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Kidney Disease Outcomes Quality Initiative (K/DOQI GUIDELINES) for Bone and Mineral Metabolism: Emerging Questions

Tejas V. Patel, MD, MPH and

Fellow, Renal Division, Brigham and Women's Hospital, Boston, Massachusetts

Ajay K. Singh, MB, FRCP

Director, Dialysis Service, Renal Division, Brigham and Women's Hospital, Boston, Massachusetts

Abstract

Since their initial publication in 2003, the National Kidney Foundation (NKF) Kidney Disease Outcomes Quality Initiative (K/DOQI) clinical practice guidelines for bone and mineral metabolism have transformed the clinical approach to the management of metabolic bone disease in both dialysis and non-dialysis chronic kidney disease (CKD) patients. These guidelines were largely based on expert opinion rather than evidence. In the past five years, with publication of several randomized controlled trials, large observational studies, and smaller clinical series, significant progress has been made in our understanding of mineral metabolism, calcium and phosphorus management, and the use of activated vitamin D irrespective of parathyroid hormone level in CKD. More recently, fibroblast growth factor-23 and serum alkaline phosphatase have been shown to predict mortality in dialysis patients, making these attractive markers to monitor. In the wake of this progress, the bone K/DOQI guidelines will need to be revised; here, we review some of the issues and controversies that will likely form the basis of these revised guidelines.

Keywords

K/DOQI; calcium; phosphorus; activated vitamin D; alkaline phosphatase; PTH; FGF-23

Background

Since the publication of the Kidney Disease Outcomes Quality Initiative (K/DOQI) clinical guidelines in 2003 (1), significant advances have been made in our understanding of altered bone and mineral metabolism in chronic kidney disease (CKD). As others have already suggested, in light of the progress, it is essential that a new iteration of the KDOQI metabolic bone disease guidelines be published (2). This article focuses on emerging issues in mineral metabolism in *adults* with CKD or end-stage renal disease.

Nomenclature

The 2003 NKF K/DOQI guidelines divide “recommendations” into “opinion” or “evidence.” In keeping with other national society guidelines, like the American Heart Association, we

Corresponding Author: Ajay K. Singh, MB, FRCP (UK), Renal Division, MRB-4, 75 Francis Street, Boston, MA 02115, Phone: (617) 732-5951; Fax: (617) 731-6392; email: E-mail: asingh@partners.org.

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suggest grading the evidence to give more information on its strength and quality. A commonly accepted grading system proposed by Liddle et al. (3) and modified by Atkins et al. (4) and by the GRADE working group (5) may be used. In this grading system, the level of evidence is rated from 1++ (for high-quality meta-analysis, systematic review, or randomized controlled trial) to 4 (expert opinion). Based on that, recommendations may be graded from A (at least one meta-analysis or randomized controlled trial) to D (based on expert opinion or case reports). This will help researchers and clinicians weigh the recommendations' validity.

There is increasing evidence linking abnormalities in mineral metabolism with cardiovascular disease in CKD (6). As a result, the Kidney Disease: Improving Global Outcomes (KDIGO) working group proposed new recommendations related to the nomenclature and diagnosis of bone and mineral disorders. Further, KDIGO developed a consensus on bone biopsy evaluation and classification and laboratory and imaging markers for assessment. The group proposed the term "CKD-MBD" (CKD-mineral and bone disease) to replace renal osteodystrophy to strengthen the link between CKD and mineral metabolism abnormalities. It suggested that "renal osteodystrophy" should be used only to describe associated bone disease (7). It is likely that these important consensus statements by experts will be incorporated into the next iteration of the K/DOQI metabolic bone disease guidelines.

Calcium

Calcium intake

The current K/DOQI guidelines recommend that total elemental calcium intake should not exceed 2gm/day to prevent vascular calcification (*Guideline 5, Opinion*). Numerous recent studies have shown higher coronary calcium score and mortality in patients consuming a high-calcium diet (8–10). As discussed by Andress, even at 1.4 to 2gm/day of calcium, the risk of calcification is present (2). Thus, a more reasonable recommendation may be a calcium intake of less than 1.4gm/day, with further restriction in diabetics due to higher burden of calcification (11). This will need to be discussed in the revised K/DOQI bone guidelines.

Serum calcium monitoring

The 2003 K/DOQI guidelines advise maintaining serum levels of total calcium, corrected for albumin level, within the "normal" range for the laboratory (*Guideline 6, Opinion*) (1). The basis for this K/DOQI recommendation favoring corrected total calcium over the active or ionized calcium (iCa) for routine measurement may be higher costs, technical difficulties, and availability of trained personnel to measure iCa. However, there is some evidence to support using iCa in CKD patients. In 691 French patients with non-dialysis CKD (CKD-ND), albumin-corrected total calcium did not predict ionized calcium better than uncorrected total calcium. Further, both uncorrected and albumin-corrected total calcium concentrations poorly predict hypo- or hypercalcemia in patients with CKD (12). Since advanced CKD patients have fluctuations in pH and albumin, measurement of total calcium may not give accurate assessment of active calcium (iCa) (13). As a result, a KDIGO position statement supported the measurement of iCa as the preferred method for evaluating serum calcium (7). The revised KDOQI bone guidelines may need to address the role of iCa in light of new findings and recommendation.

Calcium range

The K/DOQI guidelines recommend keeping corrected serum calcium within the lower end of the "normal range" (8.4 to 9.5mg/dL and not to exceed 10.2mg/dL) (*Guideline 6, Opinion*). However, there is little evidence to support that position. An international observational study found lowest mortality in patients with total calcium of 8.6–10mg/dL (14). However, this study did not appear to account for confounders adequately. In contrast, a recent study using time-

dependent models as well as adjusting for many confounders observed a 30% higher mortality in patients whose corrected serum calcium was $<8.5\text{mg/dL}$ or had decreased serum calcium by $>0.6\text{mg/dL}$ during a six-month period. Mortality was not higher within the serum calcium range of $8.5\text{--}10.5\text{mg/dL}$ (15). As discussed below, the fear of forming calcium and phosphorus precipitation in patients with high calcium has not been conclusively substantiated. Another unfounded practice is to withhold activated vitamin D from patients who have corrected serum calcium $>10.2\text{mg/dL}$. As discussed further in this article, vitamin D may have benefits beyond its regulation of mineral metabolism. K/DOQI guidelines may have to relax the serum calcium range to reflect these findings.

Phosphorous

Phosphorus range

The 2003 K/DOQI guidelines proposed maintaining serum phosphorus levels in CKD-ND between 2.7mg/dL and 4.6mg/dL and between 3.5 and 5.5mg/dL in dialysis CKD (CKD-D) patients (*Guideline 3, Evidence*). Even though the evidence cited is based on small cross-sectional studies, the cut-offs were ultimately based on a consensus opinion of the working group. A large study analyzing data from more than 58,000 patients evaluated the association of mortality with serum calcium, phosphorus, and parathyroid hormone (PTH). The authors of this study observed that mortality was not increased with serum phosphorus of $3.0\text{--}7.0\text{mg/dL}$ (15). Thus, most patients can be safely managed with activated vitamin D up to serum phosphorus level of 7mg/dL . This would give latitude to the dialysis provider to use activated vitamin D. We believe this issue will also need to be discussed in the revised KDOQI bone guidelines.

Phosphate binders

Since publication of the 2003 K/DOQI guidelines, the class of phosphate binder to be used to lower serum phosphorus has been hotly debated. The K/DOQI guidelines recommend either calcium-based or non-calcium-based phosphate-binders as the first line of treatment (*Guideline 5, Opinion*). However, an association between cumulative dosage of oral calcium and progression of vascular calcification has been reported (16). Because of this data as well as the publication of two randomized trials (TREAT to Goal and Dialysis Clinical Outcomes Revisited (DCOR)), non-calcium-based binders (Sevelamer hydrochloride (Renagel®) or Lanthanum carbonate (Fosrenol®)) have gained popularity over calcium-based binders (calcium carbonate or calcium acetate (PhosLo®)) among nephrologists. Unfortunately, recent studies comparing Sevelamer and calcium-based binders have generated conflicting results. Sevelamer has been the most studied non-calcium-based binder. The DCOR study did not report a significant mortality difference in *prevalent* CKD-D patients treated with Sevelamer versus a calcium-based phosphate binder. However, much emphasis was placed on a significant age interaction with significant reduction of mortality in patients >65 years of age (17). This conclusion has generated much controversy. On the other hand, Block et al. found in patients treated with Sevelamer versus calcium-based phosphate binders a reduction in mortality (18) and progression of coronary artery calcification (19) in *incident* CKD-D patients. In contrast, other studies (funded by Fresenius Medical Care, the maker of calcium acetate) have reported no difference between Sevelamer and calcium acetate in pre-specified outcome measures. Calcium Acetate Renagel Evaluation (CARE) showed that calcium acetate lowered serum phosphorus more effectively than Sevelamer over an 8-week period in CKD-D patients. Cost-effective analysis favored calcium acetate (20). Since Sevelamer also lowers low-density lipoprotein-cholesterol (LDL-cholesterol), a subsequent study by the same investigators randomized patients to Sevelamer or calcium acetate controlling LDL-cholesterol to a target of $<70\text{mg/dL}$ with the use of atorvastatin (CARE-2) (21). The investigators reported that after one year of follow-up, there was no difference in progression of coronary calcification in both

groups. Despite rigorous trials, the evidence is conflicting. Evidence on Lanthanum carbonate and magnesium-based phosphate binders is too limited to advocate widespread use. Given that non-calcium-based binders lack direct benefit and cost substantially more than calcium-based binders, (22) the K/DOQI guideline working group should consider the cost-benefit ratio for the entire CKD population. Except in special circumstances (e.g., hypercalcemia, severe peripheral vascular disease, etc.) the present evidence does not favor non-calcium-based binders as the first line of treatment for hyperphosphatemia. As eloquently pointed out in a recent review, pharmaceutical companies are heavily targeting nephrologists with the findings that promote their products and point out drawbacks in the competitor's study design or outcome measures (23). A recent editorial urged caution in interpreting study results, focusing on the objective analysis of the evidence rather than on opinion that might be swayed by marketing influences (24). A review of the relationship between phosphate bone turnover and cardiovascular disease is included in this *Seminars*.

Parathyroid Hormone

PTH measurement

The current K/DOQI guidelines have proposed measuring intact PTH (iPTH) to assess secondary hyperparathyroidism in CKD patients. *In vivo* studies showed that the iPTH (1–84) assay is not specific and also measures the N-terminus truncated PTH peptides (25). In contrast to active PTH peptides, the N-terminus truncated PTH fragments (7–84) may in fact lower serum calcium levels. Further, N-terminus fragment concentration rises with declines in renal function (26). To complicate matters further, these fragments are highly variable between different assays across different laboratories (27). It would be useful for the revised K/DOQI guidelines to recommend standardization of the plethora of PTH assays (similar to prothrombin time and serum creatinine) to minimize confusion at the provider level.

PTH range

The 2003 K/DOQI bone guidelines acknowledged that there is insufficient sensitivity and specificity of serum levels of PTH to predict the presence of adynamic bone disease reliably (*Guideline 1, Opinion*). This opinion was based on meta-analysis of five small cross-sectional studies using different PTH assays. Since adynamic bone disease is associated with calcium imbalance and CVD, the prevailing notion is that activated vitamin D may exacerbate the condition, and clinicians have been reluctant to administer vitamin D or vitamin D analogues to patients with iPTH <100pmol/L. Interestingly, a clinical study by Teng et al. showed lower mortality when patients with iPTH <100pmol/L were given activated vitamin D (28). Furthermore, this study showed improved outcome in patients with iPTH <150pmol/L in CKD-D patients (28). Thus, treatment with vitamin D in the setting of low iPTH needs to be reevaluated and should be addressed in the revised K/DOQI bone guidelines. Another important issue is the use of calcium dialysate in patients with low turnover bone disease. The K/DOQI bone guidelines recommend maintaining dialysate calcium at 1.25mmol/L in CKD-D patients (*Guideline 9, Opinion*). Recent evidence suggests that patients with adynamic bone disease can be safely treated with lower calcium dialysate solution with improvement in bone density (1.0–1.25mmol/L) (29). We believe that the revised K/DOQI bone guidelines may need to consider recommending a lower target range of iPTH in CKD-D. Furthermore, as suggested by Andress, other causes of adynamic bone disease should also be considered, including poor glucose control and hypogonadism in men (30).

The 2003 K/DOQI bone guidelines recommendation regarding iPTH levels in CKD stage 3 and 4 is opinion based (*Guideline 1, Opinion*). Recent studies have shown that treating modestly elevated levels of iPTH (up to 120pmol/L) in CKD-ND with vitamin D results in improved bone density and bone formation (31,32). Based on these studies, vitamin D status

should be corrected in these patients and normal PTH levels targeted. The upper range of iPTH of 300pmol/L in CKD-D patients is also based on thin evidence from a meta-analysis of small studies. Since iPTH>200pmol/L has been associated with CVD outcome, it is important to treat it with activated vitamin D aggressively (15). Taken together, the recommended iPTH range in CKD patients will need to be reanalyzed and revised by the K/DOQI working group.

Calcium and Phosphorus Product

The 2003 K/DOQI guidelines recommend maintaining the $\text{Ca} \times \text{P} < 55 \text{mg}^2/\text{dL}^2$ (*Guideline 6, Evidence*). The evidence for this recommendation is based on small uncontrolled studies (33, 34). Kalanta-Zadeh et al. analyzed a large database from DeVita patients on chronic hemodialysis (>58,000) using a time-dependent model (as described in the phosphorus section) and observed that all-cause mortality did not differ for the $\text{Ca} \times \text{P}$ range of 40–75 mg^2/dL^2 . This study adjusted for known confounders as well as for co-morbid conditions and the malnutrition-inflammation complex (MICS) (15). The biologic basis that calcium and phosphorus would precipitate at a $\text{Ca} \times \text{P}$ product $> 55 \text{mg}^2/\text{dL}^2$ is speculative. A recent review evaluating *in vitro* and *in vivo* studies related to calcium and phosphorus interaction concluded that the cut-off of $> 55 \text{mg}^2/\text{dL}^2$ is over-simplified and scientifically flawed. The author argued that CaHPO_4 precipitation does not occur in plasma until the $\text{Ca} \times \text{P}$ product is *three* times the KDOQI threshold (35). Finally, the $\text{Ca} \times \text{P}$ product is one of the limiting factors in the decision to administer activated vitamin D. Given the beneficial effects of vitamin D and the less than impressive strength of evidence on the $\text{Ca} \times \text{P}$, we believe that the next version of the K/DOQI bone guidelines should relax the range of the $\text{Ca} \times \text{P}$ product.

Use of calcimimetic agents

Even prior to the cloning of the calcium sensing receptor (CaSR) by Edward M. Brown et al. (36), there was intense interest in lowering the PTH level (and plasma calcium) by pharmacologically targeting the parathyroid gland (37). The 2003 K/DOQI guidelines were published before the CaSR agonist cinacalcet (Sensipar®, Amgen, Thousand Oaks, CA) became available. Cinacalcet effectively lowers PTH and calcium in secondary hyperparathyroidism related to CKD (38). Recently, cinacalcet has been shown to reduce parathyroid hyperplasia in a rat model of secondary hyperparathyroidism (39) and in patients on hemodialysis and secondary hyperparathyroidism, it reduces the set-point of calcium-PTH curve, thereby sensitizing parathyroid to lower calcium (40). However, cardiovascular events and mortality have not been evaluated. Evaluation of Cinacalcet Therapy to Lower Cardiovascular Events (EVOLVE), a double-blind, placebo-controlled, randomized trial will attempt to address the hard end-point of cardiovascular outcome in patients treated with cinacalcet versus placebo in CKD-D patients with secondary hyperparathyroidism (41). We anticipate that the revised K/DOQI bone guidelines will comprehensively evaluate the role of cinacalcet in secondary and refractory tertiary hyperparathyroidism in both CKD and post-transplant patients.

Role of Activated Vitamin D

The 2003 K/DOQI bone guidelines recommend that active vitamin D sterol should be administered if the iPTH is $> 300 \text{pmol/L}$ (*Guideline 7, Opinion*). Furthermore, the guidelines recommend holding activated vitamin D therapy if the serum calcium is $> 9.5 \text{mg/dL}$ or the serum phosphorus is $> 4.6 \text{mg/dL}$ (*Guideline 8, Opinion*). There has been tremendous progress in our understanding of vitamin D physiology and influence on bone health and mortality in CKD patients since the 2003 publication of these guidelines. For example, a small randomized trial demonstrated improved bone health (as assessed by DEXA bone density tests and serum bone biomarkers) in CKD-ND patients who received alfacalcidol compared with a placebo (31). More recently, the association of activated vitamin D therapy with reduced mortality in

CKD patients, irrespective of PTH level in CKD patients, has been reported (28,42). Animal studies have demonstrated independent beneficial effects of vitamin D through inhibiting calcification by suppression of type 1 collagen, augment matrix Gla protein, and bone morphogenic protein 2, thereby inhibiting calcification and reducing interleukin-6 synthesis (43). Evidence is mounting for more aggressive use of activated vitamin D in CKD patients. Given the benefits of activated vitamin D, the revised K/DOQI bone guidelines may need to modify the target serum calcium and serum phosphorus ranges used in determining vitamin D treatment. Does every patient with CKD-D need to receive activated vitamin D irrespective of the PTH levels? Whether treating patients deficient in 25-vitamin D with a course of ergocalciferol improves clinical outcome remains unknown. We refer readers to the accompanying section of this issue for details on the role of vitamin D in CKD patients.

Diagnosis and Management of Osteoporosis in CKD

The 2003 K/DOQI bone guidelines highlight the need to assess the status of bone disease in CKD patients, transplant recipients with fracture(s) from minimal trauma, and patients receiving glucocorticoids. The guidelines advocate the use of a dual energy X-ray absorptiometry (DEXA) scan, which is limited in identifying the type of bone disease in CKD (*Guideline 2, Opinion*). The utility of a quantitative CT scan, serum, or urine bone biomarkers of formation and resorption (e.g., osteoprotegerin, N-telopeptide, bone-specific alkaline phosphatase, tartrate-resistant acid phosphatase, etc.), were not addressed probably due to lack of evidence. In fact, the use of bisphosphonates was also not discussed.

The DEXA scan accurately predicts fracture risk in the general population but loses its predictive value as CKD progresses, eventually becoming severely limited in patients with advanced CKD (44). In patients with advanced CKD or those on dialysis, the utility of bone turnover biomarkers, especially serum biomarkers, needs to be explored. Small studies have demonstrated an association between some of these newly described markers of bone turnover and bone mineral density in dialysis patients (45,46). Whether these biomarkers correlate with bone histology and predict risk of fractures in CKD patients remains to be seen and will need to be weighed in the revised KDOQI bone guidelines. Treatment for osteoporosis also rests largely on opinion rather than evidence. To date, some nephrologists and transplant physicians have used bisphosphonates in CKD patients with osteoporosis by extrapolating from non-CKD patient data. The best evidence comes from the experience with bone loss in glucocorticoid-treated patients. A small study in CKD-ND patients receiving glucocorticoids for more than 6 months demonstrated improvement in patients taking oral risedronate plus vitamin D compared with vitamin D alone after one year of follow-up. Bone biomarkers (N-telopeptide and bone-specific alkaline phosphatase) were also lower in the risedronate-treated group (47). Another study reported that bisphosphonate was effective and safe in preventing bone loss in transplant recipients treated with glucocorticoid (48). On the other hand, the use of bisphosphonate therapy in adynamic bone disease is likely to be of no benefit or even harmful. This is because bisphosphonate treatment in low-bone turnover patients would further lower bone turnover and likely increase the risk of fracture. Taken collectively, however, a recommendation regarding the use of bisphosphonates remains largely opinion based since there is a paucity of studies in advanced CKD.

Newer agents such as receptor activator of nuclear kappa B ligand (RANKL) inhibitor (e.g., denosumab), which blocks osteoclast differentiation, activation, and survival, appear to be promising in postmenopausal osteoporosis (49). However, the role of these agents in CKD patients remains to be evaluated. In summary, the revised K/DOQI guidelines need to address the diagnosis and treatment of metabolic bone disease in CKD patients. These topics are addressed by experts in the field in the separate manuscripts in this issue by Susan Ott and Paul Miller.

Alkaline Phosphatase

Serum alkaline phosphatase is a direct marker of bone turnover. Surprisingly, the 2003 K/DOQI bone guidelines did not opine on the desired target range for serum alkaline phosphatase, even though it is measured at regular intervals in almost all CKD-D patients. Regidor et al. took advantage of the existing measurements of serum alkaline phosphatase in 73,960 chronic hemodialysis patients in the DaVita network. The authors reported that after adjusting for multiple known confounders, patients with serum alkaline phosphatase >120U/L had higher all-cause mortality at 3 years (hazard ratio 1.25) (50). Given that this test is routinely performed in CKD-D patients, the K/DOQI working group may need to evaluate the application of alkaline phosphatase in the management of metabolic bone disease in the next revision.

Role of Fibroblast Growth Factor-23

FGF-23 is a potent phosphaturic hormone that belongs to the phosphatonin group. Serum levels of FGF-23 are inversely related to renal function (51). Although the interaction of FGF-23 with phosphorus, PTH, and vitamin D are discussed in more detail in a separate section of this issue it is important to point out that this marker has been associated with progression of CKD (52) and has been recently associated with increased mortality in CKD-D patients (53). This marker is not yet commercially available but appears to be an exciting future tool to guide management of metabolic bone disease.

Summary

Since the publication of the 2003 K/DOQI guidelines for bone and mineral metabolism, there has been tremendous advancement in our understanding of mineral metabolism in CKD patients. As proposed by Al-Badr et al. (54) and Andress (2), major modifications of K/DOQI bone guidelines are essential and should reflect our improved understanding of calcium and phosphorus metabolism. While observational studies provide valuable insights into the treatment of patients, at best they are hypothesis setting. There is a desperate need for randomized trials to better inform decision making and further optimize care of CKD patients.

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