Bone and Mineral Guidelines for Patients with Chronic Kidney Disease: A Call for Revision

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Recent clinical studies of mineral metabolism in patients with chronic kidney disease have helped to verify and extend the Kidney Disease Outcomes Quality Initiative practice guidelines for bone metabolism and disease that were published in 2003. In particular, investigations that examined calcium loading, vitamin D therapy, and mortality risk associated with serum calcium and phosphate in dialysis patients have been the most helpful clinically. As a consequence, there is now a growing interest to have the previous guidelines amended accordingly, which will be performed through the Kidney Disease: Improving Global Outcomes working group after a debate within the nephrology community. The new data support this call for revision in an attempt to improve survival of the dialysis patient by emphasizing the importance of intravenous vitamin D therapy and of preventing excess calcium loading. These studies also suggest avenues for future investigation into nontraditional causes and treatments of cardiovascular disease in patients with chronic kidney disease.


Early 4 yr ago, bone and mineral guidelines for the evaluation and treatment of patients with chronic kidney disease (CKD) were published after extensive assessment and review of the existing literature (1). Because of the paucity of evidence-based data, most of the recommendations by the Kidney Disease Outcomes Quality Initiative (KDOQI) committee relied on expert opinion. Since then, a large amount of data have emerged, requiring a re-evaluation of our management choices for diagnosing and treating CKD-mineral bone disorder (2). Although most of these new findings still lack the preferred highest level of evidence—the randomized, controlled trial—they will nevertheless be included in the discussion as consensus recommendations are made for new practice guidelines. Because of the volume of new data relating to calcium loading; vitamin D receptor activator (VDRA) therapy; and target levels for calcium, phosphate, and parathyroid hormone (PTH), the debate has already begun regarding how to incorporate these new findings into our clinical practice.

Calcium Loading
The recommendation that total elemental calcium intake be limited to 2 g/d (1) was a good first step in identifying excess oral calcium loading as a risk factor for cardiovascular disease in dialysis patients. At that time, several studies had established that patients with the highest calcium intakes had the largest vascular calcium burdens as detected by sensitive radiologic techniques (3,4). Since then, additional studies not only have corroborated the association of excess calcium intake with vascular calcification (5–7) and with increased mortality (7,8) but also have identified that intakes of 1.4 to 2 g/d also carry risks for calcification (5). In addition, patients with diabetes seem to be particularly prone to vascular calcification even before the presence of CKD (9,10), raising the question as to whether any patient with diabetes should be receiving more than the standard allowance of 1 g/d elemental calcium. Finally, several prospective studies in dialysis patients have now established that oral calcium loading is associated with accelerated aortic and coronary artery calcification (11), bone loss (12), and increased mortality (13).

What should be the new limit for oral calcium intake? For patients without diabetes, oral elemental calcium intakes in the range of 1 to 1.2 g/d (elemental), including dietary sources, is one suggested alternative because intakes above this level are associated with higher rates of calcification (5,13). This also makes sense in the context of the prevailing use of a dialysate calcium concentration of 2.5 mEq/L, which transfers 100 to 200 mg of elemental calcium to the patient with each dialysis session (2.25 mEq/L is closer to neutral calcium balance). Alternatively, one may consider using a 2.0-mEq/L dialysate calcium concentration if calcium-based phosphate binders are the preferred binder of choice, although studies that show the safety of this approach with respect to vascular calcification are lacking. For patients with diabetes, who are more susceptible to early vascular calcification, it may be wise not to exceed 1 g/d oral elemental calcium if a 2.5-mEq/L calcium bath is being used. Prospective studies are urgently needed to investigate how the different calcium intakes and dialysate calcium concentrations affect vascular calcification.

Another potential problem is in the use of calcium loading in patients who develop hypocalcemia during cinacalcet treatment. Hypocalcemia in cinacalcet users is often treated with
large dosages of oral calcium supplements (14) and/or increased dialysate calcium concentrations (>2.5 mEq/L), with or without concomitant VDRA therapy, to maintain serum calcium >8.5 mg/dl. Unfortunately, because serum calcium is a poor reflection of total body calcium content, an accurate assessment of calcium accumulation cannot be made during these episodes of calcium loading unless radiologic evaluations of arterial calcification are also used. Clinical studies are needed to assess changes in vascular calcification during cinacalcet therapy.

**VDRA Therapy**

The most intriguing new data with respect to VDRA treatment for hyperparathyroidism in patients who receive dialysis is the finding that VDRA therapy is associated with a clinically significant survival benefit (15–20). Survival benefits of 10 to 35% have now been described in several database surveys that include more than 200,000 dialysis patients worldwide. Although many clinicians have accepted this association as probably true, concerns have lingered about the retrospective nature of this finding and the potential for confounding by unknown factors; however, a new prospective study (21) indicated that incident dialysis patients who received the selective injectable VDRA paricalcitol had a 40% survival benefit during the first 90 d of dialysis, when compared with those who did not receive vitamin D. In addition, it was found that patients who were at the greatest risk for premature death were those who were not taking intravenous vitamin D and also had low 25-hydroxyvitamin D and 1,25-dihydroxyvitamin D levels (21). This supports a growing interest in 25-hydroxyvitamin D insufficiency in CKD, which is present in the majority of patients and which is a treatable problem (22–24). For example, Saab et al. (22) demonstrated that 50,000 U/mo ergocalciferol was effective in restoring serum levels of 25-hydroxyvitamin D without causing hypercalcemia or hyperphosphatemia despite continued use of intravenous VDRA therapy. In predialysis patients with CKD, ergocalciferol treatment reduced PTH levels by 20 to 25% in those with stage 3 CKD, although it was ineffective in patients with stage 4 CKD (23,24). Whether higher dosages of ergocalciferol or cholecalciferol would be more effective remains for future study.

To assess possible mechanisms for a potential cardiac benefit of VDRA, Kim et al. (25) found that the use of intravenous calcitriol in patients who were receiving hemodialysis was associated with a 13% reduction in the left ventricular mass index (P < 0.01) and a 32% reduction in the electrocardiogram QT dispersion (P < 0.01), compared with untreated control subjects. Preclinical studies also showed that paricalcitol treatment prevented left ventricular hypertrophy (LVH) and reduced cardiac atrial natriuretic factor in a rat model of salt-sensitive hypertension and heart failure (26). Because these beneficial cardiac effects occurred in animals with neither CKD nor elevated phosphate, paricalcitol may prevent LVH through its activation of cardiac myocyte VDR to inhibit directly effectors of LVH (e.g., atrial natriuretic factor [26]).

What should we do with the new VDRA data? The most prudent would be to maximize this form of therapy in all dialysis patients who are not hypercalcemic (serum calcium >10.5 mg/dl). Because it is possible that direct VDR activation within cardiac cells to improve cardiac function may be independent of serum phosphate levels, it now makes sense at least to consider continuous VDRA therapy in dialysis patients with elevated levels of serum phosphate or calcium-phosphate product. The choice of which VDRA to use should be based on clinically exposed differences in efficacy and safety. New preclinical studies indicate that calcitriol and doxercalciferol but not paricalcitol stimulate aortic expression of cbfa1/runx2 and osteocalcin, in addition to promoting marked aortic calcium accumulation (27). This suggests a potential protective effect for paricalcitol for not stimulating aortic vascular smooth muscle cells to undergo a transition to the osteoblast phenotype under conditions of hyperphosphatemia (28). Thus, differences in the action of these VDRA may extend beyond the previously documented differences in the intestinal absorption of calcium and phosphate to include differences in the vascular response to calcification. Future studies need to validate this finding in patients with CKD.

**Target Levels for Serum Calcium, Phosphate, and PTH**

Recommended target levels for serum calcium, phosphate, calcium-phosphate product, and PTH have now been incorporated into every dialysis unit protocol. Although there is some variability in these protocols from unit to unit, most dialysis units subscribe to the KDOQI opinion-based recommendations of serum calcium 8.5 to 10.2 mg/dl, phosphate 3.5 to 5.5 mg/dl, calcium-phosphate product <55 mg²/dl², and intact PTH (iPTH) 150 to 300 pg/ml (1). These recommendations were based largely on the only data at the time showing an association of elevated levels of calcium, phosphate, and PTH with mortality (29). Although a more recent analysis using the same statistical methods in a larger database (30) has corroborated the earlier study, newer data from analyses of other large dialysis databases using more robust statistical methods are available (15,18). One important new difference in these analyses is the use of time-dependent variable modeling with repeated measures (15,18) in place of the fixed-variable model used previously (29,30). Time-dependent modeling uses quarterly serum measurements to reflect more accurately the ability of calcium, phosphate, and PTH to predict mortality as these values change over time. As a result of using this technique, along with also adjusting for vitamin D use and the presence of malnutrition and inflammation using surrogate markers, Kalantar-Zadeh et al. (18) showed that the mortality risk in >58,000 dialysis patients was not increased for serum calcium between 8.5 and 10.5 mg/dl, for phosphate between 3.0 and 7.0 mg/dl, and for calcium-phosphate product between 40 and 75 mg²/dl². Mortality was also increased (30%) for calcium levels <8.5 mg/dl and for a decrease in serum calcium of ≥0.6 mg/dl during a 6-mo period (18). Why are these ranges different from those in previous studies? Because the use of repeated measures and the inclusion of vitamin D use and presence of malnutrition/inflammation into the model more accurately reflect the ability of the mineral levels to predict mortality. The
new findings that hypocalcemia or significant declines in serum calcium predict mortality (18) raise the concern that patients with LVH and QT dispersion on electrocardiogram (25,31) will be more prone to sudden death from arrhythmias during periods of low serum calcium.

What clinical impact will this have if we decide to incorporate these new target levels for use in our dialysis units? Probably the most important will be the improved delivery of injectable vitamin D. Vitamin D treatment would be enhanced because protocols would allow for the use of injectable vitamin D at higher levels of phosphate (up to 7.0 mg/dl), calcium (up to 10.5 mg/dl), and calcium-phosphate product (up to 75 mg²/dl²); therefore, more patients would receive injectable vitamin D for longer periods of time, thereby making PTH control more easily achievable. If these new ranges are adopted, then does that mean that we should worry less about high phosphate levels? Perhaps, because it seems that vitamin D therapy may offer protection from mildly elevated phosphate (levels <7.0 mg/dl). Should we still be aggressive in maintaining good phosphate control? Yes, even though no study to date has demonstrated that lowering the phosphate level improves mortality. For example, it has been shown only that the prevention of calcium loading is associated with less calcification and lowered mortality in incident dialysis patients (13).

Controversy exists as to the appropriate PTH level for stages 4 and 5 CKD. The recommended range for iPTH for patients with stage 4 CKD is 70 to 110 pg/ml and for stage 5 is 150 to 300 pg/ml (1); however, several new studies question the reliability of these PTH targets. The first is the discovery that even modest elevations of iPTH (60 to 120 pg/ml) in patients with stage 4 CKD are associated with low bone density (32). The second is that treatment with activated vitamin D to suppress PTH into the normal range in patients with stages 3 and 4 CKD is associated with improved spine and hip bone density (33) and improved bone formation in patients with adynamic bone (34). The third is the finding that dialysis patients with relatively low PTH levels and adynamic bone do not experience bone loss (35), suggesting that elevated PTH and high bone turnover are more important causes of bone loss than low PTH. Taken together, these new data provide evidence that patients with stages 3 and 4 CKD should have their PTH levels suppressed into the normal range with activated vitamin D to prevent bone loss and parathyroid gland enlargement. VDRA therapy may also prevent proteinuria in patients with stages 3 and 4 CKD (36).

In dialysis patients, the commonly accepted target for iPTH, 150 to 300 pg/ml, was based on bone biopsy evidence indicating a range at which many patients have normal rates of bone formation (37). Arguments have been made, however, against PTH’s being predictive of bone turnover (38) and that other surrogate markers (e.g., bone-specific alkaline phosphatase) may be more useful in predicting bone formation (39). Notably, high levels of PTH and alkaline phosphatase have recently been shown to predict mortality in dialysis patients, after adjusting for vitamin D intake and malnutrition/inflammation (18), emphasizing the association of high bone turnover and cardiovascular mortality. High bone turnover in dialysis patients is associated with bone loss, and VDRA therapy not only stops bone loss but also increases bone mineral density (40), consistent with its known anabolic effect. The prevention of bone loss by VDRA therapy has the potential to slow the progression of vascular calcification because recent findings showed a high correlation between high rates of bone loss with high rates of aortic calcification ($r = 0.72, P < 0.01$) from high bone turnover induced by estrogen deficiency in postmenopausal women with osteoporosis (41).

Studies are mixed about the mortality risk of PTH levels <150 pg/ml. One long-term study of dialysis patients demonstrated a 15% survival benefit in those who underwent parathyroidectomy, compared with matched control subjects (42). A more recent analysis of this population revealed that fracture rates were reduced in patients who had undergone a parathyroidectomy (43) despite the known high proportion with adynamic bone after parathyroidectomy. Moreover, Teng et al. (15) found lower mortality rates in those with iPTH levels <100 pg/ml regardless of whether they received injectable vitamin D; however, Kalantar-Zadeh et al. (18) found a 30% increased risk for mortality for PTH levels <200 pg/ml, although this seems to be confounded by the low vitamin D intake in that group because of protocols that limited vitamin D treatment for PTH levels <150 pg/ml. So far, there seems to be more evidence for elevated PTH (>200 pg/ml) to be a risk factor for cardiovascular mortality than for PTH levels <100 pg/ml. Future studies are needed to determine the potential benefit of intravenous and oral vitamin D in patients who have relatively low or normal PTH levels.

Conclusions
The new data support a revision of the KDOQI guidelines relating to calcium loading; VDRA therapy; and target levels for calcium, phosphate, and PTH. Kidney Disease: Improving Global Outcomes (KDIGO) is assessing evidence-based studies using a graded evidence format to address and resolve potential conflicting studies and to extrapolate from studies performed in patients without CKD (44). With a more focused attention to applying intravenous vitamin D therapy to as many patients as possible for as long as possible while preventing excess calcium loading, we should expect a significant decline in cardiovascular events and mortality rates. Future studies should investigate the effectiveness of VDRA therapy (intravenous and oral) to suppress PTH to normal levels without causing vascular calcification and bone loss in incident dialysis patients who are not taking calcium-containing phosphate binders.

Disclosures
D.L.A. is a speaker and consultant for Abbott and Shire.

References
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