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Bone disease in patients with kidney disease: A tricky interplay

Managing bone disease in patients with kidney disease involves frequent lab testing and careful evaluation of therapeutic options. This review provides guidance.

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PRACTICE RECOMMENDATIONS

› *Perform laboratory testing for chronic kidney disease (CKD)-induced bone disease at CKD stage 3.* (B)

› *Avoid calcium-based phosphate binders in patients with known vascular calcifications.* (B)

› *Consider the use of phosphate binders in non-dialysis patients on a case-by-case basis, particularly in those with hyperphosphatemia not controlled by dietary measures.* (B)

› *Prescribe native vitamin D (ergocalciferol or cholecalciferol) to patients with CKD stages 3 to 4 who have secondary hyperparathyroidism and vitamin D deficiency.* (B)

Strength of recommendation (SOR)

(A) Good-quality patient-oriented evidence

(B) Inconsistent or limited-quality patient-oriented evidence

(C) Consensus, usual practice, opinion, disease-oriented evidence, case series

About 14% of the US general population has chronic kidney disease (CKD).[1] Limited data exist regarding the exact prevalence of CKD-mineral and bone disorder (MBD), but abnormal mineral metabolism is believed to start in stage 3 CKD, implying that 8% of the adult US population could be at risk for, or already have established, CKD-MBD.[2] Although the disorder has traditionally been managed by nephrologists, this earlier onset suggests that many patients should be screened and treated by their primary care physicians.

Because CKD-MBD can lead to significant morbidity (ie, increased fracture risk) and mortality, identification and treatment are of utmost importance.[3] This review provides information from the current literature and the KDIGO (Kidney Disease: Improving Global Outcomes) guidelines, and focuses primarily on the non-dialysis CKD population.

CKD-MBD: A broad spectrum of disorders

CKD-MBD is defined as a systemic disorder of mineral and bone metabolism due to CKD. Traditionally referred to as renal osteodystrophy, the term CKD-MBD is meant to indicate and describe a broad clinical spectrum of CKD-associated bone mineral metabolism disorders that manifest from one or a combination of the following:

- Abnormalities of calcium, phosphorus, parathyroid hormone (PTH), or vitamin D metabolism
- Abnormalities in bone turnover, mineralization, volume, linear growth, or strength
- Vascular or other soft-tissue calcification.[4]

Renal bone disease can be divided into low bone turnover (adynamic bone disease) and high bone turnover states. Both can lead to a decrease in bone strength and an increase in pathological fractures.[5]

TABLE 1

Recommended lab monitoring frequency by stage of CKD[6]*

Parameter	Stage 3	Stage 4	Stage 5, dialysis and non-dialysis
Phosphorus, calcium	Every 6-12 months	Every 3-6 months	Every 1-3 months
Alkaline phosphatase	Not recommended	Every 12 months	Every 12 months
iPTH	Based on baseline level and rate of CKD progression	Every 6-12 months	Every 3-6 months

*More frequent monitoring may be reasonable in patients receiving treatment for CKD-MBD in order to evaluate treatment efficacy and safety.

CKD, chronic kidney disease; iPTH, intact parathyroid hormone.

Pathophysiology: Difficult to know where the cascade begins

Understanding the pathophysiology and treatment of bone disease in patients with CKD can be challenging. Because of abnormalities of mineral metabolism and changes in hormones and cytokines, bone remodeling is severely disrupted in patients with CKD, and it remains unclear where this cascade begins.

As an adaptive response to decreased kidney function, PTH levels increase. Elevations of fibroblast growth factor 23 (FGF23) lower blood phosphate levels by inhibiting phosphate reabsorption in the kidneys, thus increasing urinary excretion of phosphorus. Secondary hyperparathyroidism (SHPT), driven by hypocalcemia, responds to normalize serum calcium levels by increasing the number and size of osteoclasts actively breaking down bone matrix. This escalates fracture risk. In addition, the inability of damaged kidneys to convert vitamin D to an active form further deranges calcium and phosphate homeostasis.

Successful management of serum levels begins with monitoring

KDIGO, an independent nonprofit foundation that seeks to improve the care and outcomes of kidney disease patients worldwide, developed guidelines for the diagnosis, evaluation, prevention, and treatment of CKD-MBD in 2009.[6] These guidelines recommend that treatment of CKD-MBD be aimed at managing serum phosphate, PTH, and calcium levels. The recommended frequency for laboratory monitoring of these levels varies by stage of CKD and is described in **TABLE 1**.[6] (For more on chronic kidney disease staging, see KDIGO's 2012 Clinical Practice Guideline for the Evaluation and Management of Chronic Kidney Disease, available at: http://www.kdigo.org/clinical_practice_guidelines/pdf/CKD/KDIGO_2012_CKD_GL.pdf.)

Because of the interrelated nature of these minerals and hormones, drug therapy aimed at treating one may impact the others. This must be considered when designing treatment regimens.

Aim treatment of CKD-MBD at managing serum phosphate, parathyroid hormone, and calcium levels.

Hyperphosphatemia: Manage with diet, drugs, dialysis

Observational studies have shown an association between higher serum phosphate levels and mortality.[6-8] KDIGO recommends maintaining serum phosphorus levels within the normal range of the assay in patients with CKD who are not receiving dialysis.[6] For dialyzed patients, the recommendation is to lower the phosphorus level toward the normal range as much as possible.[6] Maintaining an appropriate phosphorus level is accomplished through dietary phosphate restriction, the use of phosphate binders, and, in dialyzed patients, dialytic removal of phosphate.[6]

Dietary phosphate restriction is often challenging for patients, in part, because phosphorous content is not always included on food labels in the United States.[9] Phosphorus is highly absorbed from additives in processed food (approaching 100% absorption), less absorbed from animal sources such as meat and dairy products (40%-60%), and is the least absorbed from plant sources such as beans and nuts (20%-40%).[10] Advise patients

to avoid fast food, processed foods, cheese, frozen meals, colas, and certain ready-to-eat cereals and prepared meats, as these products may have additives from which phosphorus is readily absorbed.[11] A patient-friendly list of high-phosphorus foods, as well as other dietary advice and recipes, can be found on the National Kidney Foundation Web site at https://www.kidney.org/atoz/content/phosphorus. Tables listing the phosphorus content of common foods are also available in the literature and online.[11,12] Keep in mind that not all resources take into account phosphate bioavailability. Dietician referral may be helpful to assure that patients maintain adequate protein intake while restricting dietary phosphate.

Restrict the dose of calcium-based binders in the setting of persistent or recurrent hypercalcemia, known vascular calcification, or low parathyroid hormone levels.

Phosphate binders are recommended by the KDIGO guidelines for use in patients with kidney disease and hyperphosphatemia.[6] Most of the data to support the use of phosphate binders was gleaned from the dialysis population. The use of phosphate binders in non-dialyzed patients with CKD has both proponents and opponents, with literature supporting both positions.[13,14] A recent KDIGO conference on controversies in CKD-MBD identified this as an area that should be evaluated further for the next guideline update.[15]

Phosphate binders—which bind the phosphorus in food to prevent absorption—should be taken with meals or high-phosphorus snacks. Products and formulations of commonly used phosphate binders are shown in **TABLE 2**.[16,17] Taste, formulation, adverse effects, pill burden, and cost are issues to discuss with patients when initiating or adjusting phosphate binder therapy. It's estimated that more than half of all patients receiving dialysis do not adhere to their prescribed phosphate binder regimen, highlighting the need to assess adherence before adjusting dose and to involve the patient in the decision-making process to select a phosphate binder product.[18]

Avoid calcium-based binders? The risk of hypercalcemia and the potentially increased risk of vascular calcifications with calcium-based binders have led some nephrologists to favor non-calcium-based products. Two recent meta-analyses found a reduced risk of all-cause mortality with the non-calcium-based binders sevelamer or lanthanum as compared to calcium-based binders.[19,20] Current KDIGO guidelines were published prior to these meta-analyses and do not recommend one phosphate binder over another. They do, however, recommend restricting the dose of calcium-based binders in the setting of persistent or recurrent hypercalcemia, known vascular calcification, or low PTH levels.[6]

Secondary hyperparathyroidism

Due to a lack of data, the goal PTH level in patients not receiving dialysis is unknown.[6] A reasonable approach in non-dialyzed patients, however, is to correct 25-OH vitamin D (25[OH]D) deficiency, elevations in serum phosphate, and hypocalcemia when the level of intact PTH (iPTH) exceeds the normal range for the assay because correcting these derangements may result in a decline in iPTH.[6,21] If this approach fails and PTH levels continue to rise, use of calcitriol or vitamin D analogues is recommended.[6] Characteristics of medications used to treat SHPT are presented in **TABLE 3**.[16,17]

In dialysis patients, the target iPTH range suggested by KDIGO is 2 to 9 times the upper limit of normal for the assay.[6] Elevated PTH levels in the dialysis population may be managed with activated vitamin D and/or cinacalcet.

Native vitamin D (ergocalciferol, cholecalciferol) and activated vitamin D analogs (calcitriol, doxercalciferol, paricalcitol). Native vitamin D products are recommended for non-dialyzed patients with CKD to correct vitamin D deficiencies. Although many approaches may be used clinically to replenish low vitamin D stores, one reasonable recommendation in patients with a 25(OH)D level <30 ng/mL is to prescribe ergocalciferol 50,000 units/week for 8 weeks and then to repeat the serum 25-OH vitamin D test. If the level is still <30 ng/mL, a second 8-week course of weekly ergocalciferol 50,000 IU may be administered.[21]

Following repletion with ergocalciferol, maintenance doses of cholecalciferol (1000-2000 IU/d) or ergocalciferol (50,000 IU/-month) may be initiated.[21] Discontinue na-

TABLE 2

An at-a-glance review of phosphate binders[16,17]

Medication	Formulations available	Common adverse effects	Notes
Calcium acetate (PhosLo, Eliphos, Phoslyra, Calphron)	Capsule, tablet, oral solution	Hypercalcemia	25% elemental calcium
Calcium carbonate (Tums, others)	Chewable or non-chewable tablets	Hypercalcemia	40% elemental calcium
Ferric citrate (Auryxia)	Tablet	Diarrhea, nausea, constipation, dark-colored stool	Increases serum iron
Lanthanum carbonate (Fosrenol)	Chewable tablet, oral powder packet	Nausea, vomiting, abdominal pain	Less than .002% absorbed. Accumulation in bone observed. Radiopaque on x-ray. Bowel obstruction, impaction, and perforation have been reported.
Sevelamer carbonate, sevelamer hydrochloride (Renvela, Renagel)	Tablet, oral powder packet	Nausea, vomiting, diarrhea, abdominal pain	Resin that is not absorbed. Hydrochloride salt may worsen metabolic acidosis. Bowel perforation and obstruction have been reported.
Sucroferric oxyhydroxide (Velphoro)	Chewable tablet	Diarrhea, nausea, dark-colored stool	Limited iron absorption

tive vitamin D in patients who develop hypercalcemia.

Native vitamin D becomes less effective at reducing PTH levels as kidney disease advances. This is likely due to a decline in renal conversion of 25(OH)D to 1,25-$(OH)_2$ vitamin D ($1,25[OH]_2D$), the most active form of vitamin D and the form of vitamin D that decreases PTH production. By stage 5 CKD, it is unlikely that native vitamin D will significantly decrease PTH levels; treatment with activated vitamin D products or cinacalcet is generally required.

Because the enzyme responsible for converting 25(OH)D into the most active form can be found in multiple tissues outside of the kidney, and the $1,25(OH)_2D$ converted for use by these organs may help prevent such conditions/events as hypertension, type 2 diabetes, myocardial infarction, and stroke (in patients with and without kidney disease), some specialists prescribe native vitamin D to patients with CKD for reasons unrelated to PTH suppression. There are no data, however, confirming that 25(OH)D supplementation mitigates these outcomes.[21]

Don't forget calcium

All of the active vitamin D products can increase serum calcium and phosphate levels. Calcitriol, however, may cause more hypercalcemia than paricalcitol.[22] If hypercalcemia develops, you may need to stop, or reduce the dose of, vitamin D analogues. Or you may need to switch patients from calcium-based to non-calcium-based phosphate binders. If hyperphosphatemia develops, intensify phosphate binder therapy or reduce the dose of, or stop, vitamin D analogues. If iPTH levels go below the target range, reduce the dose of the vitamin D analogue to avoid iatrogenic adynamic bone disease.

Avoid this agent in the non-dialyzed patient. Cinacalcet effectively treats SHPT in patients receiving dialysis, but is not recommended for use in undialyzed patients.[23] That's because unacceptably high rates of hypocalcemia have been observed in non-dialyzed patients who were taking the drug.[23,24] In addition, while cinacalcet neutrally affects, or causes a slight decrease in, serum phosphate in patients receiving dialysis, it increases serum phosphate in patients who are not.[24,25]

Drug therapy for osteoporosis

Therapy to prevent and treat fractures in patients with CKD is controversial because patients with CKD stage 3 to 5 with and without

TABLE 3
Medications used to lower parathyroid hormone levels[16,17]

Medication	Mechanism of action	Formulations available	Common adverse effects	Notes
Calcitriol (Rocaltrol, Calcijex), paricalcitol (Zemplar), doxercalciferol (Hectorol)	Decreases PTH hormone production	Capsule, oral solution (calcitriol only), IV injection	Hypercalcemia, hyperphosphatemia	—
Cinacalcet (Sensipar)	Increases sensitivity of the calcium-sensing receptor on cells within the parathyroid gland	Tablet	Hypocalcemia, nausea and vomiting	Give with food; do not initiate when serum calcium is below the normal range
Ergocalciferol, cholecalciferol	Requires conversion within the kidney to active vitamin D that decreases PTH hormone production	Capsule, tablet, oral solution	Hypercalcemia	Not effective for lowering PTH in patients with severe kidney dysfunction

IV, intravenous; PTH, parathyroid hormone.

MBD were excluded from clinical trials of commercially available treatments. Furthermore, in adynamic bone disease, bones are capable of neither breaking down nor building (ie, reduced resorption). Bisphosphonates and other antiresorptive therapies are more effective at decreasing fractures in patients who are in a state of increased bone resorption, such as menopausal women, so the benefits of these medications in terms of their ability to reduce fractures in CKD patients are questionable, as is their safety.[26,27]

In addition, while dual-energy x-ray absorptiometry (DXA) is typically used to identify patients who would benefit from these agents, studies have recently demonstrated that femoral neck bone density measured via DXA may underestimate fracture risk in patients with CKD-MBD (ie, bone density may actually be lower than measured).[26,28]

Antiresorptive agents and teriparatide

Osteoporosis treatments include antiresorptive agents (ie, the bisphosphonates, raloxifene, denosumab), and the anabolic bone agent teriparatide.

Evidence supports treating patients with stage 1 to 3 CKD the same as patients without CKD.[15] Bisphosphonates are labeled as contraindicated in patients with a glomerular filtration rate (GFR) <30 mL/min/1.73m^2, due to concerns arising from animal trials and subsequent human case reports (both with intravenous formulations only) regarding acute kidney injury.[27]

While raloxifene lacks a warning regarding use in patients with stage 3 to 5 CKD, it has not been shown to prevent hip fractures in any population.[29]

Denosumab is not contraindicated for use in patients with CKD stage 3 to 5 without MBD, but it can worsen hypocalcemia, particularly in patients receiving dialysis.[30]

Teriparatide is contraindicated in patients with CKD and SHPT,[31] and there are no studies of its use in patients with CKD-MBD.

What the guidelines say about antiresorptive treatment

For patients with stage 3 to 5 CKD with manifestations of MBD, 2009 KDIGO guidelines recommend a bone biopsy to evaluate for adynamic bone disease before initiating antiresorptive treatment.[6] Because few physicians in most communities are trained to conduct and evaluate bone biopsies, this recommendation is infrequently followed. Without a bone biopsy to rule out adynamic bone disease, options to prevent or treat fractures in the setting of CKD-MBD are limited. JFP

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