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CKD–Mineral and Bone Disorder: Core Curriculum 2011

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Introduction

Chronic Kidney Disease–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 within the normal range in people without kidney disease. In CKD stages 2 and 3, compensatory mechanisms in the form of elevated PTH, elevated fibroblast growth factor 23 (FGF-23), and decreased calcitriol 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).

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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Suggested Reading

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Biochemical Abnormalities of CKD-MBD

Phosphorus

Physiological Levels and Dietary Sources

- Normal serum phosphorus concentration is 2.5–4.5 mg/dL; total body stores of phosphorus equal 700g
- Of total body stores, 85% is in bone as hydroxyapatite, 14% intracellular, and 1% extracellular
 - Of the extracellular phosphorus, 70% is within phospholipids (organic), 30% is inorganic
 - ◆ 15% of inorganic fraction is 15% protein-bound
 - ◆ 85% of inorganic fraction 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
- A typical American diet contains ~1000–1400 mg/day of phosphorus; 2/3 excreted in urine, 1/3 in stool
- Processed foods and foods rich in animal-based protein are high in phosphorus, thus difficult for patients with CKD to control serum phosphorus by diet alone while also eating the recommended amounts of protein
- 60%–70% dietary phosphorus is absorbed in all intestinal segments
 - Dependent on luminal concentration
 - Absorbed via sodium/phosphate cotransporter 2b (Npt2b)
 - Stimulated by calcitriol

Renal Handling

- Inorganic phosphorus is filtered by glomeruli, then 70%–80% gets reabsorbed in proximal tubule via 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

FGF-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 1 α -hydroxylase (*CYP27B1*), decreasing the conversion of 25-hydroxyvitamin D ((25[OH]D) to 1,25-dihydroxyvitamin D (25(OH)₂D; 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, 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 excretion of phosphorus
 - Regulatory feedback loops for both PTH and FGF-23 are dependent on calcitriol
 - ◆ PTH increases 1 α -hydroxylase and therefore production of calcitriol, which in turn inhibits further PTH release
 - ◆ In contrast, FGF-23 inhibits 1 α -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 falls below 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 below 30 mL/min, and measured serum phosphorus levels may rise above the normal 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 5D, the level of phosphorus associated with increased mortality varies from > 5.5 mg/dL to > 7 mg/dL
- Even in the non-CKD population, serum phosphorus in high-normal ranges is associated with increased risk of cardiovascular and all-cause mortality
- No interventional study has shown that lowering phosphorus to a certain “target” are associated with better outcomes

CKD, FGF-23, and PTH

- In early CKD, FGF-23 levels start rising
- 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 appear to rise as GFR decreases
- Dialysis patients have FGF-23 levels that may be up to 1000 fold greater than in non-CKD populations
- In dialysis patients, serum FGF-23 levels are associated with mortality even when adjusted for the serum phosphorus levels and can predict development of secondary hyperparathyroidism and responsiveness to calcitriol therapy

Calcium

Physiological Levels and Dietary Sources

- Serum calcium levels are controlled tightly in the 8.5–10.5 mg/dL range
- Total body stores are ~1000 g (99% is in bone, 0.9% is 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% bound to albumin
- Average dietary intake of calcium: 500–1000 mg/day
- Calcium absorption occurs across intestinal epithelium via 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 tubule with sodium and water reabsorption
 - 10% is reabsorbed in the thick ascending limb via paracellular route
 - The remainder is reabsorbed through transcellular pathways in the distal convoluted tubule, the connecting tubule, and the cortical collecting duct via 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; 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 the tubules
 - ◆ Activation of CaSR on thick ascending limb decreases paracellular calcium reabsorption
 - ◆ Upregulation of CaSR in hypercalcemia inhibits ADH-induced free water reabsorption, leading to urinary dilution
 - ◆ Renal effects of CaSR are both dependant and independent of PTH

Calcium Abnormalities in CKD

- In CKD stages 2–3, serum calcium levels are maintained in “normal” range at the cost of secondary elevations in PTH
- 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 net positive calcium balance in late CKD, the KDOQI (Kidney Disease Outcomes Quality Initiative) guidelines recommend maximum total elemental intake of calcium of 2 grams a day (1.5 g from phosphate binder + 500 mg 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, though there is no definitive evidence for this
- KDIGO (Kidney Disease: Improving Global Outcomes) guidelines also recommend limiting calcium-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 the risk of all-cause mortality with high serum calcium
 - Levels at which this becomes significant vary in different analyses from >9.5mg/dL to >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 then converted to Vitamin D₃ (cholecalciferol; nomenclature of vitamin D compounds provided in Box 2)
- Vitamin D₂ (ergocalciferol) is obtained from dietary sources
- D₂ and D₃ are hydroxylated by CYP27A1 in the liver to 25(OH)D₂ (ercalcidiol) and 25(OH)D₃ (calcidiol), together termed 25(OH)D
- Ercalcidiol and calcidiol have a half life of ~3 wk and are the best assessment of Vitamin D intake from sun and food
- 25(OH)D is converted by 1 α -hydroxylase in the kidney to calcitriol (1,25-dihydroxycholecalciferol, or 1,25(OH)₂D₃) (See Fig 2)
- 1,25(OH)₂D₃ actions:
 - Increases TRPV5 and TRPV6, the calcium adenosine triphosphatase, and the sodium/calcium transporters in the intestine and kidney
 - This increases the absorption of oral calcium and the reabsorption of calcium in the 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

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)₂D₃.

Vitamin D analogs: derivatives of vitamin D₂ and vitamin D₃, of which the clinically investigated synthetic derivatives include doxercalciferol, paricalcitol, alfacalcidol, falecalcitriol, and 22-oxacalcitriol (maxacalcitol)

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Abbreviation: KDIGO, Kidney Disease: Improving Global Outcomes.

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
- Institute of Medicine (IOM) published report on vitamin D in 2010
 - 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/day (800 IU/d for those over 70); maximum daily intake is 4000 IU
- In vitro, 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 levels of Vitamin D
 - In the general population, Vitamin D supplementation may reduce risk of cancers
 - Nevertheless, the IOM 2010 report notes Vitamin D’s effects outside of bone health are not yet reliably studied and there are not definitive randomized controlled trials

Vitamin D and CKD

- In observational studies in CKD, low 25(OH)D has been associated with progression to dialysis, 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 levels of 1,25(OH)₂D
- Reduced phosphorus excretion leads to a rise in serum phosphorus and in FGF-23, which suppress 1 α -hydroxylase activity and thereby decreases 1,25(OH)₂D
- Lower 1,25(OH)₂D decreases intestinal calcium absorption, and the lower serum calcium stimulates PTH release, which restores 1,25(OH)₂D levels (providing kidney function 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
- 1,25(OH)₂D levels in CKD are variable depending on whether calcitriol or one of its analogs are administered, as paricalcitol can suppress levels
- It is not recommended that 1,25(OH)D₃ levels be measured routinely

PTH

Physiological 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 (iPTH)

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

PTH Assays (see Fig 3)

- First-generation assays
 - Radioimmunoassays using an antibody against the mid-region or carboxy-terminal end
 - Detects full-length PTH as well as the multiple carboxy- and amino-terminal fragments
 - Unreliable
- Second-generation assay/intact PTH assays/two-step first generation immunoradiometric assays (IRMA)
 - Involve two antibodies, one that detects the amino terminus and the other 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 antagonistic effects to full-length PTH on bone

- Third generation assays/whole PTH assays/Biointact PTH assays only detect 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

Pathophysiology

- PTH is significantly associated with mortality in observational studies at levels varying from >400 pg/mL to >600 pg/mL, depending on the population analyzed
- There is inconsistent data on the underlying bone histology by biopsy in dialysis patients whose PTH levels were maintained in the 150–300 pg/mL range recommended by KDOQI guidelines
- Given above 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 the values of the specific assay used
 - However, trends of PTH within that range should be evaluated and medications 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 the 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, less than 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- κ B) system regulated by hormones (PTH, calcitriol, estrogen, glucocorticoids, as well as cytokines and interleukins)

Renal Osteodystrophy

- The term is specific to bone pathology in CKD patients and is a component of CKD-MBD
- Renal osteodystrophy is assessed by doing bone biopsies 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, volume; TMV system) and replace the terms adynamic bone, mild hyperparathyroidism, osteitis fibrosa, mixed uremic osteodystrophy, and osteomalacia (see Fig 4)
- Biomarkers such as PTH and bone alkaline phosphatase are only modestly predictive of underlying bone histology but are the currently 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 when compared with aged-matched general population

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Vascular Calcification in CKD

Background

- Extraskelatal calcification is highly prevalent in CKD
- Vascular calcification prevalence in dialysis patients ranges from 50%–90% in >20 studies that have addressed this using different modalities, and is even present in children on dialysis
- Vascular calcification appears to start early in CKD and > 50% of patients initiated on hemodialysis 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 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
- Traditionally, the CAC score obtained by electron beam CT is used to quantify calcification burden
- Other available techniques can provide semi-quantitative evidence of calcification, including duplex ultrasonography, echocardiography, pulse wave velocity, and even plain X rays
- A study of these techniques showed good correlation between lateral abdominal aortic X rays and electron beam CT in quantifying calcification

Pathogenesis of vascular calcification (see Fig 5)

- Features a phenotypic switch in which vascular smooth muscle cells (VSMC) dedifferentiate to osteo/chondrocytic-like cells

- 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 can also 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, pyrophosphate), calcification occurs
 - Levels of calcium and phosphorus are influenced by the bone status in a particular individual; the extent of bone turnover alters the release of these minerals from bone
 - CKD patients 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 a 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 is also associated with increased pulse wave velocity, increased pressure, and increased mortality

Calciphylaxis

- Also called “calcific uremic arteriopathy”; 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 gender, dialysis vintage, warfarin use, and hypoalbuminemia
- Potential treatments: parathyroidectomy, cessation of calcium-containing phosphate binders, 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 press) in 14 dialysis patients showed decreased pain and improvement in skin lesions, though mortality rate remained unchanged at 70%

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CKD-MBD

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 are together called CKD-MBD

Management

- KDOQI bone and mineral guidelines were published in 2003 and 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, majority of guideline recommendations were weak in strength (see Table 1)

Suggested Reading

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Control of Hyperphosphatemia

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

Diet

- Dietary phosphorus restriction to 800–1000 mg/day recommended
- Difficult to maintain this and consume adequate protein, since 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 to be low in their phosphorus to protein ratio
 - Additionally, phosphorus in plant-based foods is bound to phytate and may be less bioavailable since humans lack 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 FDA does not mandate the reporting of phosphorus content on food labels, making it challenging to counsel patients

Phosphate Binders

Background

- Dietary restriction is often insufficient to control elevated phosphorus 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 exists 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 per 667 mg capsule) and calcium carbonate (40% elemental calcium: 200 mg elemental calcium per 500 mg calcium carbonate)
- No studies have examined calcium-based binders versus placebo or compared the two forms of calcium-based binders with extra skeletal calcification or with patient-centered outcomes such as mortality, fractures, hospitalizations etc
- Both formulations have the potential to cause hypercalcemia as a side effect, but a metaanalysis showed calcium acetate may be less likely to do so
- Gastrointestinal 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 LDL levels
 - Most trials were performed using the hydrochloride salt
- Lanthanum Carbonate
 - Chewable; poorly, although not incompletely, absorbed and is 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 human studies
 - No increased risk of osteomalacia have been noted in human studies

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
 - ◆ 2103 prevalent HD patients randomized to sevelamer or a calcium based binder (70% acetate and 30% carbonate forms)
 - ◆ Primary outcome of all-cause mortality or cause-specific mortality was not different between the two arms

- ◆ However there was a significant drop out rate of about 50% in both arms, with only 1068 patients completing the study
- ◆ When dialysis records were used to determine end points, a subgroup analysis of subjects > 65 years did show a survival advantage for sevelamer
- ◆ However, another analysis that used Medicare claims to determine end points did not show mortality benefit in this group
- ◆ The analysis of Medicare claims also showed all-cause hospitalizations were lower for the sevelamer subjects
- RIND (Renagel in New Dialysis) study
 - ◆ Randomized 148 incident HD patients to sevelamer hydrochloride or calcium based binder
 - ◆ Showed an adjusted increased mortality in the calcium-based binder arm (HR, 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 is inconsistent data on the beneficial effect of sevelamer as compared with calcium based binders on vascular calcification, as shown in the following RCTs
 - A study of low phosphorus diet vs low phosphorus diet plus calcium carbonate vs low phosphorus diet plus sevalamer in 90 predialysis patients showed no progression of calcification in the diet plus sevalamer group though calcification progressed in the other 2 groups
 - TTG (Treat to Goal) study assessed the progression of calcification in 200 HD subjects randomized to sevalemer or calcium based binders; showed absolute increases in the CAC score in the calcium treated arm but not in 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 randomized to calcium acetate plus atorvastatin vs sevalamer plus a statin if needed to achieve LDL to 70 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 versus sevalemer in 101 Brazilian dialysis patients) showed that the annual rate of CAC progression was not different between calcium based binders and sevalamer; 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 two arms in turnover mineralization or bone volume
- Another RCT of 119 HD patients randomized to sevelamer or calcium carbonate showed no changes in mineralization or volume at 1 year, but did show 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 with Lanthanum arm
 - RCT of 20 subjects showed that no patients 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 their initial bone status
- In summary, there are limited data to suggest the use of one 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 till more conclusive data is available
 - In the KDOQI guidelines, maximal dose of elemental calcium was recommended at 1500 mg/day, with total calcium intake from diet plus binders recommended not to exceed 2000 mg/day
 - KDIGO guidelines recommend avoidance of calcium-based binders if there is arterial calcification, the PTH is persistently low, or in persistent or recurrent hypercalcemia; no daily ceiling was given due to the lack of balance studies

Clearance of Phosphorus in Dialysis

- Patients receiving nocturnal hemodialysis (HD) remove twice the amount of phosphorus per week compared with those on thrice-weekly intermittent HD
- Intermittent HD removes 1000 mg of phosphorus per session and because 1000 mg is also absorbed each day, net phosphorus balance is about 4000 mg per week
- An RCT of 51 patients randomized to 6-times weekly nocturnal HD versus thrice weekly intermittent HD demonstrated significant and sustained decreases in serum phosphorus over a 6 month period
 - Also noted were a significant rate of discontinuation or lowering of phosphorus binder dose in the nocturnal hemodialysis group
 - No significant difference in PTH between groups
- A frequent dialysis study that randomized 245 patients to daily versus thrice-weekly dialysis found a reduction in serum phosphorus levels in the frequent HD group ($P=0.002$)
- With 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 in CKD stages 3–5D demonstrate an association between PTH levels at extremes (less than 2 and greater than 9 times the normal assay limits) and mortality

- Similar to phosphorus, there are no mortality studies that have randomized patients to different PTH cut-offs
- 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 within that range should also be treated
- The measures available for this include oral calcium, vitamin D, calcitriol, 1,25(OH)₂ analogs, calcimimetics, and parathyroidectomy

Treatment of Elevated PTH in CKD 3 and 4

- PTH increases as an adaptive response to hyperphosphatemia; in individual patients this becomes maladaptive at a certain point and treatments for elevated PTH should be individualized and based on trends
- KDIGO guidelines recommend correcting modifiable factors: treating hypocalcemia, elevated phosphorus, 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 3–4, however its effects on arterial calcification are unclear
- Treating hyperphosphatemia to lower PTH seems important physiologically but again has not been well studied
- One 8-week trial of Lanthanum carbonate versus placebo in CKD 3–4 found a reduction in PTH
- 25(OH)D likely lowers but may not normalize PTH in CKD 3–5
- Use of 25(OH)D to suppress PTH was studied retrospectively (meta-analysis) in 322 patients with CKD and found to lower PTH levels when given in conjunction with calcium
- In CKD 3 and 4 patients with low 25(OH)D levels (< 30ng/ml) using ergocalciferol showed significant reductions in PTH in CKD3, however an RCT of 20 patients with CKD showed no significant effect of 25(OH)D therapy on PTH
- KDIGO guidelines recommend that if PTH levels continue to rise in CKD 3–4, calcitriol or other vitamin D analogs may be used to suppress PTH
- Role of Vitamin D analogs in treating elevated PTH in non-dialysis dependent CKD patients
 - Four placebo controlled RCTs of various vitamin D analogs (doxercalciferol, paricalcitol, alfacalcidol, calcitriol) all showed efficacy for PTH lowering as compared with placebo
 - No RCTs using Vitamin D analogs in pre-HD CKD address patient-level outcomes (mortality, hospitalizations, fractures, parathyroidectomy, quality of life) or vascular calcification
 - Two studies have shown improvement in bone turnover with Vitamin D analogs compared with the placebo

- Observational studies have shown a lower risk of progression to ESRD and death in CKD stage 3–4 patients on a Vitamin D analog 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 lower PTH as compared with placebo in CKD 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 analogs for Treating Elevated PTH in CKD-5D

- Vitamin D analogs and calcitriol are traditionally 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 analog
- One study demonstrated 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, though there was no difference in the number of subjects who had one episode of hypercalcemia
- No head-to-head comparison of doxercalciferol, paricalcitol, or calcitriol have evaluated vascular calcification or patient-related endpoints
- Therefore the KDIGO guidelines do not recommend one vitamin D analog over another or over calcitriol at this point

Suggested Reading

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Calcimimetics for Treating Elevated PTH in CKD-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 1100 subjects from Phase 3 RCTs of Cinacalcet showed reductions in the risk of parathyroidectomy, fracture, cardiovascular hospitalization, and quality of life
- An observational study found a significant survival benefit associated with cinacalcet use in dialysis patients receiving vitamin D analogs
- 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 vs the flexible dose of Vitamin D analogs arm when analyzed by the Agatston method, but did show a reduction using the volumetric method
- RCTs are needed on 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 4000 subjects is examining impact of cinacalcet on mortality and cardiovascular events in hemodialysis patients with secondary hyperparathyroidism; EVOLVE is ongoing with results anticipated in late 2012 or 2013

- KDIGO guidelines recommend that calcitriol, vitamin D analogs, or calcimimetics can be used in CKD 5D to lower PTH; the choice is dependent on serum calcium and phosphorus levels

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Parathyroidectomy for Treating Elevated PTH in CKD-5D

- Parathyroidectomy is effective in optimizing PTH control and has been traditionally offered to patients with sustained PTH > 1000 pg/mL
- Advantages are the lack of adverse effects from continuous Vitamin D analog or cinacalcet therapy
- It would be difficult to perform a RCT of vitamin D/cinacalcet vs parathyroidectomy, and to date no such study has been performed
- A retrospective analysis of USRDS data showed a lower mortality risk in patients who underwent parathyroidectomy
- Current KDIGO guidelines recommend no specific level of PTH for which parathyroidectomy would be an absolute indication

Suggested Reading

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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 CKD. This requires an integrated approach and an understanding of physiology since all three 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.

Acknowledgments

Support: None

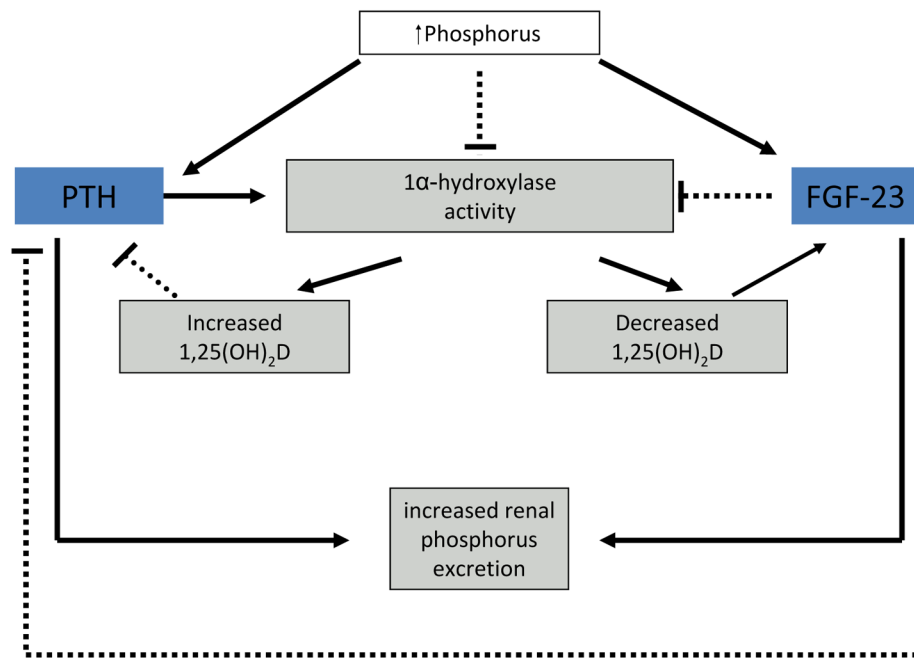


Figure 1. Regulation of Serum Phosphorus

A solid line indicates stimulation; a dashed line indicates inhibition. 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.

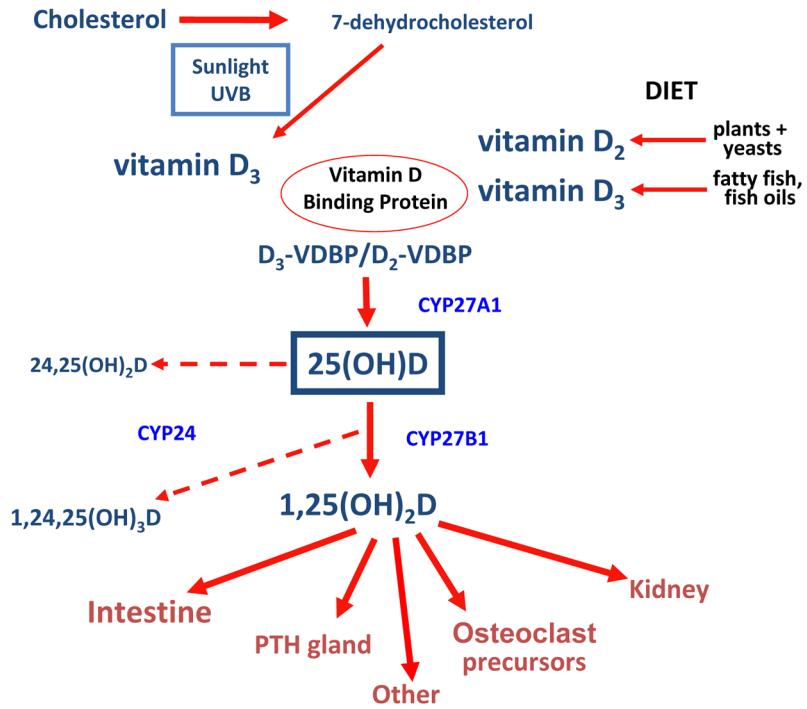


Figure 2. Overview of Vitamin D Metabolism

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.

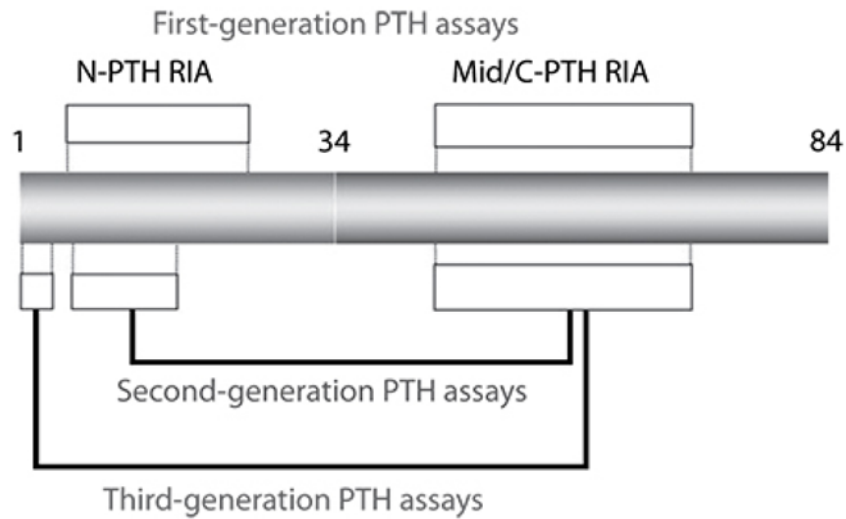


Figure 3. Assays for parathyroid hormone (PTH)

The intact PTH molecule is composed of 84 amino acids; different regions of the protein are targeted by first through third generation assays. 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.

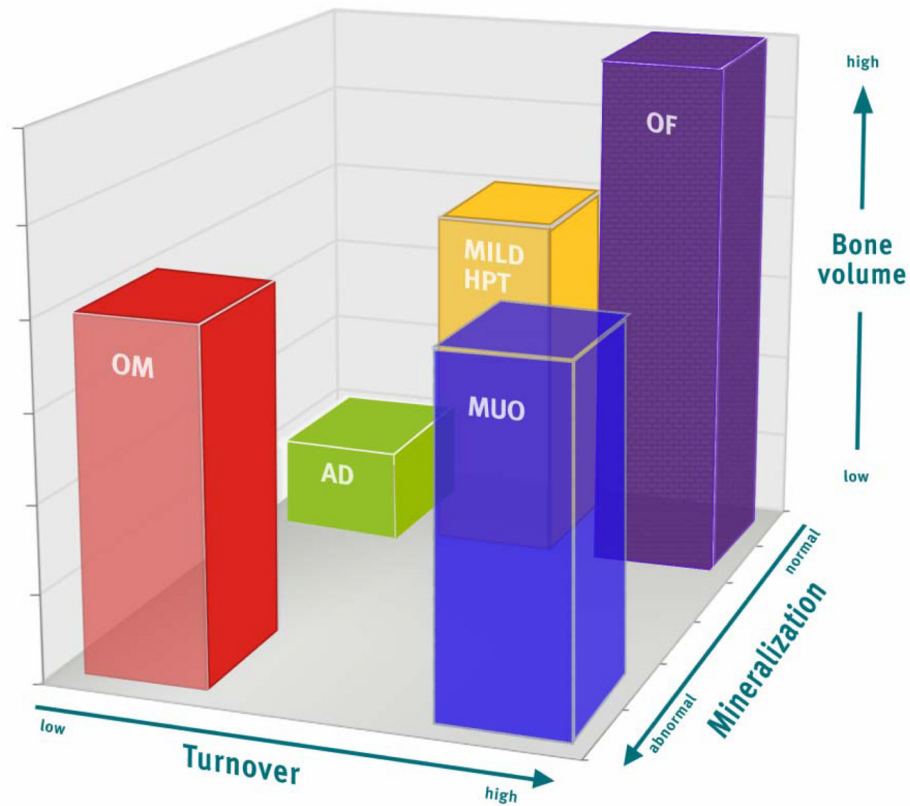


Figure 4. Turnover Mineralization Volume (TMV) Classification System for Bone Histomorphometry

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 means 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 (OM, osteomalacia) was previously described as low-turnover bone with abnormal mineralization. The 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 (AD, adynamic bone disease) was previously described as low-turnover bone with normal mineralization, and the 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 HPT, mild hyperparathyroid-related bone disease) and purple bar (OF, osteitis fibrosa or advanced hyperparathyroid-related bone disease) were previously 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 (MUO, mixed uremic osteodystrophy) is variably defined internationally. In the present graph, it is depicted 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 CKD. Reproduced with permission of Nature Publishing Group from Figure 1 in Moe et al. *Kidney Int.* 2006;69(11):1945–53.

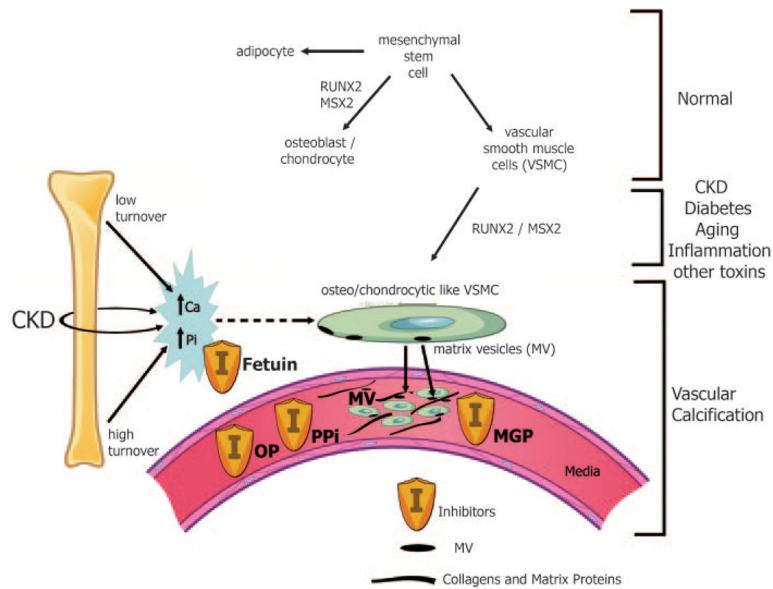


Figure 5. Pathogenesis of Vascular Calcification

Normally, mesenchymal stem cells differentiate to adipocytes, osteoblasts, chondrocytes, and vascular smooth muscle cells (VSMC). In the setting of CKD, diabetes, aging, inflammation, and multiple other toxins, these VSMC 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 VSMC is indicative of a phenotypic switch. These osteo/chondrocytic-like VSMC 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 chronic kidney disease (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 or not depends on the strength of the army of inhibitors (I) standing by in the circulation (fetuin A) and in the arteries (PPI = pyrophosphate, MGP = matrix Gla protein, and 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.

Table 1

Recommendations for Ranges of Mineral Metabolism Parameters in CKD

	CKD Stage 3	CKD Stage 4	CKD Stage 5D
Phosphorus	Maintain in “normal” range (2C)	Maintain in “normal” range (2C)	Lower towards 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 <9x the upper limit of normal (if there is a trend changing within that range, adjust prescription) (2C)

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

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)).

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