Bone Disease in Chronic Kidney Disease

This article is the eighth of a series about chronic kidney disease and its management based on the new National Kidney Foundation guidelines. If you missed previous articles in this series, please log onto the IHS website. Archived issues are found at the Clinical Support Center's web page.

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Metabolic bone disease starts early in chronic kidney disease (CKD), as early as stages 2 and 3 (GFR<60 mL/min/1.73m^2). Several factors are involved. These include phosphorus, calcium, active vitamin D, and parathyroid hormone (PTH). As GFR declines, less phosphorus is excreted and less calcium is absorbed. Phosphate retention may directly interfere with the kidney's ability to activate vitamin D. Decreased active vitamin D impairs intestinal calcium absorption. This relative hypocalcemia results in higher levels of PTH. PTH maintains serum calcium levels by enhancing tubular calcium resorption as well as resorption of calcium from the bones and increases phosphorus excretion by reducing tubular resorption. High levels of PTH also increase skeletal resistance to calcium.

- The serum level of phosphorus is maintained within the normal range until the GFR falls below 20 - 25 mL/min. At that time, severely damaged kidneys can no longer respond to the higher levels of PTH.
- The serum level of calcium is generally maintained despite reduced intestinal absorption, due mainly to increased calcium resorption from the bones and in the tubules.
- The serum level of active vitamin D is generally lower at stage 4 (GFR 15- 29 mL/min).
- Elevated levels of intact PTH may be seen when the GFR falls below 60 mL/min.

This cycle continues even when the patient receives renal replacement therapy (dialysis). Serum levels of phosphorus, calcium, iPTH, and active vitamin D remain important across the CKD spectrum. Active vitamin D supplements are now available and are useful in treating vitamin D deficiency/insufficiency, and help to lower iPTH and potentially control these imbalances. Both oral and injectible supplements are available. Keep in mind, however, that active vitamin D is involved in both calcium and phosphorus absorption. Vitamin D supplements can help lower iPTH but serum phosphorus and serum calcium levels may be elevated due to improved absorption. New guidelines provide a path to follow for monitoring and treating this complicated metabolic disease process.

Phosphorus can be controlled by restricting high phosphorus foods. Refer patients to a registered dietitian for guidance. Most patients will require phosphate binding medication as well. Commonly used calcium-based binders include calcium carbonate and calcium acetate. Avoid use of calcium citrate as citrate increases aluminum absorption. New evidence suggests that the total amount of elemental calcium should not exceed 2000 mg/day. Since damaged kidneys cannot excrete the excess calcium, the potential exists for soft tissue calcification; so limiting total elementary calcium will reduce this risk of soft tissue calcification (see more below about calcium and phosphorus product). A new noncalcium-based phosphorus binder/resin (sevalamer HCl) reduces LDL levels as well as serum phosphorus. The old aluminum-based binders are used as a last resort and only temporarily when serum phosphorus > 7.0 mg/dL for patients on dialysis.

There is limited but rather compelling evidence that the product of serum calcium x serum phosphorus should not exceed 55. When this product is higher than 55, the risk for soft tissue calcification increases — in nonvisceral tissue (periarticular and vascular calcification), visceral organs (skeletal and myocardial muscle), and in the skin (itching due to cutaneous calcification). The itching in particular causes the most immediate discomfort for patients. Use of phosphate binders can help this appreciably over time.

The pending K/DOQI Clinical Practice Guidelines for Bone Metabolism and Disease in CKD provide a framework for monitoring serum phosphorus, calcium, PTH, and 25-hydroxyvitamin D. **The guideline suggests measuring serum calcium, phosphorus, and intact parathyroid hormone (iPTH) when GFR falls below 60 mL/min.**

Table 1. Recommendations for monitoring calcium, phosphorus, and iPTH

CKD Stage	GFR range (mL/min/1.73 m^2)	Measure Ca and P	Measure iPTH	Target iPTH levels
3	30 - 59	Every 12 mos.	Every 12 mos.	35-70 pg/mL
4	15 - 29	Every 3 mos.	Every 3 mos.	70-110 pg/mL
5	< 15 or dialysis	Every month	Every 3 mos.	150-300 pg/mL

In CKD stages 3 and 4, serum phosphorus should be maintained between 2.7 - 4.6 mg/dL.

- Restrict dietary phosphorus to 800 - 1000 mg/day (adjusted for protein) if serum phosphorus levels are

higher than those listed OR when iPTH levels are higher than target iPTH levels.
- Monitor serum phosphorus every 3 months when dietary phosphorus is restricted.
- If serum phosphorus is not maintained by dietary restriction OR if iPTH is not controlled to target levels, calcium-based phosphate binders should be prescribed.

Corrected total calcium should be maintained within the "normal range" of the lab used. Corrected total calcium in hypoalbuminemic patients can be calculated by using the following formula:

Corrected total calcium (mg/dL) = total calcium (mg/dL) + 0.8 x (4 - serum albumin (g/dL))

- Total elemental calcium (calcium from the diet and calcium-based binders) should not exceed 2000 mg/day.
- **Serum Ca x P should be < 55**; control serum phosphorus first (binders and P restriction).
- If corrected total calcium is below normal laboratory range (< 8.4 mg/dL) AND patient has clinical signs of hypocalcemia (paresthesia, Chvostek's and Trousseau's signs, bronchospasm, laryngospasm, tetanus and/or seizures) OR iPTH is above target range for CKD stage, treat with calcium salts or vitamin D supplements.

Vitamin D Supplements

Measure serum 25-hydroxyvitamin D "25(OH) D" when iPTH is above target range for CKD stage (see Table 1). If serum 25-hydroxyvitamin D is < 30 ng/mL, start supplementing with active vitamin D.

Table 2. Recommendations for Vitamin D supplementation (if low 25(OH)D)

25 (OH)D ng/dL	Vitamin D_2	Duration	Measure corrected total Ca and P
< 5 (Severe D deficiency)	ORAL: 50,000 IU/wk x 12 wks, then monthly INJECTABLE: 50,000 IU as single intramuscular injection	6 months then recheck 25(OH)D Recheck 25(OH)D at 6 months	Every 3 months
5 - 15 (Mild D deficiency)	ORAL: 50,000 IU/wk x 4 wks, then monthly	6 months then recheck 25(OH)D	Every 3 months
16 - 30 (insufficiency)	ORAL: 50,000 IU/month		Every 3 months

- Discontinue vitamin D therapy if corrected calcium exceeds 10.2 mg/dL.
- Add or increase phosphate binder if serum phosphorus exceeds 4.6 mg/dL. If high phosphorus continues, discontinue vitamin D therapy.
- Once vitamin D level acceptable, continue supplementation with multivitamin that has vitamin D and reassess 25(OH)D annually.

If serum 25-hydroxyvitamin D is > 30 ng/mL and iPTH is elevated, an active oral Vitamin D sterol should be started. The starting dose of calcitriol is 0.25mcg/day. Following initiation of calcitriol therapy, calcium and phosphorus should be monitored monthly and iPTH measured every three months. If iPTH falls below target, calcium exceeds 9.5 mg/dl, or phosphorus exceeds 4.6 mg/dl, calcitriol should be held until the levels again fall within the threshold level. Calcitriol should then be restarted at half the previous dose.

Bone metabolism in chronic kidney disease is an intellectual and clinical challenge. Although many providers may wish to avoid dealing with this problem, management of calcium, phosphorus, and parathyroid hormone is essential to maintain the health of our patients with chronic kidney disease. □