Advances in Practice

New Approaches for Managing Bone Metabolism and Disease in Chronic Kidney Disease

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Publication in 2003 of the National Kidney Foundation's Kidney Disease Outcomes Quality Initiative (NKF-K/DOQI) Clinical Practice Guidelines for Bone Metabolism and Disease in Chronic Kidney Disease (CKD) focused attention on managing serum calcium, phosphorus and parathyroid hormone (PTH) in this population (1). If these parameters are not effectively controlled, their impact on morbidity and mortality in patients with CKD may be severe.

Serum phosphorus, PTH and calcium-phosphorus product all increase when kidney function declines. These changes promote bone disease, as well as the calcification of soft tissue and changes in lipoprotein metabolism that are associated with cardiovascular disease (CVD) (2-4). If dietary phosphorus restriction, phosphate binders and vitamin D analogs are unsuccessful in controlling serum phosphorus and PTH, patients may require surgical parathyroidectomy (1).

Data from the United States Renal Database indicate that rates of parathyroidectomy declined by approximately 30% between 1995 and 1999, suggesting an improvement in the effectiveness of therapy for elevated PTH (5). However, PTH and serum phosphorus remain elevated in many patients undergoing maintenance dialysis therapy, and results from a recent study indicate that phosphorus restrictions are abused more commonly than other dietary restrictions (2,6,7).

Clearly, there is a need to explore new strategies for managing calcium, phosphorus and PTH to improve health outcomes in patients with CKD. This column will review the pathophysiology of bone disease, examine recommendations for appropriate serum calcium, phosphorus and PTH levels, and explore interventions for controlling these parameters in patients with CKD.

Pathophysiology of bone disease in CKD

CKD is defined as kidney damage, or glomerular filtration rate (GFR) below 60 mL/min/1.73 m2 for ≥ 3 months reflecting decreased kidney function (8). Five stages of CKD are recognized based on the level of kidney function. Table 1 summarizes the disturbances in mineral and hormonal balance that accompany each stage of CKD.

Phosphorus excretion starts to decrease during Stage 2 and hyperphosphatemia is evident at Stage 4 (1). When GFR approaches 35 mL/min/1.73 m2 (Stage 3), synthesis of 1,25- dihydroxyvitamin D declines and serum vitamin D levels drop below normal (9). PTH subsequently begins to rise, and this process is exacerbated by hyperphosphatemia and a drop in serum calcium (1,9).

Elevated PTH, or hyperparathyroidism, impacts bone metabolism and causes the high turnover bone diseases osteitis fibrosa and uremic osteodystrophy (1). In osteitis fibrosa, abnormal bone formation results from increased activity of cells involved in modeling bone. Osteodystrophy is characterized by defects in bone mineralization. Net bone loss in high turnover bone disease leads to reduced bone strength and increased risk of fracture.

Persistently elevated PTH also contributes to cardiovascular morbidity and mortality. When mineral storage in bone decreases, extraskeletal mineralization may result in calcification of vascular tissues. In patients undergoing continuous ambulatory peritoneal dialysis (CAPD), hyperparathyroidism and high calcium and phosphorus levels are associated with calcification of the aortic and mitral valves in the heart (10). Calcification of the cardiac valves, aorta and carotid arteries have been linked to increased risk of CVD.

PTH also suppresses the lipid regulating enzyme hepatic triglyceride lipase (HTGL), resulting in increased intermediate-density lipoprotein (IDL) and decreased high-density lipoprotein (HDL). These changes in lipoprotein levels are strongly associated with progression of atherosclerosis in patients undergoing dialysis (4). Furthermore, animal studies show that PTH promotes thickening of arteriole walls in the heart, which may impair vasodilation when there is a need for increased blood flow to the heart wall (11).

Recommendations for appropriate serum calcium, phosphorus and PTH levels in patients with CKD

The NKF-K/DOQI Clinical Practice Guidelines for Bone Metabolism and Disease in CKD are directed at adults, age 18 years and older, with CKD (1). Goals

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Table 1. Stages of Chronic Kidney Disease (CKD) and associated changes in mineral and hormonal balance (1,8,9)

Stage	Level of Kidney Function	GFR (mL/min/1.73 m^2)	Changes in mineral/ hormonal balance
1	Kidney damage with normal or increased GFR	≥90	
2	Kidney damage with mild decrease in GFR	60-89	Decrease in phosphorus excretion
3	Moderate decrease in GFR	30-59	Decrease in serum vitamin D and calcium
4	Severe decrease in GFR	15-29	Hyperphosphatemia and hyperparathyroidism
5	Kidney failure	<15	Hyperphosphatemia and hyperparathyroidism

GFR = glomerular filtration rate

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for managing bone metabolism and disease include:

- Measuring calcium, phosphorus and intact PTH (iPTH) in all patients with GFR<60mL/min/1.73m^2 (CKD stages 3 – 5);
- Measuring vitamin D and correcting deficiency if iPTH is elevated;
- Implementing dietary phosphorus restriction and phosphate binders for serum phosphorus control;
- Maintaining Ca x P < 55mg^2/mL^2. Precise targets for serum calcium, phosphorus and iPTH levels depend on the stage of CKD. Target levels, and recommended strategies for achieving them, are summarized in Table 2.

Interventions for controlling serum calcium, phosphorus and PTH in CKD

Concern regarding the potential for adverse outcomes from therapeutic management of renal bone disease predates publication of the NKF - K/DOQI Clinical Practice Guidelines for Bone Metabolism and Disease in CKD. Vitamin D analogs may increase risk of soft tissue calcification by raising serum calcium and phosphorus levels (12). Calcium-based phosphate binders can also contribute to hypercalcemia (13). For these reasons, alternative strategies for managing serum calcium, phosphorus and PTH have been investigated.

Serum phosphorus levels must be controlled early in the course of CKD if hyperparathyroidism and renal bone disease are to be reduced. However, dietary phosphorus restrictions are difficult to follow, calcium-based binders can increase the risk of soft tissue calcification and use of aluminum binders is limited by their potential toxicity (7,14).

Sevelamer hydrochloride (GelTex Pharmaceuticals, Inc., Waltham, MA), a phosphate-binding, calcium-free polymer, decreases rates of vascular calcification when compared with phosphate binders containing calcium (15). Nevertheless, results from an 8-week randomized double blind study of hemodialysis patients suggest that sevelamer hydrochloride may be less effective than calcium-based binders in controlling serum phosphorus and calcium-phosphorus product (16).*

Lanthanum carbonate (Shire Pharmaceuticals Group plc, Basingstoke, UK) is undergoing evaluation for treatment of hyperphosphatemia in patients with CKD Stage 5 on maintenance dialysis therapy. One 16-week study assessed effects of lanthanum carbonate on serum phosphorus, calcium, calcium-phosphorus product and PTH in 126 hemodialysis (HD) patients aged ≥18 years (17). During dose titration, patients received divided doses of lanthanum carbonate with meals to achieve serum phosphorus ≤ 5.9 mg/dL. Patients were then randomized to receive either lanthanum carbonate or placebo during a

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Table 2. Strategies for achieving recommended levels for serum calcium, phosphorus and intact parathyroid hormone (iPTH) in Chronic Kidney Disease (CKD) (1)

Intervention	CKD Stages 3 and 4	CKD Stage 5
Dietary phosphorus restriction	Restricted dietary phosphorus to 800 - 1000 mg if serum phosphorus >4.6 mg/dL or iPTH elevated [>70 (Stage 3) or> 110 pg/mL. (Stage 4)].	Restricted dietary phosphorus to 800-1000mg/day if serum phosphorus >5.5 mg/dL or iPTH >300 pg/mL.
Phosphate binders	Implement phosphate binders if serum phosphorus/iPTH remain elevated despite dietary phosphorus restriction; Calcium (Ca)-based phosphate binders may be used as initial therapy.	Implemented Ca-based or non-Ca, non-aluminum, non-magnesium binders for elevated serum phosphorus; If serum phosphorus remains > 5.5 mg/dL, use a combination of phosphate binders: • Total Ca intake from binders and diet should not exceed 2000 mg/day; • Avoid Ca-based binders if serum Ca>10.2 mg/dL or iPTH<150 pg/mL on consecutive measurements or if there are vascular and/or soft tissue calcifications; • If serum phosphorus>7.0 mg/dL, use one 4-week course of aluminum-based binder and consider more frequent dialysis.
Vitamin D therapy	Initiate oral vitamin D therapy (0.25 mcg calcitriol or alfacalcidol/day or 2.5 mcg doxercalciferol 3x/week) when serum 25(OH) - vitamin D>30 ng/mL and iPTH > 70 pg/mL (Stage 3) or > 110 pg/mL (Stage 4). Hold oral vitamin D for: • iPTH < target range for CKD stage. Resume therapy at 50% previous dose or use alternate day dosing when iPTH > target range for CKD stage; • Serum Ca > 9.5 mg/dL. Resume therapy at 50 % previous dose or use alternate day dosing when Ca < 9.5 mg/dL. • Serum Phosphorus > 4.6 mg/dL. Initiate/increase phosphate binder and resume prior oral vitamin D dose when serum phosphorus ≤ 4.6 mg/dL.	Initiate vitamin D therapy the iPTH > 300 pg/mL; • 0.5-1.5 mcg calcitriol, 2.5-5 mcg paricalcitol or 2 mcg doxercalciferiol IV each treatment for hemodialysis patients; • 0.5-1 mcg calcitriol or 2.5-5 mcg doxercalciferol by mouth 2-3x/week, or 0.25 mcg calcitriol by mouth daily for peritoneal dialysis patients. Adjust vitamin D therapy based on changes in iPTH, serum Ca and phosphorus according to algorithms provided in K/DOQI Clinical Practice Guidelines for Bone Disease and Metabolism in CKD.

* Editor's note: FDA-approved labeling for sevelamar hydrochloride does not mention use in CKD stage 1-4

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4-week maintenance phase. At the study end-point, there was a mean difference in serum phosphorus of 1.91 mg/dL between the lanthanum carbonate and placebo groups. Calcium-phosphorus product and serum PTH were also significantly lower with lanthanum carbonate than placebo.

In a multi-center study of 98 maintenance dialysis patients, bone biopsies were taken at baseline and after one year of treatment with either lanthanum carbonate or calcium carbonate (18). The incidence of hypercalcemia was much lower in the lanthanum carbonate group (6%) than in the calcium carbonate group (49%). The percentage of patients with bone abnormalities decreased from 36% to 18% in the lanthanum carbonate group, while renal osteodystrophy increased from 43% to 53% in those who received calcium carbonate.

Mixed metal hydroxy-carbonate (MMHC) compounds, based on magnesium and iron, have also been evaluated for their effectiveness as phosphate binders. MMHCs were found to be much more effective at binding phosphorus than established binders including calcium carbonate, calcium acetate, aluminum hydroxide, magnesium hydroxide and lanthanum carbonate (19). Thus, MMHCs may provide a better alternative to existing and emerging phosphate binders for managing hyperphosphatemia.

Nonpharmacological intervention to improve serum phosphorus control was the focus of a recent small study in HD patients (20). Weekly dialysate phosphate removal was the end-point of an investigation into the impact of dialysis duration on serum phosphorus levels in nine stable patients. In a separate investigation, the effect of exercising with a bicycle ergometer on dialysate phosphate removal was measured in 12 different patients. Both increased dialysis time (five hours versus four hours) and exercising before or during dialysis increases dialytic removal of phosphorus and is anticipated in the long term to improve serum phosphorus control.

Vitamin D analogs have been used with varying degrees of success to suppress production of PTH in patients with CKD. However, vitamin D therapy may raise serum calcium and phosphorus by increasing intestinal absorption, placing the patient at increased risk for soft tissue calcification (21). Use of vitamin D therapy has also been associated with increased frequency of low turnover bone disease (1).

Identification of a specific calcium-binding receptor in cell membranes of parathyroid tissue has allowed the development of a new therapy for hyperparathyroidism. Organic molecules, called calcimimetics, increase sensitivity of this receptor to calcium leading to decreased PTH secretion (22,23). Calcimimetics can be administered orally and do not elevate serum calcium and phosphorus levels.

The calcimimetic cinacalcet hydrochloride (Amgen, Thousand Oaks, CA) decreases both iPTH and calcium-phosphorus product in HD patients with secondary hyperparathyroidism (24,25). Efficacy of this calcimimetic was demonstrated in a double-blind, randomized, placebo-controlled study of 78 HD patients with secondary hyperparathyroidism (26). Patients received either calcimimetic or placebo, and baseline iPTH was similar in both groups (632 ± 280.1 pg/mL versus 637 ± 455.9 pg/mL respectively). However, during the course of the 18-week study, iPTH decreased by 26% in the calcimimetic group compared with a 22% increase in the placebo group. Patients receiving calcimimetic had an 11.9% decrease in calcium-phosphorus product compared with a 10.9% increase in those receiving placebo.

Calcimimetics are also effective in reducing PTH in HD patients with severe secondary hyperparathyroidism (27). Twenty-one patients with iPTH up to 1200 pg/mL were randomly assigned to receive either a calcimimetic or placebo for 15 days. iPTH levels decreased by 70 ± 3% at four hours on the first treatment day in the calcimimetic group, declined progressively until day nine and remained below pre-treatment levels until the end of the study. Blood ionized calcium levels also decreased after the first dose of calcimimetic, but neither iPTH nor blood calcium levels declined in the placebo group.

Summary

Renal bone disease and soft tissue calcification remain important contributors to morbidity and mortality in patients with CKD. The NKF-K/DOQI Clinical Practice Guidelines for Bone Metabolism and Disease in CKD provide guidance for treating these disorders. Therapeutic strategies continue to evolve, and novel approaches including calcium-free phosphate binders and calcimimetics offer the potential to control hyperparathyroidism without elevating serum calcium. Nonpharmacological interventions, including exercise regimens and longer dialysis times, are also receiving attention as strategies for improving serum phosphorus control.

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