D
Calcitriol: 1,25-dihydroxycholecalciferol; abbreviated as $1,25(OH)_2D_3$
Vitamin D analogs: derivatives of vitamin D_2 and vitamin D_3, of which the clinically investigated synthetic derivatives include doxercalciferol, paricalcitol, alfacalcidol, falecalcitriol, and 22-oxacalcitriol (maxacalcitol)

Abbreviation: KDIGO, Kidney Disease: Improving Global Outcomes.
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based phosphate binders in this setting, but no absolute limit is given due to the lack of hard data
- Observational studies in dialysis patients show an increase in risk of all-cause mortality with high serum calcium levels
  - Levels at which this becomes significant vary in different analyses from >9.5->11.4 mg/dL
  - There are no studies that have treated patients to different calcium levels to determine mortality benefit

Vitamin D

Sources and Role

- Cholesterol is converted to 7-dehydrocholesterol, which in the presence of sunlight is converted to vitamin D_3 (cholecalciferol; nomenclature of vitamin D compounds listed in Box 2)
- Vitamin D_2 (ergocalciferol) is obtained from dietary sources
- D_2 and D_3 are hydroxylated by CYP27A1 in the liver to $25(OH)D_2$ (ercalcidiol) and $25(OH)D_3$ (calcidiol), together termed 25(OH)D
- Ercalcidiol and calcidiol have a half life of ~3 weeks and are the best assessment of vitamin D intake from sun and food
- 25(OH)D is converted by 1α-hydroxylase in the kidney to calcitriol (1,25-dihydroxycholecalciferol, or $1,25[OH]_2D_3$; Fig 2)
- $1,25(OH)_2D_3$ actions:
  - Increase TRPV5 and TRPV6, the calcium adenosine triphosphatase and sodium/calcium transporters in the intestine and kidney
  - This increases oral calcium absorption and calcium reabsorption in renal tubules
  - Decreases PTH synthesis by binding to the vitamin D receptor in the parathyroid gland, inhibiting PTH gene expression, and decreasing PTH cell proliferation

Recommended Levels and Health Effects

- In many studies, 25(OH)D deficiency is defined as <10 ng/mL, and insufficiency, as ≥10 ng/mL, but <20-32 ng/mL
- The Institute of Medicine (IOM) published a report on vitamin D in 2010

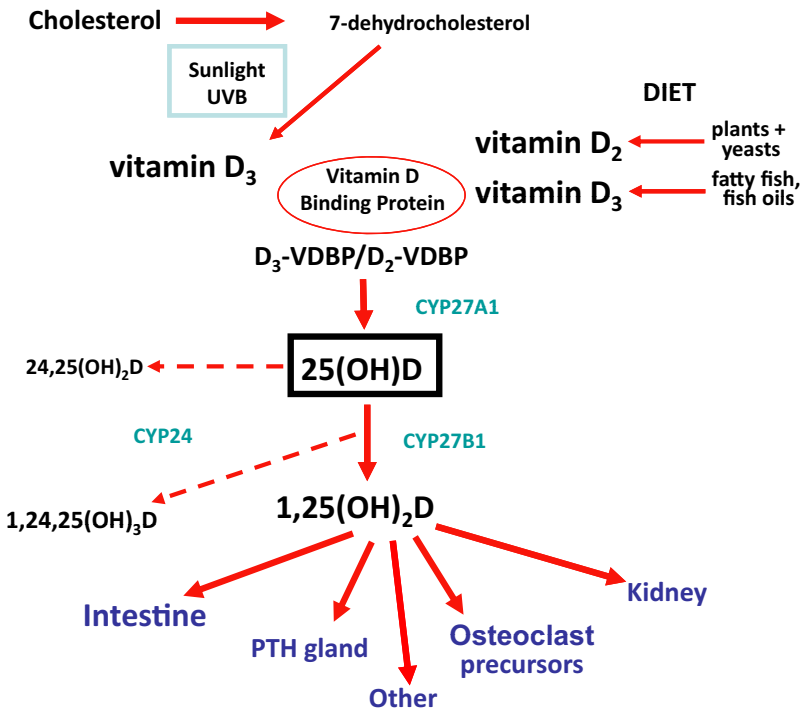

Figure 2. Overview of vitamin D metabolism. Abbreviations: $24,25(OH)_2D$, 24,25 dihydroxyvitamin D; 25(OH)D, vitamin D; 1,24, $25(OH)_3D$, 1,24,25 trihydroxycholecalciferol; $1,25(OH)_2D$, 1,25 dihydroxycholecalciferol; PTH, parathyroid hormone; VDBP, vitamin D binding protein. Adapted with permission of Elsevier from Moe SM, Sprague SM. Mineral bone disorders in chronic kidney disease. In: *Brenner and Rector's The Kidney*. 8th ed. Philadelphia, PA: WB Saunders Company; 2007:1784-1807.

- Key conclusion: "While the average total intake of vitamin D is below the median requirement, national surveys show that average blood levels of vitamin D are above the 20 nanograms per milliliter that the IOM committee found to be the level that is needed for good bone health for practically all individuals"
- Recommends daily dietary intake of 600 IU/d (800 IU/d for those >70 years); maximum daily intake is 4,000 IU

- 25(OH)D is thought to have a multitude of effects on the immune system, muscle activity, and endothelial function
  - Falls, cancers, immune diseases, and mortality in the general population have all been associated with low vitamin D levels
  - In the general population, vitamin D supplementation may reduce the risk of cancers
  - Nevertheless, the IOM 2010 report notes that vitamin D's effects outside of bone health are not yet reliably studied and there are no definitive randomized controlled trials (RCTs)

Vitamin D and CKD

- In observational studies of CKD, low 25(OH)D level has been associated with progression to dialysis therapy, cardiovascular events, and mortality
- However, no study has shown a clinical benefit of treating patients with CKD to a specific vitamin D level
- Many patients with CKD have decreased $1,25(OH)_2D$ levels
- Reduced phosphorus excretion leads to an increase in serum phosphorus and FGF-23 levels, which suppress 1α-hydroxylase activity and thereby decrease $1,25(OH)_2D$ levels
- Lower $1,25(OH)_2D$ levels decrease intestinal calcium absorption, and the lower serum calcium level stimulates PTH release, which restores $1,25(OH)_2D$ levels (providing kidney function is still adequate) and increases phosphorus excretion
- As CKD progresses, these compensatory mechanisms fail (see Fig 1)
- KDIGO guideline recommendations
  - 25(OH)D levels should be measured at baseline in patients with CKD and then further testing as needed, individualized based on replacement or treatment
  - Deficiency and insufficiency are to be corrected using treatment strategies recommended for the general population

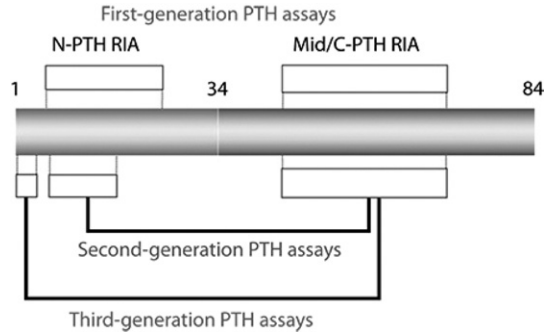

Figure 3. Assays for parathyroid hormone (PTH). The intact PTH molecule is composed of 84 amino acids; different regions of the protein are targeted by first- through third-generation assays. Abbreviations: Mid/C-PTH, mid/carboxyl terminus of PTH; N-PTH, amino terminus of PTH; RIA, radioimmunoassay. Reproduced with permission of Elsevier from Moe SM, Sprague SM. Mineral bone disorders in chronic kidney disease. In: *Brenner and Rector's The Kidney.* 8th ed. Philadelphia, PA: WB Saunders Company; 2007:1784-1807.

- $1,25(OH)_2D$ levels in CKD are variable depending on whether calcitriol or one of its analogues is administered because paricalcitol can suppress levels
- It is not recommended that $1,25(OH)D_3$ levels be measured routinely

Parathyroid Hormone

Physiologic Role

- PTH is secreted by the parathyroid glands in response to hypocalcemia, hyperphosphatemia, and/or calcitriol deficiency
- Minute-to-minute concentrations of PTH are most sensitive to low ionized calcium concentrations
- The sensitivity of this response may be blunted in the presence of hyperphosphatemia in CKD

Intact PTH

- This 84–amino acid protein is cleaved from pre-pro PTH in the parathyroid gland
- Intact PTH (iPTH) has a short half-life (2-4 minutes)
- Cleaved into amino-terminal, carboxy-terminal, and midlength fragments, which are metabolized in the liver and kidney
- Amino-terminal fragments remain active; carboxy-terminal fragments accumulate in CKD

PTH Assays

- First-generation assays (Fig 3)
  - Radioimmunoassays using an antibody against the midregion or carboxy-terminal end
  - Detects full-length PTH and the multiple carboxy- and amino-terminal fragments
  - Unreliable

- Second-generation assay/iPTH assays/2-step first-generation immunoradiometric assays (IRMAs)
  - Involve 2 antibodies, one that detects the amino terminus and the other detects the carboxy terminus
  - Most commonly used assay in clinical practice
  - However, in addition to detecting full-length PTH, it also detects fragments commonly referred to as 7-84 PTH
  - This 7-84 PTH may have effects antagonistic to full-length PTH on bone
- Third-generation assays/whole PTH assays/biointact PTH assays detect only 1-84 PTH
- Poor correlation between any of the PTH assays and bone histology in CKD
  - Likely because a single-time-point PTH level may not correlate with bone remodeling, which occurs over several months
  - Also, significant assay-to-assay variability exists, even in the same individual

Pathophysiologic Characteristics

- PTH is associated significantly with mortality in observational studies at levels varying from >400->600 pg/mL, depending on the population analyzed
- There are inconsistent data for the underlying bone histology by biopsy in dialysis patients for whom PTH levels were maintained in the range of 150-300 pg/mL recommended by KDOQI guidelines
- Given these issues, recent KDIGO guidelines recommend extremes of risk for PTH at less than 2 times the lower-limit and greater than 9 times the upper-limit values of the specific assay used
  - However, trends of PTH levels within that range should be evaluated and medications should be adjusted as needed

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BONE DISEASE IN CKD

Bone Biology

- Cancellous bone is present in the epiphyses, and cortical bone, in the shafts of long bones
- Bone consists of crosslinked type 1 collagen fibers (90%) and proteoglycans, osteopontin, osteocalcin, osteonectin, and other noncollagenous proteins
- Cells in bone are cartilage cells, osteoblasts, and osteoclasts
- Mesenchymal cells in bone marrow are differentiated to form osteoprogenitor cells and eventually mature osteoblasts
- After bone formation, osteoblasts may undergo apoptosis or become a part of mineralized bone as osteocytes
- Osteoclasts are formed from hematopoietic cells, fusing at bone to become multinucleated cells that reabsorb bone using enzymes
- At any time, <20% of bone surface undergoes remodeling, a process that takes 3-6 months
- Phases of bone remodeling are osteoclast resorption, reversal, maturation of osteoblasts, filling of lacunae with osteoid or unmineralized bone, mineralization, and finally a quiescent stage
- Bones are chosen to undergo remodeling through the osteoprotegerin (OPG) and the RANK (receptor activator of nuclear factor-κB) system regulated by hormones (PTH, calcitriol, estrogen, and glucocorticoids, as well as cytokines and interleukins)

Renal Osteodystrophy

- The term is specific to bone pathologic states in patients with CKD and is a component of CKD-MBD
- Renal osteodystrophy is assessed by bone biopsy at the trabecular bone at iliac crest

- Patients are given tetracycline 3 weeks and 3-5 days before bone biopsy
- Tetracycline binds to hydroxyapatite and labels bone for visualization by fluorescence microscopy
- The amount of bone formed between the 2 tetracycline labels is used to calculate bone turnover
- Three key parameters are used to assess bone (turnover, mineralization, and volume; TMV system) and replace the terms adynamic bone, mild hyperparathyroidism, osteitis fibrosa, mixed uremic osteodystrophy, and osteomalacia (Fig 4)

- Biomarkers such as PTH and bone alkaline phosphatase are only modestly predictive of underlying bone histology, but currently are the best available noninvasive tools for the assessment of renal osteodystrophy
- Overall, impaired bone quality (altered architecture, remodeling, mass, and volume) is seen in CKD
  - This can be superimposed on pre-existing age-related changes in bone, such as loss of bone mass due to osteoporosis
  - This translates to an increased prevalence of fractures in dialysis patients compared with age-matched general population

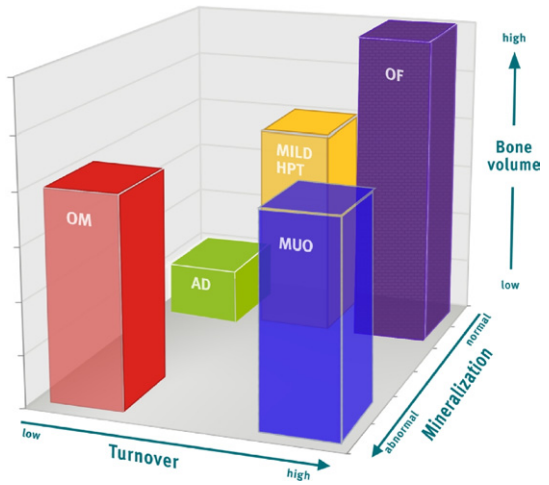

Figure 4. Turnover mineralization volume (TMV) classification system for bone histomorphometry. The TMV system provides more information than the previously used classification scheme. Each axis represents one of the descriptors in the TMV classification: turnover (from low to high), mineralization (from normal to abnormal), and bone volume (from low to high). Individual patient parameters can be plotted on the graph, or mean values and ranges of grouped data can be shown. For example, many patients with renal osteodystrophy cluster in areas shown by the bars. The red bar (osteomalacia [OM]) previously was described as low-turnover bone with abnormal mineralization. Bone volume may be low to medium, depending on the severity and duration of the process and other factors that affect bone. The green bar (adynamic bone disease [AD]) previously was described as low-turnover bone with normal mineralization, and bone volume in this example is at the lower end of the spectrum, but other patients with normal mineralization and low turnover will have normal bone volume. The yellow bar (mild hyperparathyroid-related bone disease [HPT]) and purple bar (osteitis fibrosa [OF], or advanced hyperparathyroid-related bone disease) previously were considered distinct categories, but in actuality represent a range of abnormalities along a continuum of medium to high turnover and any bone volume depending on the duration of the disease process. Finally, the blue bar (mixed uremic osteodystrophy [MUO]) is variably defined internationally. In the present graph, it is shown as high-turnover, normal bone volume, with abnormal mineralization. In summary, the TMV classification system more precisely describes the range of pathologic abnormalities that can occur in patients with chronic kidney disease. Reproduced with permission of Nature Publishing Group from Figure 1 in Moe et al. *Kidney Int.* 2006;69(11):1945-1953.

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VASCULAR CALCIFICATION IN CKD

Background

- Extraskeletal calcification is highly prevalent in CKD
- Vascular calcification prevalence in dialysis patients ranges from 50%-90% in more than 20 studies that have addressed this using different modalities and is even present in children on dialysis therapy
- Vascular calcification appears to start early in CKD and >50% of patients initiated on hemodialysis (HD) therapy already have evidence of coronary artery calcification (CAC)
- Age and dialysis vintage are consistently associated with CAC
- Use of calcium-based phosphate binders and elevated phosphorus levels are risk factors in some studies
- Two types of vascular calcification
  - Intimal calcification leads to calcific plaques or circumferentially calcified atherosclerosis
  - Medial calcification is nonocclusive and leads to vascular stiffening; it can cause local ischemia and also affect the capacity of the vasculature to dampen increases in arterial pressure with each ventricular systole, leading to left ventricular hypertrophy

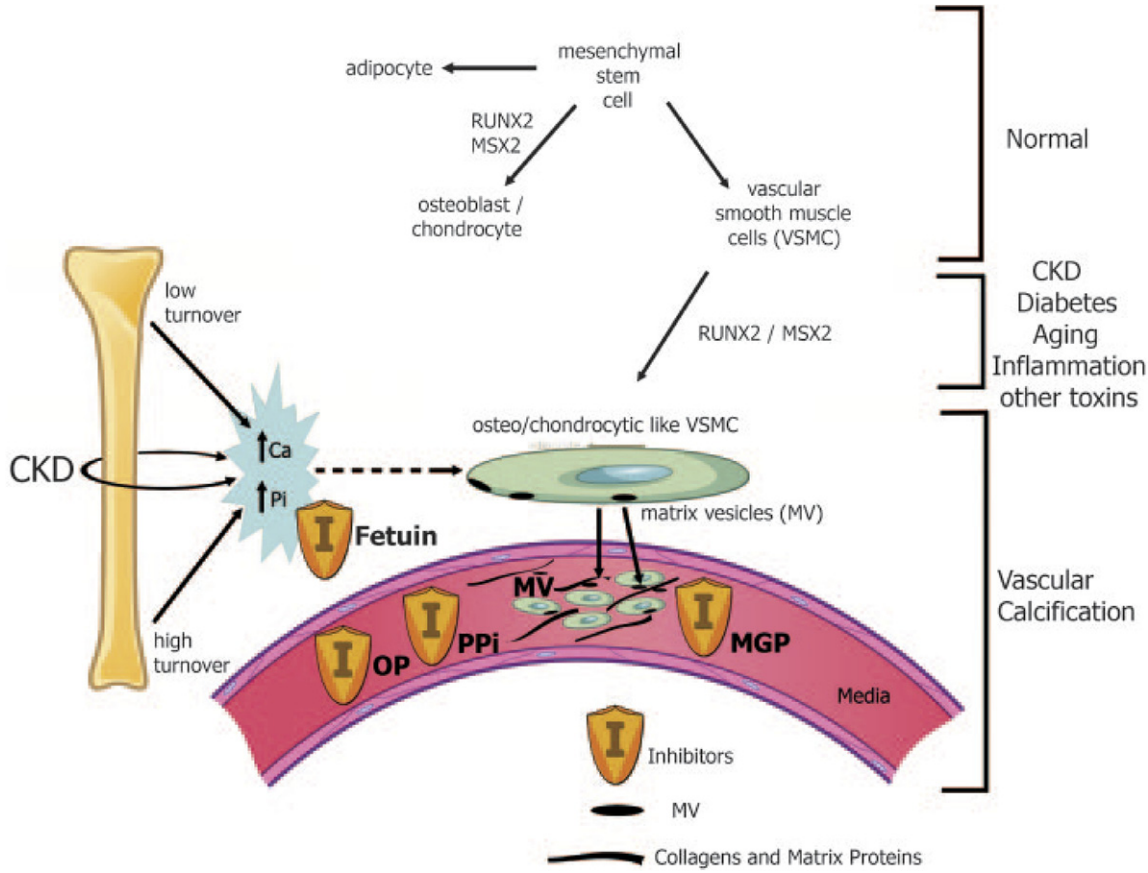

Figure 5. Pathogenesis of vascular calcification. Normally, mesenchymal stem cells differentiate to adipocytes, osteoblasts, chondrocytes, and vascular smooth muscle cells (VSMCs). In the setting of chronic kidney disease (CKD), diabetes, aging, inflammation, and multiple other toxins, these VSMCs can dedifferentiate or transform into osteo/chondrocytic-like cells by upregulation of transcription factors such as RUNX-2 and MSX2. These transcription factors are critical for normal bone development and thus their upregulation in VSMCs is indicative of a phenotypic switch. These osteo/chondrocytic-like VSMCs then become calcified in a process similar to bone formation. These cells lay down collagen and noncollagenous proteins in the intima or media and incorporate calcium and phosphorus into matrix vesicles to initiate mineralization and further mineralize into hydroxyapatite. The overall positive calcium and phosphorus balance of most dialysis patients feeds both the cellular transformation and the generation of matrix vesicles. In addition, the extremes of bone turnover in CKD (low and high or adynamic and hyperparathyroid bone, respectively) will increase the available calcium and phosphorus by altering the bone content of these minerals. Ultimately, whether an artery calcifies depends on the strength of the army of inhibitors standing by in the circulation (fetuin A) and arteries (PPI, pyrophosphate; MGP, matrix Gla protein; OP, osteopontin as examples). Reproduced with permission of the American Society of Nephrology from Figure 1 in Moe et al. *J Am Soc Nephrol.* 2008;19:213-216.

- Traditionally, the CAC score obtained by electron beam computed tomography (CT) is used to quantify calcification burden
- Other available techniques can provide semiquantitative evidence of calcification, including duplex ultrasonography, echocardiography, pulse wave velocity, and even plain radiographs
- A study of these techniques showed good correlation between lateral abdominal aortic radiographs and electron beam CT in quantifying calcification

Pathogenesis of Vascular Calcification

- Features a phenotypic switch in which vascular smooth muscle cells (VSMCs) dedifferentiate to osteo/chondrocytic-like cells (Fig 5)
  - Switch associated with upregulation of transcription factors such as RUNX-2 and MSX-2
  - The most important stimulus appears to be hyperphosphatemia, but other uremic factors, such as inflammation, cytokines, oxidative stress, and advanced glycation end products, also can enhance this transformation
  - Osteo/chondrocytic-like cells lay down collagen and noncollagenous proteins (extracellular matrix) in the intima or media
  - Calcium and phosphorus are incorporated into matrix vesicles to initiate mineralization in the form of hydroxyapatite
- When the balance favors promineralizing factors (eg, elevations in calcium and phosphorus) over inhibitors of calcification (eg, fetuin A, matrix GLA protein, osteopontin, and pyrophosphate), calcification occurs

  - Levels of calcium and phosphorus are influenced by bone status in a particular individual; the extent of bone turnover alters the release of these minerals from bone
  - Patients with CKD who have low-turnover bone disease appear to have the greatest risk of vascular calcification
  - It is likely that adynamic bone is not able to take up high calcium loads and this excess calcium may become deposited in the vasculature
- Observational studies have shown increased CAC and valvular calcification to be associated with increased mortality in patients with CKD
- Calcification of large peripheral arteries also is associated with increased pulse wave velocity, pressure, and mortality

Calciphylaxis

- Also called "calcific uremic arteriolopathy"; type of soft-tissue/medial calcification in small skin arterioles leading to tissue ischemia and ulceration
- Debilitating, with mortality rates as high as 80%
- Risk factors: hyperphosphatemia, obesity, female sex, dialysis vintage, warfarin use, and hypoalbuminemia
- Potential treatments: parathyroidectomy, cessation of calcium-containing phosphate-binder use, frequent dialysis, hyperbaric oxygen therapy, use of bisphosphonates or calcimimetics, and use of sodium thiosulfate
  - No randomized trials have been performed for any of the potential treatments
  - A recent case series of 6 patients treated with sodium thiosulfate showed that the 2 responders who survived at 1 year of follow-up improved with respect to pain, wound size, and imaging
  - A systematic review of sodium thiosulfate in 14 dialysis patients showed decreased pain and improvement in skin lesions, although the mortality rate was unchanged at 70%

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CKD–MINERAL AND BONE DISORDER

Definition

- Patients with CKD have biochemical abnormalities of calcium, phosphorus, vitamin D, and PTH; bone changes associated with these abnormalities; and extraskeletal calcification
- These 3 interrelated processes account for morbidity and mortality in CKD and together are called CKD-MBD

Management

- KDOQI bone and mineral guidelines published in 2003 were based largely on opinion of the work group members due to lack of strong evidence in the field
- KDIGO guidelines were published in 2009 after a rigorous evidence review process based on the internationally used GRADE (Grades of Recommendation, Assessment, Development and Evaluation) criteria
  - There was a lack of high-quality evidence (RCTs) for patient-level outcomes for treatments
  - Hence, most guideline recommendations were weak in strength (Table 1)

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Table 1. Recommendations for Ranges of Mineral Metabolism Parameters in CKD

	CKD Stage 3	CKD Stage 4/5	CKD Stage 5D
Phosphorus	Maintain in "normal" range (2C)	Maintain in "normal" range (2C)	Decrease toward the "normal" range (2C)
Calcium	Maintain in "normal" range (2C)	Maintain in "normal" range (2C)	Maintain in "normal" range (2C)
Intact PTH	Ideal level unknown	Ideal level unknown	Maintain within >2 and <9× the upper limit of normal (if there is a trend changing within that range, adjust prescription) (2C)

Note: Grades are given in parentheses (number refers to strength of recommendation; level 1 is strong and level 2 is weak; letter refers to quality of evidence; A is high, B is moderate, C is low, and D is very low).

Abbreviations: CKD, chronic kidney disease; CKD stage 5D, dialysis-dependent chronic kidney disease stage 5; KDIGO, Kidney Disease: Improving Global Outcomes; PTH, parathyroid hormone.

Based on the *KDIGO Clinical Practice Guideline for the Diagnosis, Evaluation, Prevention, and Treatment of Chronic Kidney Disease-Mineral and Bone Disorder* (*Kidney Int.* 2009;76[suppl 113]).

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CONTROL OF HYPERPHOSPHATEMIA

Hyperphosphatemia is associated with poor cardiovascular outcomes, mortality, secondary hyperparathyroidism, and extraskeletal calcification. Although the benefits of treating to certain target phosphorus levels have not been proved in RCTs, the KDIGO guidelines suggested that it is reasonable to treat hyperphosphatemia in patients with CKD (Table 1). Currently available modalities for normalizing phosphorus levels include restriction of dietary phosphorus, use of phosphorus binders, and attempts to increase phosphorus removal in dialysis.

Diet

- Dietary phosphorus restriction to 800-1000 mg/d is recommended
- Difficult to maintain this and consume adequate protein because most foods high in protein tend to be high in phosphorus
- Foods with a low phosphorus to protein ratio need to be encouraged and formal dietary counseling may be required to achieve this
  - Plant-based foods tend be low in phosphorus to protein ratio
  - Additionally, phosphorus in plant-based foods is bound to phytate and may be less bioavailable because humans lack the enzymes required to break the phosphorus-phytate bond
- Preservatives present in many fast foods and processed foods tend to be high in phosphorus
- Currently, the US Food and Drug Administration (FDA) does not mandate the reporting of phosphorus content on food labels, making it challenging to counsel patients

Phosphate Binders

Background

- Dietary restriction often is insufficient to control elevated phosphorus levels in CKD; the next step includes the use of phosphate binders
- An ideal binder should be minimally absorbed in the gut, have no side effects, and be effective in binding phosphorus at the lowest dose
- Use of aluminum-based binders is now minimized in CKD due to evidence showing their toxicity in the form of osteomalacia, anemia, and dialysis encephalopathy
- Magnesium carbonate and hydroxide have not been studied well, but there is the risk of magnesium toxicity in patients with CKD; currently not widely used or recommended due to lack of long-term studies
- Types of phosphorus binders in common use include calcium-based binders (calcium carbonate or acetate), anion-exchange resins (eg, sevelamer hydrochloride and sevelamer carbonate), and lanthanum carbonate; other binders are in development

Calcium-Based Binders

- Commonly used forms are calcium acetate (25% elemental calcium: 169 mg of calcium/667-mg capsule) and calcium carbonate (40% elemental calcium: 200 mg of elemental calcium/500 mg of calcium carbonate)
- No studies have examined calcium-based binders versus placebo or compared the 2 forms of calcium-based binders with extraskeletal calcification or patient-centered outcomes, such as mortality, fractures, and hospitalizations
- Both formulations have the potential to cause hypercalcemia as a side effect, but a meta-analysis showed that calcium acetate may be less likely to do so

- Gastrointestinal (GI) intolerance, notably constipation, may be a limiting side effect

Non–Calcium-Based Binders

- Sevelamer
  - Previously formulated as sevelamer hydrochloride, but now marketed as sevelamer carbonate
  - Side effects include GI intolerance
  - May also decrease low-density lipoprotein (LDL) cholesterol levels
  - Most trials were performed using the hydrochloride salt
- Lanthanum carbonate
  - Chewable; poorly, although not incompletely, absorbed; and cleared primarily by the liver
  - Initial concerns included toxicity similar to that of aluminum; however, no liver toxicity, changes in cognition, or bone marrow suppression have been noted in studies of humans
  - No increased risk of osteomalacia has been noted in studies of humans

Calcium- Versus Non–Calcium-Based Binders

- Two studies have examined the effect of calcium-based binders versus sevelamer on mortality:
  - DCOR (Dialysis Clinical Outcomes Revisited) Study
    - 2,103 prevalent HD patients randomly assigned to sevelamer or a calcium-based binder (70% acetate and 30% carbonate forms)
    - Primary outcome of all-cause or cause-specific mortality was not different between the 2 arms
    - However, there was a significant dropout rate of ~50% in both arms, with only 1,068 patients completing the study
    - When dialysis records were used to determine end points, a subgroup analysis of participants older than 65 years did show a survival advantage for sevelamer
    - However, another analysis that used Medicare claims to determine end points did not show a mortality benefit in this group
    - Analysis of Medicare claims also showed that all-cause hospitalizations were lower for sevelamer participants
  - RIND (Renagel in New Dialysis) Study
    - Randomly assigned 148 incident HD patients to sevelamer hydrochloride or calcium-based binder
    - Showed an adjusted increased mortality in the calcium-based-binder arm (hazard ratio, 3.1; $P = 0.016$)
- Therefore, it is unclear at this time whether there is a mortality benefit of sevelamer compared with calcium-based binders
- There are no studies comparing the effect of calcium-based binders versus lanthanum or any of the other non–calcium-, non–sevelamer-based binders with patient-centered outcomes
- There are inconsistent data for the beneficial effect of sevelamer compared with calcium-based binders on vascular calcification, as shown in the following RCTs
  - A study of low-phosphorus diet versus low-phosphorus diet plus calcium carbonate versus low-phosphorus diet plus sevelamer in 90 predialysis patients showed no progression of calcification in the diet-plus-sevelamer group, although calcification progressed in the other 2 groups
  - TTG (Treat to Goal) Study assessed the progression of calcification in 200 HD patients randomly assigned to sevelamer or calcium-based binders; showed absolute increases in CAC score in the calcium-treated arm, but not the sevelamer arm
  - RIND Study also showed a significant increase in calcification in the calcium-based binder arm at 18 months compared with sevelamer
  - CARE-2 (Calcium Acetate Renagel Comparison) Study of long-term dialysis patients in the United States randomly assigned to calcium acetate plus atorvastatin versus sevalamer plus a statin if needed to achieve LDL cholesterol level of 70 mg/dL showed no difference in the progression of arterial calcification and similar lipid profiles in both arms
  - BRIC (Bone Remodeling and Coronary Calcification) Study (calcium acetate vs sevelamer in 101 Brazilian dialysis patients) showed that the annual rate of CAC progression was not different between calcium-based binders and sevelamer; however, this study allowed multiple medication and dialysate calcium changes based on baseline bone biopsy studies and thus was subject to considerable bias
- Effect on bone of calcium-based binders versus sevelamer
  - BRIC Study showed no significant changes in the 2 arms in turnover mineralization or bone volume
  - Another RCT of 119 HD patients randomly assigned to sevelamer or calcium carbonate showed no changes in mineralization or volume at 1 year, but showed an increase in bone turnover in the sevelamer arm
- Effect on bone of calcium-based binders versus lanthanum

  - RCT of 1 year of treatment favored lanthanum carbonate over calcium-based binders
  - RCT of 65 patients showed an improvement in turnover and volume, but worsened mineralization in lanthanum arm
  - RCT of 20 participants showed that no patient receiving lanthanum developed low turnover compared with 3 patients developing low-turnover bone in the calcium arm
  - Therefore, bone changes in response to binder therapy are not consistent and are dependent on the individual patient and initial bone status
- In summary, there are limited data to suggest the use of 1 type of binder over another; however, in the presence of arterial calcification or adynamic bone disease, it is prudent to restrict the dose of calcium-based binders until more conclusive data are available
- In the KDOQI guidelines, the maximal dose of elemental calcium was recommended at 1,500 mg/d, with total calcium intake from diet plus binders recommended not to exceed 2,000 mg/d
- KDIGO guidelines recommend avoidance of calcium-based binders if there is arterial calcification, PTH level is persistently low, or with persistent or recurrent hypercalcemia; no daily ceiling was given due to the lack of balance studies

Clearance of Phosphorus in Dialysis

- Patients receiving nocturnal HD remove twice the amount of phosphorus per week compared with those on thrice-weekly intermittent HD
- Intermittent HD removes 1,000 mg of phosphorus per session, and because 1,000 mg also is absorbed each day, net phosphorus balance is about 4,000 mg/wk
- An RCT of 51 patients randomly assigned to 6-times-weekly nocturnal HD versus thrice-weekly intermittent HD showed significant and sustained decreases in serum phosphorus levels over a 6-month period
  - Also noted was a significant rate of discontinuation or lowering of phosphorus-binder dose in the nocturnal HD group
  - No significant difference in PTH levels between groups
- A frequent dialysis study that randomly assigned 245 patients to daily versus thrice-weekly dialysis found a decrease in serum phosphorus levels in the frequent-HD group ($P = 0.002$)
- With the increasing popularity of nonconventional HD modalities, increased clearance of phosphorus by this route might complement diet and binder therapies; further studies are needed to provide more evidence for this

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CONTROL OF PTH

Rationale

- Observational studies of CKD stages 3-5D show an association between PTH levels at extremes (<2 and >9 times the assay reference limits) and mortality
- Similar to phosphorus, there are no mortality studies that have randomly assigned patients to different PTH level cutoffs
- An ideal PTH level would be correlated with a normal bone formation rate, but current assays of PTH are poorly correlated with bone formation rates
- Therefore, KDIGO guidelines recommend "maintaining iPTH in the range of approximately 2-9 times limits for the assay"
- Marked changes in PTH levels within that range also should be treated
- Measures available for this include oral calcium, vitamin D, calcitriol, 1,25(OH)D_2 analogues, calcimimetics, and parathyroidectomy

Treatment of Elevated PTH in CKD Stages 3-4

- PTH level increases as an adaptive response to hyperphosphatemia; in individual patients, this becomes maladaptive at a certain point and treatments for elevated PTH levels should be individualized and based on trends
- KDIGO guidelines recommend correcting modifiable factors: treating hypocalcemia, elevated phosphorus levels, and vitamin D deficiency to attempt to reverse progressive hyperparathyroidism, however, there is a paucity of evidence to support this at the present time
- Oral calcium has been used to suppress PTH in CKD stages 3-4; however, its effects on arterial calcification are unclear
- Treating hyperphosphatemia to decrease PTH levels seems important physiologically, but again, has not been well studied
- An 8-week trial of lanthanum carbonate versus placebo in CKD stages 3-4 found a decrease in PTH levels
- 25(OH)D likely decreases but may not normalize PTH levels in CKD stages 3-5
- Use of 25(OH)D to suppress PTH was studied retrospectively (meta-analysis) in 322 patients with CKD and found to decrease PTH levels when given in conjunction with calcium
- In patients with CKD stages 3 and 4 with low 25(OH)D levels (<30 ng/mL), using ergocalciferol showed significant decreases in PTH levels in CKD stage 3; however, an RCT of 20 patients with CKD showed no significant effect of 25(OH)D therapy on PTH levels
- KDIGO guidelines recommend that if PTH levels continue to increase in CKD stages 3-4, calcitriol or other vitamin D analogues may be used to suppress PTH
- Role of vitamin D analogues in treating elevated PTH levels in non–dialysis-dependent patients with CKD
  - Four placebo-controlled RCTs of various vitamin D analogues (doxercalciferol, paricalcitol, alfacalcidol, and calcitriol) all showed efficacy for PTH lowering compared with placebo
  - No RCTs using vitamin D analogues in pre-HD CKD address patient-level outcomes (mortality, hospitalizations, fractures, parathyroidectomy, and quality of life) or vascular calcification
  - Two studies have shown improvement in bone turnover with vitamin D analogues compared with placebo
  - Observational studies have shown a lower risk of progression to end-stage renal disease (ESRD) and death in patients with CKD stages 3-4 using a vitamin D analogue, although no prospective studies have examined this
- Theoretically, it may be beneficial to correct both vitamin D deficiency and calcitriol deficiency, but no studies have been performed to assess this
- Calcimimetics also decrease PTH levels compared with placebo in CKD stages 3-4, but with a significant risk of hyperphosphatemia
- Given this risk, further studies need to be performed before this can be recommended

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CALCITRIOL AND VITAMIN D ANALOGUES FOR TREATING ELEVATED PTH IN CKD STAGE 5D

- Vitamin D analogues and calcitriol traditionally are used for their PTH-lowering effects and are effective in patients receiving dialysis
- Retrospective data from multiple analyses show survival benefits in patients receiving any vitamin D analogue
- One study showed a survival benefit of paricalcitol compared with calcitriol, but another study showed no benefit of either paricalcitol or doxercalciferol over calcitriol
- These studies are all retrospective and have not been confirmed in prospective analyses
- Paricalcitol was observed to lead to less sustained hypercalcemia than calcitriol in a secondary analysis of an RCT, although there was no difference in number of patients who had one episode of hypercalcemia
- No head-to-head comparison of doxercalciferol, paricalcitol, or calcitriol has evaluated vascular calcification or patient-related end points
- Therefore, the KDIGO guidelines do not recommend one vitamin D analogue over another or over calcitriol at this point

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CALCIMIMETICS FOR TREATING ELEVATED PTH IN CKD STAGE 5D

- Calcimimetics are allosteric activators of the extracellular CaSR, sensitizing the parathyroid gland to extracellular calcium
  - This decreases PTH release from the parathyroid
  - These actions are independent of vitamin D
- Cinacalcet is the only FDA-approved calcimimetic in the United States
- RCTs have shown suppression of PTH, calcium, phosphorus, and calcium-phosphorus product
- Retrospective analyses of pooled data of 1,100 participants in phase 3 RCTs of cinacalcet showed reductions in risks of parathyroidectomy, fracture, cardiovascular hospitalization, and improved quality of life
- An observational study found a significant survival benefit associated with cinacalcet use in dialysis patients receiving vitamin D analogues
- ADVANCE (A Randomized Study to Evaluate the Effects of Cinacalcet plus Low-Dose Vitamin D on Vascular Calcification in Subjects With Chronic Kidney Disease Receiving Hemodialysis Study) showed no reduction in CAC in the cinacalcet/low-dose paricalcitol arm versus the flexible dose of vitamin D analogue arm when analyzed by the Agatston method, but showed a reduction using the volumetric method
- RCTs are needed for the effects of calcimimetics on patient-related outcomes and bone histology
  - EVOLVE (Evaluation of Cinacalcet Therapy to Lower Cardiovascular Events), a global, phase 3, double-blind, randomized, placebo-controlled trial of 4,000 patients, is examining the impact of cinacalcet on mortality and cardiovascular events in HD patients with secondary hyperparathyroidism; EVOLVE is ongoing, with results anticipated in late 2012 or 2013
- KDIGO guidelines recommend that calcitriol, vitamin D analogues, or calcimimetics can be used in CKD stage 5D to decrease PTH levels; the choice is dependent on serum calcium and phosphorus levels

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PARATHYROIDECTOMY FOR TREATING ELEVATED PTH IN CKD STAGE 5D

- Parathyroidectomy is effective in optimizing PTH control and traditionally has been offered to patients with sustained PTH levels >1,000 pg/mL
- Advantages are the lack of adverse effects from continuous vitamin D analogue or cinacalcet therapy
- It would be difficult to perform an RCT of vitamin D/cinacalcet versus parathyroidectomy, and to date, no such study has been performed
- A retrospective analysis of US Renal Data System (USRDS) data showed lower mortality risk in patients who underwent parathyroidectomy
- Current KDIGO guidelines recommend no specific PTH level for which parathyroidectomy would be an absolute indication

SUGGESTED READING

» Kestenbaum B, Andress DL, Schwartz SM, et al. Survival following parathyroidectomy among United States dialysis patients. *Kidney Int*. 2004;66(5):2010-2016.

CONCLUSION

CKD-MBD includes a constellation of biochemical and hormone abnormalities, impaired bone architecture, growth and fragility, and extraskeletal calcification. Management of CKD-MBD is important to decrease morbidity and mortality in patients with CKD. This requires an integrated approach and an understanding of physiology because all 3 components are interrelated and affecting one typically affects the others. Studies focused on combination therapy to improve all aspects of CKD-MBD simultaneously will be the challenge of the future.

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