

## KDOQI US Commentary on the 2017 KDIGO Clinical Practice Guideline Update for the Diagnosis, Evaluation, Prevention, and Treatment of Chronic Kidney Disease–Mineral and Bone Disorder (CKD-MBD)

Tamara Isakova, MD, MMSc,<sup>1</sup> Thomas L. Nickolas, MD, MS,<sup>2</sup> Michelle Denburg, MD, MSCE,<sup>3,4</sup> Sri Yarlagadda, MD,<sup>5</sup> Daniel E. Weiner, MD, MS,<sup>6</sup> Orlando M. Gutiérrez, MD, MMSc,<sup>7,8</sup> Vinod Bansal, MD,<sup>9</sup> Sylvia E. Rosas, MD,<sup>10</sup> Sagar Nigwekar, MD, MMSc,<sup>11</sup> Jerry Yee, MD,<sup>12</sup> and Holly Kramer, MD, MPH<sup>9,\*</sup>

Chronic kidney disease–mineral and bone disorder (CKD-MBD) encompasses laboratory and bone abnormalities and vascular calcification and has deleterious effects on clinical outcomes. KDOQI (Kidney Disease Outcomes Quality Initiative), an initiative of the National Kidney Foundation, addressed this issue with the publication of a clinical practice guideline for bone metabolism and disease in CKD in 2003, and 2 years later, a new definition and classification scheme for CKD-MBD was developed following a KDIGO (Kidney Disease: Improving Global Outcomes) Controversies Conference. The initial KDIGO guideline on CKD-MBD was then published in 2009. New evidence was subsequently reviewed at the 2013 KDIGO Controversies Conference, and in 2017, KDIGO issued a clinical practice guideline update for the diagnosis, evaluation, prevention, and treatment of CKD-MBD. This commentary presents the views of the KDOQI CKD-MBD work group convened by the National Kidney Foundation. The KDOQI work group agrees with most of the KDIGO guideline update recommendations, particularly the suggestions regarding bone mineral density testing, joint assessments of longitudinal trends in mineral metabolism markers, and dietary phosphate counseling focused on phosphate additives. However, the KDOQI work group has some concerns about the suggestions related to hypocalcemia and hypercalcemia, phosphate-binder choice, and treatment of abnormal parathyroid hormone concentrations. The overall goal of this commentary is to provide a broad discussion for the US nephrology community regarding CKD-MBD and its diagnosis, prevention, and treatment.

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**INDEX WORDS:** Chronic kidney disease–mineral and bone disorder (CKD-MBD); renal osteodystrophy; clinical practice guideline; bone mineral density (BMD); mineral metabolism; phosphate binders; parathyroid hormone (PTH); calcium; phosphate; nephrology best practices; evidence-based medicine; dialysis; end-stage renal disease (ESRD).

*As they are designed to reflect the views and recommendations of the responsible KDOQI Commentary work group and because they are reviewed and approved by KDOQI leadership, KDOQI Commentaries are not peer reviewed by AJKD. This article was prepared by a KDOQI Commentary work group comprising the authors and co-chaired by Drs Isakova and Kramer. It was reviewed and approved by Michael Rocco, MD, MSCE (KDOQI Chair), Bernard B. Jaar, MD, MPH (KDOQI Vice Chair, Education), and Michael J. Choi, MD (National Kidney Foundation President).*

### INTRODUCTION

Chronic kidney disease–mineral bone disorder (CKD-MBD) is a nearly universal complication of progressive loss of kidney function. Biochemical abnormalities, vascular calcification, and bone fragility constitute the CKD-MBD syndrome, and each is consistently associated with increased risks for morbidity and mortality in large observational studies across the spectrum of CKD.<sup>1-3</sup> Evidence from

From the <sup>1</sup>Division of Nephrology and Hypertension, Department of Medicine and Center for Translational Metabolism and Health, Institute for Public Health and Medicine, Northwestern University Feinberg School of Medicine, Chicago, IL; <sup>2</sup>Division of Nephrology, Department of Medicine, Columbia University Medical Center, New York, NY; Departments of <sup>3</sup>Pediatrics and <sup>4</sup>Epidemiology, The Children's Hospital of Philadelphia, Perelman School of Medicine at the University of Pennsylvania, Philadelphia, PA; <sup>5</sup>Division of Nephrology and Hypertension, Department of Medicine and Kidney Institute, University of Kansas Medical Center, Kansas City, KS; <sup>6</sup>Division of Nephrology, Department of Medicine, Tufts Medical Center, Tufts University School of Medicine, Boston, MA; <sup>7</sup>Division of Nephrology, Department of Medicine, and <sup>8</sup>Department of Epidemiology, University of Alabama at

Birmingham, Birmingham, AL; <sup>9</sup>Division of Nephrology, Department of Medicine, Loyola School of Medicine, Chicago, IL; <sup>10</sup>Joslin Diabetes Center, Harvard Medical School; <sup>11</sup>Division of Nephrology, Department of Medicine, Massachusetts General Hospital, Boston, MA; and <sup>12</sup>Division of Nephrology and Hypertension, Henry Ford Hospital, Detroit, MI.

\*KDOQI Vice Chair of Commentaries.

Address correspondence to Tamara Isakova, MD, MMSc, 633 N St. Clair St, Ste 18-089, Chicago, IL 60611. E-mail: [tamara.isakova@northwestern.edu](mailto:tamara.isakova@northwestern.edu)

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experimental studies supports causal links between disordered bone and mineral metabolism and adverse clinical outcomes.<sup>3-5</sup> Based largely on observational and preclinical data and expert opinion, KDOQI (Kidney Disease Outcomes Quality Initiative), an initiative of the National Kidney Foundation, issued its clinical practice guideline for bone metabolism and disease in CKD in 2003.<sup>6</sup> This was followed by the KDIGO (Kidney Disease: Improving Global Outcomes) CKD-MBD guideline, which was published in 2009, following a KDIGO Controversies Conference held in 2005.<sup>1</sup> Both guidelines led to substantial changes in clinical practice, including more frequent laboratory testing of parathyroid hormone (PTH), serum calcium, phosphate, and vitamin D levels. With the emergence of additional evidence, which was reviewed at the 2013 KDIGO Controversies Conference, the KDIGO issued a clinical practice guideline update for the diagnosis, evaluation, prevention, and treatment of CKD-MBD in 2017.<sup>7</sup> The updated guideline continues to recommend monitoring of mineral metabolism parameters, but a more individualized approach is now suggested for medical management of CKD-MBD given the lack of benefit on intermediate biochemical and cardiovascular end points, but evident risks, such as hypercalcemia. Due to lack of evidence for many CKD-MBD management decisions, a large number of updated recommendations continue to be opinion based. This commentary presents the views of a KDOQI-convened work group. This work group assessed the KDIGO guideline update to assist clinical providers in the United States in interpreting and determining the clinical utility of the guideline and to facilitate its implementation.

#### REVIEW AND APPROVAL PROCESS FOR THIS COMMENTARY

The KDOQI Steering Committee selected Co-Chairs and members of the KDOQI work group based on their clinical and research expertise, as well as interest in the guideline process or familiarity with end-stage renal disease quality metrics. During the selection process, particular emphasis was placed on identifying individuals with diverse perspectives and with experience in taking care of adult and pediatric patients with CKD, transplant recipients, and patients undergoing dialysis.

KDOQI work group members worked in groups of 3 to review recent literature and provide commentary on the KDIGO guideline update regarding diagnosis and management of bone disease, phosphate lowering and PTH monitoring, and treatment. The work group discussed the guideline via teleconference, and all work group members and KDOQI leadership reviewed and approved the commentary after reaching

consensus. In the following, numbered text within horizontal rules is quoted directly from the KDIGO document, using the same numbering scheme as in the original. Not all guideline statements are included; only those that were revised in the 2017 guideline update are reproduced here. Immediately following the text of each included guideline recommendation, we present comments on the recommendation and discuss its clinical utility and implementation in the United States (see [Box 1](#) for an overview). All material is reproduced with permission of KDIGO.

#### GUIDELINE STATEMENTS AND COMMENTARY

##### Diagnosis of CKD-MBD: Bone Mineral Density Testing

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3.2.1: In patients with CKD G3a-G5D with evidence of CKD-MBD and/or risk factors for osteoporosis, we suggest BMD testing to assess fracture risk if results will impact treatment decisions (2B).

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##### Commentary

Renal osteodystrophy is defined as an alteration of bone quality in patients with CKD that is classified based on 3 histologic descriptors: bone turnover, mineralization, and volume.<sup>8</sup> Dual-energy x-ray absorptiometry bone mineral density (DXA BMD) cannot delineate renal osteodystrophy type, and at the time of writing of the 2009 KDIGO guideline, there was a lack of evidence that DXA BMD predicted fracture risk in patients with CKD, as is the case in the general population. Therefore, the 2009 KDIGO guideline suggested that routine BMD testing not be performed.<sup>1</sup> The guideline update represents a marked departure from the 2009 recommendation, and it is backed by 4 prospective cohort studies that demonstrated that measurement of BMD by DXA predicted fractures in adults with CKD stages G3a to G5D.<sup>9-12</sup> Studies also demonstrated that the World Health Organization (WHO) T-score thresholds are predictive of fracture risk in CKD. The KDOQI work group agrees with the revised guideline and its justification. However, the KDOQI work group stresses that in patients with CKD-MBD, BMD does not predict bone turnover type, which is an important determinant of selecting a pharmacologic treatment in this population. The KDOQI work group also notes that the data on predictive performance of BMD in the dialysis population came from a single study conducted in Japan.<sup>9</sup> Additional studies in the US dialysis population are needed.

##### Clinical Utility

The guideline now allows for stratification of fracture risk based on objective evidence. While nonpharmacologic strategies such as weight-bearing

**Box 1.** Key Points addressed by the KDOQI work group**Diagnosis and Treatment of Bone**

The commentary addresses:

- Recommendations related to BMD testing, bone biopsy, and treatment
- Importance of bone biopsy data to provide information on type of renal osteodystrophy and the necessity of this information to guide treatment
- Limited availability to bone biopsy data and the suggestion to consider retraining nephrologists in this technique
- Lack of evidence to guide treatment to prevent fractures in patients with CKD

**Treatment of CKD-MBD Targeted at Lowering High Serum Phosphate and Maintaining Serum Calcium**

The commentary addresses:

- Recommendations related to management of phosphate and calcium levels
- Concern for calcium overload in CKD and its impact on the KDIGO guideline update
- Impediments related to implementation of recommendations for dietary phosphate intake

**Treatment of Abnormal PTH levels in CKD-MBD**

The commentary addresses:

- Recommendations related to management of elevated PTH levels
- Impact on the KDIGO guideline update of the opinion that early PTH rise is appropriately adaptive and that there may be skeletal resistance to PTH, and of the concern for hypercalcemia with the use of calcitriol and active vitamin D analogues
- Potential unintended consequences of updated recommendations with regard to management of secondary hyperparathyroidism in patients with advanced CKD

Abbreviations: BMD, bone mineral density; CKD, chronic kidney disease; CKD-MBD, chronic kidney disease–mineral bone disorder; KDIGO, Kidney Disease: Improving Global Outcomes; KDOQI, Kidney Disease Outcomes Quality Initiative; PTH, parathyroid hormone.

exercise can potentially be implemented in all patients at higher risk for fracture, pharmacologic strategies can be implemented in patients who fit the characteristics of patients enrolled into the osteoporosis registration trials.

**Implementation and Challenges**

Recommendation 3.2.1's criterion of "if results will impact treatment decisions" creates some ambiguity and does not provide actionable recommendations. This deficiency stems from lack of established pharmacologic fracture prevention strategies for patients with CKD. Currently, no clinical trials with any pharmacologic agent that prevents fracture in the general population are being conducted in patients with CKD. A recently published meta-analysis of 13 trials (n = 9,850) that included kidney transplant recipients, patients with CKD stages 3 to 5D, or postmenopausal women with CKD concluded that the impact of medications for osteoporosis (bisphosphonates, teriparatide, raloxifene, and denosumab) on BMD, fracture risk, and safety in CKD were not clear.<sup>13</sup> Secondary analyses of the bisphosphonate registration trials are post hoc and are applicable only to patients with CKD stages 3 to 4 without evidence of CKD-MBD. Data are especially limited for patients with CKD stages G5 to G5D.

The KDIGO guideline provides no specific recommendations for children, acknowledging that there are no studies examining the association of DXA BMD and fractures in children and adolescents with CKD. One prospective study in children with CKD

stages G2 to G5D found that lower cortical volumetric BMD (based on tibia peripheral quantitative computed tomography [pQCT]) predicted incident fractures.<sup>14</sup> In this cohort study, the correlations of height-adjusted lumbar spine and whole-body DXA with pQCT volumetric BMD measures were modest, and there were differential effects on cortical versus trabecular bone in young children. To date, there are no data regarding use of DXA BMD for fracture risk prediction in children with CKD.

**Diagnosis of CKD-MBD: Bone Biopsy**

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- 3.2.2: In patients with CKD G3a-G5D, it is reasonable to perform a bone biopsy if knowledge of the type of renal osteodystrophy will impact treatment decisions (*Not Graded*).
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**Commentary**

The update to 3.2.2 recommends that when a patient is identified as having a high risk of fracture, bone biopsy is not needed to select a treatment strategy (ie, vitamin D analogues, antiresorptive agents, and anabolic agents) unless the underlying bone turnover or renal osteodystrophy type will help define the treatment. This guideline statement was changed in light of the growing experience with osteoporosis medications in patients with mild to moderate CKD. Lack of ability to perform a bone biopsy may not justify withholding treatment for patients at high risk for fracture.

**Clinical Utility**

Fracture is a painful and debilitating event that is associated with increased mortality; therefore, patients with or at risk for fractures require treatment. Growing experience in patients with CKD with agents that prevent fractures in the general population suggests that these agents are safe and effective. Knowledge of the type of renal osteodystrophy informs treatment strategy beyond control of secondary hyperparathyroidism. For example, prior to starting antiresorptive treatment, ruling out osteomalacia and/or adynamic bone disease is necessary. If the clinician is confident in his or her ability to noninvasively rule out those disorders, treatment with an antiresorptive agent can be started without the need for bone biopsy. If the clinician believes that the underlying type of renal osteodystrophy needs to be determined prior to starting treatment but is unable to noninvasively make that assessment, bone biopsy should be performed.

**Implementation and Challenges**

Noninvasive assessments of renal osteodystrophy type are limited by the performance of PTH and bone turnover markers to predict low and high turnover. Some nephrologists may not be comfortable interpreting noninvasive assessments of bone turnover; therefore, they may consider referring patients with high fracture risk to physicians with expertise in metabolic bone disorders for decisions regarding treatment strategies that may include initiation of antiresorptive or anabolic agents. The determination of whether the bone biopsy will impact treatment decisions is limited by the lack of clinical trial evidence on the efficacy of osteoporosis medications in patients with CKD, in particular in patients with advanced CKD. The widespread lack of availability of trained personnel to perform and evaluate bone biopsies may be an impediment to implementing this guideline recommendation and guideline recommendation 4.3.3, which refers to treatment choices.

**Treatment of CKD-MBD: Guidance For Phosphate, Calcium, and PTH Levels**


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4.1.1: In patients with CKD G3a-G5D, treatments of CKD-MBD should be based on serial assessments of phosphate, calcium, and PTH levels, considered together (*Not Graded*).

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**Commentary**

The KDOQI work group endorses the rationale behind this recommendation, particularly given the diurnal variability in phosphate, calcium, and PTH concentrations.<sup>15</sup> This recommendation stands in

accordance with the 2009 KDIGO guidance on this issue,<sup>1</sup> and in the absence of evidence supporting a substantive change, the updated language is justified.

**Clinical Utility**

Serum calcium, phosphate, and PTH are commonly measured together in clinical practice, and the results of each value are generally interpreted in the context of the other individual metabolites.

**Implementation and Challenges**

There will likely be few barriers to adopting the suggestion to obtain serial measurements in calcium, phosphate, and PTH because these are already commonly obtained together repeatedly, especially in patients undergoing dialysis. However, because individual providers may be inclined to react to abnormal laboratory values at a single time point, it may be challenging to implement the suggested response to temporal trends rather than isolated abnormalities. Substantial biological variability in PTH levels further complicates interpretation of serial PTH assessments. For a given individual, up to 26 measurements may be needed to estimate a patient's intact PTH homeostatic set point to within 10% with 95% probability.<sup>16,17</sup> Because the guideline recommendation does not provide specific recommendations regarding management of temporal changes in calcium, phosphate, and PTH concentrations and there are no definitive thresholds for interventions, the utility of serial measurements may be attenuated.

**Treatment of CKD-MBD: Phosphate Levels**


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4.1.2: In patients with CKD G3a-G5D, we suggest lowering elevated phosphate levels toward the normal range (2C).

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**Commentary**

Recommendation 4.1.2 represents one of the most noticeable revisions from the 2009 KDIGO guidance on this issue with regard to non-dialysis-dependent CKD. The 2009 guideline suggested maintaining serum phosphate concentrations in the normal range in patients with CKD stages 3 to 5 and lowering elevated phosphate levels toward the normal range in individuals treated with dialysis.<sup>1</sup> After evidence accumulated showing that higher serum phosphate concentrations are associated with worse outcomes in individuals with CKD when other factors, including nutritional sufficiency, are accounted for, the nephrology community generally embraced the concept that lowering serum phosphate concentrations, either through dietary manipulation or the use of oral phosphate binders, may improve outcomes across the spectrum of CKD.<sup>2</sup> The 2009 KDIGO

guideline largely reflected the enthusiasm for the concept of lowering serum phosphate concentrations and suggested that serum phosphate concentrations should be maintained in the normal range in non-dialysis-dependent CKD.<sup>1</sup>

In reviewing this previous recommendation and studies published after the last guideline was released, the KDIGO 2017 guideline update noted the lack of evidence supporting the efficacy of phosphate-lowering therapies in normophosphatemic individuals with CKD. The KDIGO guideline update also considered new evidence that suggested potential for harm from use of phosphate binders in this population. A trial of 148 patients with CKD stages 3 to 4 and a mean serum phosphate concentration of  $4.2 \pm 0.2$  mg/dL showed that oral phosphate binders compared to placebo provided modest reductions in serum phosphate and no change in fibroblast growth factor 23 (FGF-23) concentrations despite a 22% decline in urinary phosphate excretion.<sup>18</sup> This trial also showed increased vascular calcification in participants treated with oral phosphate binders as compared to placebo (perhaps driven by participants randomly assigned to calcium acetate). The prescription of low-phosphate diets in individuals with normal serum phosphate concentrations was also seen as potentially problematic given the lack of efficacy data and the possibility of harm in promoting lower protein intake in a population at high risk for protein malnutrition.<sup>19</sup> On the basis of these findings, the guideline update avoids language that could be interpreted as recommending active interventions to prevent the development of hyperphosphatemia (ie, prescribing oral phosphate binders or lower dietary phosphate intake) in individuals with normal serum phosphate concentrations and instead suggests that treatment should be focused on individuals who develop sustained hyperphosphatemia.

This guideline recommendation also applies to individuals with CKD stage 5D, in whom phosphate levels above the normal range are common. The guideline maintains the prior recommendation that phosphate levels should be lowered toward normal but does not recommend that phosphate levels must be in the normal range, recognizing the lack of data to support a benefit of phosphate lowering on important clinical outcomes such as all-cause mortality.

### Clinical Utility

The KDOQI work group acknowledges the lack of sufficient evidence supporting the prescription of phosphate-lowering therapies to patients with CKD with normal serum phosphate concentrations. However, it is not common practice for individuals with normal serum phosphate concentrations to be prescribed phosphate-lowering therapies.<sup>20</sup> The KDOQI

work group has concern that there may be an unintended consequence of discouraging clinicians from recommending reductions in dietary phosphate intake (in a way that does not impede adequate protein intake) in a patient with gradually increasing serum phosphate levels within the normal range. Such dietary interventions might prevent or delay the onset of secondary hyperparathyroidism, and their reduced use may result in greater incidence of severe secondary hyperparathyroidism later in the course of CKD, which may lead to greater use of expensive PTH-lowering therapies. It is important to emphasize that no studies have shown that lowering serum phosphate concentrations improves clinical outcomes, such as mortality, for any CKD stage. The clinical utility of these recommendations is largely unknown and represents an important gap in knowledge.

### Implementation and Challenges

The recommendation to reduce serum phosphate levels toward the normal range presupposes that a normal range is established and widely accepted; however, there is variability in the normal range of serum phosphate from laboratory to laboratory, without any clear consensus as to what is normal or preferred in the setting of CKD. Further, diurnal variation in serum phosphate concentrations can be as great as 1 mg/dL from early morning to midafternoon,<sup>21,22</sup> meaning that an individual patient's serum phosphate concentration may be within a laboratory's normal range when measured in the morning yet above the normal range when measured later that same day. This raises the difficult question of how to define hyperphosphatemia in patients with CKD and how to standardize phosphate measurements among patients and laboratories. Without more definitive guidance on these 2 issues, the implementation of this recommendation will be difficult.

### Treatment of CKD-MBD: Calcium Levels

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4.1.3: In adult patients with CKD G3a-G5D, we suggest avoiding hypercalcemia (2C). In children with CKD G3a-G5D, we suggest maintaining serum calcium in the age-appropriate normal range (2C).

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### Commentary

Recommendation 4.1.3 maintains the prior suggestion to avoid hypercalcemia, but with regard to hypocalcemia, there is now a change from the 2009 recommendation, which stated "We suggest that, in patients with hypocalcemia, calcimimetics be reduced or stopped depending on severity, concomitant medications, and clinical signs and symptoms (2D)."<sup>1(pS7)</sup> The KDIGO guideline update now emphasizes that: "Mild and asymptomatic hypocalcemia (e.g., in the

context of calcimimetic treatment) can be tolerated in order to avoid inappropriate calcium loading in adults.”<sup>7(p19)</sup> The scientific justification provided within the KDIGO guideline update for the approach of tolerating moderate hypocalcemia reflects concerns that a possible positive calcium balance will predispose to vascular and valvular calcifications and an increased risk for cardiovascular events, including arrhythmia.<sup>23,24</sup> The KDOQI work group believes that this change provides clinicians with greater leeway in using calcimimetics to lower elevated PTH concentrations in the setting of mild hypocalcemia. The KDOQI work group agrees that avoidance of hypercalcemia and positive calcium balance are reasonable goals, but notes that many factors beyond calcium contribute to the pathogenesis of vascular and valvular calcifications.

Although measures to reduce calcium levels once they are elevated are not addressed in the KDIGO guideline update, the KDOQI work group anticipates that an unintended consequence of the suggestion to avoid hypercalcemia may be greater use of interventions aimed at reducing elevated calcium levels. The existence of hypercalcemia metrics in US dialysis quality assessment and payment policy supports the KDOQI work group’s concern. These metrics might encourage use of low dialysate calcium concentrations and calcimimetics. The KDOQI work group cautions against use of low dialysate calcium concentration for calcium reduction because observational studies have linked this maneuver with increased risk for arrhythmia and heart failure.<sup>25,26</sup> The KDOQI work group also does not endorse use of calcimimetics specifically for calcium lowering.

With respect to the updated guideline statement for children, for whom growth is an important factor, the recommendation to maintain serum calcium concentrations in the age-appropriate normal range is clinically justified; accordingly, the KDOQI work group endorses this recommendation. In contrast to adults, the growing skeleton must be in positive calcium balance to achieve normal bone accrual, with average peak calcium accretion rates of 359 and 284 mg/d in boys and girls, respectively.<sup>27</sup> Therefore, permissive mild hypocalcemia could have deleterious effects and should be avoided.

### Clinical Utility

The EVOLVE (Evaluation of Cinacalcet Hydrochloride Therapy to Lower Cardiovascular Events) Study compared cinacalcet, an oral calcimimetic agent, to placebo in 3,883 patients undergoing hemodialysis who had secondary hyperparathyroidism.<sup>28</sup> The primary composite end point consisted of death, myocardial infarction, unstable angina, heart failure, or

peripheral vascular disease. In an unadjusted intention-to-treat analysis, there was no significant effect of cinacalcet on the primary end point. Cinacalcet significantly reduced serum calcium levels compared to placebo. The KDIGO guideline update states that “no negative signals were associated with the persistently low serum calcium levels in the cinacalcet arm of the [EVOLVE] trial,”<sup>7(p27)</sup> and suggests that hypocalcemia can be tolerated. The KDOQI work group supports the intent of the update to allow for greater individualization of treatment strategies. However, the KDOQI work group believes that additional studies are needed to further address the potential risks for hypocalcemia induced by calcimimetics.

### Implementation and Challenges

Clear definitions of what constitutes hypercalcemia and hypocalcemia have not been established and definitions of the normal range of serum and plasma calcium concentrations differ across laboratories. This lack of established definitions regarding abnormal calcium levels complicates implementation of this recommendation. The KDOQI work group emphasizes the importance of considering age-appropriate calcium requirements and our limited understanding of thresholds for optimal bone and vascular health in children with CKD.

### Treatment of CKD-MBD: Dialysate Calcium Concentration

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4.1.4: In patients with CKD G5D, we suggest using a dialysate calcium concentration between 1.25 and 1.50 mmol/L (2.5 and 3.0 mEq/L) (2C).

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### Commentary

This guideline recommendation is unchanged from the 2009 KDIGO guidance on this issue. After review of the relevant literature, the KDOQI work group agrees with maintaining this largely opinion-based suggestion, but also concurs with the KDIGO guideline’s important caveat that data supporting a particular dialysate calcium level outside this range remain scarce. For this reason, the members of the KDOQI work group do not agree that the available data supporting this suggestion were sufficient to upgrade the evidence grade from 2D to 2C. In a minor comment, we also believe that the KDIGO guideline update meant for recommendation 4.1.4 to encompass dialysate calcium concentrations of 1.25 and 1.50 mmol/L (2.5 and 3.0 mEq/L) rather than focus on concentrations *between* these thresholds. This guideline recommendation is consistent with the clinical practice of many providers and provides a reasonable suggested starting point from which clinicians can individualize care on a case-by-case basis.

## Treatment of CKD-MBD: Phosphate-Lowering Strategies

4.1.5: In patients with CKD G3a-G5D, decisions about phosphate-lowering treatment should be based on progressively or persistently elevated serum phosphate (Not Graded).

### Commentary

In line with the motivation behind the revisions in guideline statement 4.1.2, this guideline discourages the prescription of phosphate-lowering therapies in individuals with normal serum phosphate concentrations. As compared to the previous 2009 KDIGO recommendations, the revision does not contain language suggesting that all phosphate binders are interchangeable. This is justified by 2 studies conducted in individuals with non-dialysis-dependent CKD and relatively normal serum phosphate levels. The first study showed that use of calcium-based phosphate binders in this population leads to a positive calcium balance.<sup>23</sup> The second study reported that compared to the placebo arm, risk for coronary artery calcification was increased in the intervention arm randomly assigned to phosphate binders, an effect that was possibly driven by calcium-containing phosphate binders.<sup>18</sup>

The KDOQI work group endorses the decision in the KDIGO guideline update to use the phrase “phosphate-lowering therapies” rather than “phosphate-binding agents.” We agree that targeted nutrition counseling can positively impact dietary phosphate intake without affecting overall nutrition,<sup>29</sup> and that other phosphate-lowering approaches may be available in the coming years.

## Treatment of CKD-MBD: Phosphate Binders

4.1.6: In adult patients with CKD G3a-G5D receiving phosphate-lowering treatment, we suggest restricting the dose of calcium-based phosphate binders (2B). In children with CKD G3a-G5D, it is reasonable to base the choice of phosphate-lowering treatment on serum calcium levels (Not Graded).

### Commentary

Based largely on 2 well-done calcium balance studies in individuals with CKD,<sup>23,24</sup> the major change in this guideline update as compared to the 2009 version involves removing qualifications for restricting calcium-based phosphate binders in certain patients with CKD and instead recommending tighter restrictions of calcium-based phosphate-binder use across all CKD stages in adults. This change was further justified in the KDIGO guideline update based on 3 new randomized clinical trials that showed a

signal toward increased morbidity and/or mortality in patients treated with calcium-based binders as compared with non-calcium-based binders.<sup>18,30,31</sup> In patients with CKD stages 3 to 4, active therapy with phosphate binders increased the risk for coronary artery calcification compared to placebo, with the more marked effects among the 30 patients randomly assigned to calcium acetate versus non-calcium-based phosphate binders.<sup>18</sup> Di Iorio et al<sup>30</sup> compared sevelamer to calcium carbonate in 212 individuals with CKD stages 3 to 4 and noted significantly fewer composite outcomes (all-cause mortality and dialysis therapy initiation) in those treated with sevelamer. Of note, baseline phosphate concentration in this trial was 4.8 mg/dL. Di Iorio and colleagues<sup>31</sup> conducted a second trial in incident hemodialysis patients, randomly assigning 466 to either sevelamer or calcium carbonate. Median sevelamer dose was 4,800 mg, and calcium carbonate dose was 2,000 mg. Phosphate control was significantly better with sevelamer and mortality was lower, with only 28 deaths in sevelamer recipients versus 100 deaths in calcium carbonate recipients.

The KDIGO guideline update stated that these data were sufficient to support a 2B grade. However, KDOQI work group members question whether the level of evidence was sufficient to support the change in the language of this guideline recommendation. In part this concern arises from lack of clarity on whether different formulations of calcium-based binders (eg, calcium acetate vs calcium carbonate) have been adequately compared against calcium-free binders with respect to hard outcomes, such as cardiovascular disease or mortality. This is underscored by an error in Supplemental Table 21 describing 2 of the major randomized controlled trials cited by this guideline update (Di Iorio et al, 2012<sup>30</sup> and 2013<sup>31</sup>) that indicated that patients undergoing hemodialysis were randomly assigned to calcium acetate versus sevelamer, when they received either calcium carbonate or sevelamer. This might leave the impression that calcium acetate is inferior to sevelamer with respect to long-term outcomes when the data to support this contention remain limited. Nonetheless, the majority of the KDOQI work group believe that the balance of available evidence supports limiting calcium-based binders *when possible*, especially because there are multiple calcium-free phosphate binders available that are effective at lowering serum phosphate concentrations and have side-effect profiles similar to calcium-based phosphate binders.

The 2B grade for the guideline recommendation to restrict use of calcium-based phosphate binders in the setting of normocalcemia implies moderate quality of evidence, which can be conceptualized as the true effect likely being close to the estimate. There is

concern among members of the KDOQI work group that a 2B grade may be overly confident given the absence of large adequately powered trials examining important clinical outcomes such as mortality, cardiovascular disease events, fractures, or patient-reported outcomes. Many of the trials are in homogeneous patient populations, with the most influential for this update enrolling patients from Italy.<sup>30,31</sup> Overall, the KDOQI work group believes that more definitive data generalizable to the US kidney disease population would be needed to justify a B grade for this statement.

As discussed previously for guideline recommendation 4.1.3, given the calcium requirements and unique vulnerability of the growing skeleton and lack of data comparing calcium-based with non-calcium-based binders in children, the KDOQI work group endorses the pediatric-specific recommendation that the choice of phosphate-lowering therapy in children with CKD stages G3a to G5D be guided by serum calcium levels.

#### **Clinical Utility**

Compared to the prior guideline, the updated recommendation provides more straightforward guidance for clinicians. Avoidance of calcium-based phosphate binders is now suggested, as compared to the prior recommendations, which had many qualifications for use of non-calcium-based binders, such as development of hypercalcemia and presence of vascular calcification. Despite the clear-cut language in the revised guideline, critical evidence gaps exist in this area. There remains a lack of knowledge regarding the efficacy of phosphate binders on hard clinical outcomes, such as mortality, and we have limited evidence regarding comparative effectiveness of one binder class versus another with regard to mortality. The KDOQI work group believes that sufficient equipoise exists to justify an adequately powered rigorously conducted clinical trial assessing the safety and efficacy of normalization of phosphate levels versus permissive mild to moderate hyperphosphatemia in hyperphosphatemic patients undergoing dialysis.

#### **Implementation and Challenges**

The major challenges related to a shift entirely away from calcium-containing binders relate to potentially higher costs, lower gastrointestinal tolerance that may vary by individual and type of non-calcium-based phosphate binder, and unquantified risks with concurrent use with calcimimetics. For many US patients with CKD stage 5D, particularly those with insufficient or no prescription medication coverage, calcium-based binders may be the only feasible option. Calcium carbonate is very inexpensive, while calcium acetate is far less expensive than commonly used

non-calcium containing binders. Therefore, even if some clinicians want to prescribe calcium-free binders, they may not prescribe them due to practical reasons. Calcimimetic-induced hypocalcemia may be accompanied by greater use of calcium-containing binders.<sup>28,32</sup> Until calcium-free binders become more accessible and additional studies establish the safety of calcimimetic-induced hypocalcemia, the implementation of the KDIGO suggested guidance to restrict the dose of calcium-based phosphate binders in adults may remain limited.

#### **Treatment of CKD-MBD: Limiting Dietary Phosphate**

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4.1.8: In patients with CKD G3a-G5D, we suggest limiting dietary phosphate intake in the treatment of hyperphosphatemia alone or in combination with other treatments (2D). It is reasonable to consider phosphate source (e.g., animal, vegetable, additives) in making dietary recommendations (*Not Graded*).

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#### **Commentary**

The level of grading as 2D or ungraded underscores the weakness of published evidence on the most effective approaches to address dietary phosphate intake in the CKD population. Although hyperphosphatemic patients who reduce their dietary phosphate intake within the setting of research studies experience a reduction in serum phosphate levels,<sup>33,34</sup> the real-world effectiveness of this approach may be limited. First, there are no readily available ways to estimate phosphate absorption. Current nutritional labeling does not require quantification of phosphate content, and there is wide variability among and within commercial products of actual phosphate additive level. These barriers create challenges for the identification of high-risk patients who are most likely to benefit from nutritional counseling. Second, because the majority of high-biological-value proteins have high phosphate content, it is not simple to devise a dietary plan that lowers dietary phosphate intake without compromising dietary protein intake. Third, maintaining adherence to dietary interventions in general is difficult but it may be especially difficult with low-phosphate diets. While vegetarian sources of protein have lower phosphate bioavailability, substituting vegetable protein for animal protein requires high levels of behavioral change.

#### **Clinical Utility, Implementation, and Challenges**

US residents, including individuals with CKD, consume high levels of processed foods. Educating patients to cook at home rather than eating out does not necessarily promote lower phosphate ingestion because many meats and baked products contain high amounts of phosphate solutions added during

processing and packaging.<sup>35</sup> Consumption of more raw, organic, and less-processed foods is often economically prohibitive, particularly given the disproportionate burden of kidney failure among those living in poverty. The recommendations emphasize the role of individualized nutrition education for the CKD population due to the complexity of the issue. Medical nutrition therapy is poorly utilized in adults with non-dialysis-dependent CKD, and this guideline recommendation may help increase the referral of adults with CKD for dietary counseling.<sup>36</sup> With regard to dietary sources of phosphate, the KDOQI work group stresses that nutritional labels on food products should accurately quantify phosphate content of foods.

### Treatment of Abnormal PTH Levels in CKD-MBD: Optimal PTH Level in CKD G3a-G5 Not on Dialysis

4.2.1: In patients with CKD G3a-G5 not on dialysis, the optimal PTH level is not known. However, we suggest that patients with levels of intact PTH progressively rising or persistently above the upper normal limit for the assay be evaluated for modifiable factors, including hyperphosphatemia, hypocalcemia, high phosphate intake, and vitamin D deficiency (2C).

#### Commentary

The KDIGO guideline update acknowledges that the incidence and severity of secondary hyperparathyroidism increase with progression of CKD; that abnormalities in calcium and phosphate homeostasis, vitamin D deficiency, and FGF-23 excess contribute to elevated PTH levels as kidney function declines; and that secondary hyperparathyroidism has adverse consequences on bone. In contrast to the 2009 KDIGO guideline, which suggested that an evaluation for modifiable factors be initiated when PTH levels were “above” the upper limit of normal, the 2017 update suggests that the updated threshold should be PTH levels that are “progressively rising or persistently above the upper normal limit.” The KDIGO guideline update provides the following rationale for its emphasis on not initiating treatment for a single elevated PTH value: (1) the optimal PTH concentration remains undefined; (2) a modest increase in PTH concentration is an appropriate adaptive response that contributes to phosphaturia in CKD and may therefore be beneficial for maintenance of normal serum phosphate levels as glomerular filtration rate (GFR) declines; and (3) resistance to skeletal effects of PTH may not necessitate correction of modestly elevated PTH to normal levels in CKD. The KDOQI work group agrees with the update and its justification, especially given the high within- and between-individual variability in PTH levels.<sup>15,17,37,38</sup>

Similar to the 2009 KDIGO guideline recommendation, the updated guideline statement suggests specifically targeting factors that influence PTH levels, including hyperphosphatemia, hypocalcemia, and hypovitaminosis D. Newly added to this list is high dietary phosphate intake, which the guideline update highlights as a modifiable risk factor for secondary hyperparathyroidism for which refined assessment methods are needed.<sup>39-42</sup>

#### Clinical Utility

This updated guideline recommendation reflects the removal of the previously ungraded suggestion to consider use of phosphate binders, calcium supplements, and/or native vitamin D to address elevated PTH. Overall, the KDOQI work group agrees with this change, but there are some implications for clinical practice. First, serial assessments of PTH have become part of routine nephrology care, in large part due to existing CKD-MBD guidelines.<sup>1,6</sup> Despite lack of emphasis in prior recommendations on treatment of persistent PTH elevation and or PTH thresholds to initiate or accelerate treatment, use of activated vitamin D in patients with CKD stages 2 to 4 and in incident hemodialysis patients is low,<sup>20,43</sup> suggesting that perhaps clinicians are already delaying treatment of secondary hyperparathyroidism. Use of phosphate binders in this population is also rare, as previously mentioned.<sup>20</sup> In contrast, nutritional vitamin D supplementation has increased substantially over time,<sup>44</sup> likely reflecting trends in the general population. Next, care of patients with CKD requires attention to multiple parameters. De-emphasizing the need to initiate treatment for a single elevated PTH value will allow providers to focus on other areas in CKD care that require attention and for which the level of evidence is higher. At the same time, recognizing the natural history of untreated secondary hyperparathyroidism during the course of CKD<sup>45</sup> and the low level of evidence for the recommendations related to its diagnosis and treatment allows for the opportunity to individualize care. For example, an elderly patient with CKD and poorly controlled diabetes and hypertension with a PTH level that is modestly elevated and slowly increasing may be treated differently than a young patient without comorbid conditions but with markedly elevated and rapidly increasing PTH levels.

#### Implementation and Challenges

Although providers already incorporate serial PTH assessments into CKD care, the emphasis on responding to persistent elevation in PTH and not a single value may lead to more frequent PTH assessments. Alternatively, the unintended consequence of the recommendation to only respond to persistently elevated PTH levels and to limit use of calcitriol and

vitamin D analogues in patients with CKD stages G4 to G5 not on dialysis therapy may generate less impetus to check PTH concentrations in the setting of non-dialysis-dependent CKD. Persistent barriers to implementation of recommendations related to PTH management in non-dialysis-dependent CKD include significant variability in PTH assays, within- and between-individual variability in PTH values,<sup>15,37,38</sup> and no evidence-based PTH threshold above which a provider is supposed to act. While the update does not elucidate practices to best manage secondary hyperparathyroidism in the overall non-dialysis-dependent CKD population, the emphasis on within-individual trends over time as a diagnostic tool may facilitate selecting an individualized approach to care.

### Treatment of Abnormal PTH Levels in CKD-MBD: Non-Dialysis-Dependent Patients

4.2.2: In adult patients with CKD G3a-G5 not on dialysis, we suggest that calcitriol and vitamin D analogs not be routinely used (2C). It is reasonable to reserve the use of calcitriol and vitamin D analogs for patients with CKD G4-G5 with severe and progressive hyperparathyroidism (Not Graded).

In children, calcitriol and vitamin D analogs may be considered to maintain serum calcium levels in the age-appropriate normal range (Not Graded).

#### Commentary

The update is a departure from the 2009 KDIGO guideline, which suggested treatment of patients with CKD stages G3 to G5 not on dialysis therapy who have a PTH level that is “progressively rising and remains persistently above the upper limit of normal for the assay despite correction of modifiable factors”<sup>1(pS7)</sup> with calcitriol or vitamin D analogues. According to the KDIGO guideline update, results from 2 recent randomized controlled trials justify avoiding routine use of calcitriol and vitamin D analogues in CKD stages G3 to G5 not on dialysis therapy.<sup>46,47</sup> The KDIGO guideline update also notes that early PTH concentration increases are appropriate and adaptive and also a function of skeletal resistance to PTH in CKD. PRIMO (Paricalcitol Capsule Benefits in Renal Failure Induced Cardiac Morbidity) and OPERA (Oral Paricalcitol in Stage 3-5 Chronic Kidney Disease) are 2 randomized trials of vitamin D analogues in patients with non-dialysis-dependent CKD.<sup>46,47</sup> The PRIMO and OPERA studies demonstrated significant reductions in PTH levels, no change in cardiovascular end points, and significant increases in risk for hypercalcemia.<sup>46,47</sup> Because the PRIMO and OPERA studies were designed to address the effects of vitamin D analogues on cardiovascular structure and function in patients with CKD, investigators used doses of vitamin D analogues that were deemed appropriate to

demonstrate efficacy for cardiovascular end points. The KDOQI work group agrees with the suggestion of the KDIGO guideline update that low doses of calcitriol or active vitamin D analogues could be initiated in patients with elevated and increasing PTH levels, with close monitoring of the PTH concentration and calcemic response. These expert opinion-based statements allow for individualization of care. The KDOQI work group also agrees that children with CKD stages G3 to G5 not on dialysis therapy may require calcitriol or active vitamin D analogue therapy to maintain age-appropriate serum calcium concentrations.

#### Clinical Utility, Implementation, and Challenges

Although recommendation 4.2.2 suggests that calcitriol or vitamin D analogues should be administered to patients with CKD stages G4 to G5 who have severe and progressive secondary hyperparathyroidism, the guideline update does not explicitly stipulate when administration of calcitriol and vitamin D analogues for PTH suppression should occur because the term “severe” is not defined. Thus, there is some ambiguity facing implementation of the guideline update. Furthermore, a potential unintended consequence of the updated guideline recommendation is decreased attention to disordered mineral metabolism during longitudinal care of a patient with CKD. It is possible that busy providers over time will manage secondary hyperparathyroidism less aggressively even in patients whom the guideline update suggests to treat. The KDOQI work group is concerned that less aggressive attention to PTH levels may lead to increased rates of tertiary hyperparathyroidism and need for parathyroidectomy or more use of expensive medications later in the course of CKD.

### Treatment of Abnormal PTH Levels in CKD-MBD: Dialysis-Dependent Patients

4.2.4: In patients with CKD G5D requiring PTH-lowering therapy, we suggest calcimimetics, calcitriol, or vitamin D analogs, or a combination of calcimimetics with calcitriol or vitamin D analogs (2B).

#### Commentary

This recommendation is similar to the 2009 guideline in some aspects. The agents (calcimimetics, calcitriol, or vitamin D analogues or a combination of calcimimetics with calcitriol or vitamin D analogues) and their indication are identical to the ones previously listed. However, the sequence is notable because the KDIGO guideline update lists the agents in an alphabetical order to convey that calcimimetics, calcitriol, or vitamin D analogues are all acceptable first-line options for this indication and that there are no data to

support prioritizing one agent over another. Unlike the 2009 guideline, the guideline update does not clearly state recommendations for reducing or stopping calcimimetics, calcitriol, or vitamin D analogues in case of hyper- or hypocalcemia or hyperphosphatemia. The KDOQI work group believes that medication selection should take into account the concomitant medical therapies and the patient's serum calcium and phosphate levels (eg, for an adult patient requiring PTH-lowering therapy with hypercalcemia and hyperphosphatemia, a calcimimetic may be preferred over calcitriol or vitamin D analogue). The KDOQI work group also notes that calcimimetics are not US Food and Drug Administration (FDA) approved for use in children.

### **Clinical Utility**

This guideline recommendation holds strong clinical importance because PTH levels in patients undergoing dialysis have increased globally, and PTH levels > 600 pg/mL are associated with higher risk for all-cause and cardiovascular mortality and cardiovascular hospitalizations.<sup>48</sup> Calcimimetics, calcitriol, and vitamin D analogues have all shown efficacy for PTH lowering in US patients with CKD stage G5D.<sup>28,49,50</sup> Although prespecified secondary analyses and post hoc analyses of the EVOLVE data noted improvement in some outcomes in a subgroup of patients (eg, reduced incidence of fracture when treated with cinacalcet vs placebo in patients  $\geq 65$  years of age),<sup>51</sup> the primary analysis was not positive. Given that superiority of cinacalcet over other agents has not been established, selection of PTH-lowering therapy in patients with CKD stage G5D may be based on cost, adverse events, and presence of other mineral metabolism abnormalities.

### **Implementation and Challenges**

There are several aspects of this guideline recommendation that present challenges for implementation in US clinical practices. While secondary hyperparathyroidism in patients with CKD stage G5D is associated with increased risks for mortality and cardiovascular events,<sup>52</sup> no studies have demonstrated that lowering PTH levels in this population with medical treatments as suggested by the KDIGO guideline update translates to reductions in mortality or cardiovascular events. Although this lack of evidence could be interpreted as a weak justification to treat secondary hyperparathyroidism in patients with CKD stage G5D, the temporal declines in extremely high PTH levels and parathyroidectomies in the United States after routine use of calcitriol or active vitamin D analogues provides sufficient reason to heed this recommendation.<sup>53</sup> In the United States, the high cost of cinacalcet may limit its use. The uptake by the

US dialysis community of etelcalcetide, a recently approved synthetic peptide that activates the calcium sensing receptor,<sup>54</sup> remains to be determined.

## **Treatment of Bone With Bisphosphonates and Other Osteoporosis Medications**

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4.3.3: In patients with CKD G3a-G5D with biochemical abnormalities of CKD-MBD and low BMD and/or fragility fractures, we suggest that treatment choices take into account the magnitude and reversibility of the biochemical abnormalities and the progression of CKD, with consideration of a bone biopsy (2D).

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### **Commentary**

Guideline statement 4.3.3 recommends basing treatment of patients at risk for fracture both on the reversibility and the severity of biochemical abnormalities associated with CKD-MBD and on the potential for progression of CKD. It also recommends that bone biopsy should be considered if it will inform treatment decisions. The recommendation implies that patients with CKD at risk for fracture and in need of treatment are patients with low BMD and/or with a history of fragility fractures. Although there is no evidence that supports this recommendation as an effective approach to the prevention of fractures in patients with CKD, there are several points worth noting.

### **Clinical Utility**

The guideline update correctly implies that BMD and a history of fragility fracture can be used to classify fracture risk in patients with CKD: both osteopenia and osteoporosis have been shown to predict fracture in patients with CKD.<sup>9,12</sup> Fragility fracture is a marker of poor bone quality that has been validated as an important risk factor for fracture in epidemiologic studies. The guideline update prioritizes the optimization of underlying CKD-MBD derangements that adversely affect bone quality. Thus, management of secondary hyperparathyroidism, hyperphosphatemia, and vitamin D insufficiency are integral and/or primary components of managing fracture risk in addition to treatment with an antifracture medication, such as an antiresorptive or anabolic agent. The guideline update also asks the clinician to inform their treatment decision on the future trajectory of kidney function. Declining kidney function has been reported to be a risk factor for increased fracture risk,<sup>55,56</sup> and fracture rates increase in parallel with declining GFR.<sup>56</sup> Whether this is due to increasing severity of the CKD-MBD phenotype or other metabolic derangements that are associated with declining kidney function is not clear. However, the known negative impact of CKD severity on the skeleton provides the clinician with additional objective data on the need for treatment.

### Implementation and Challenges

The clinician is asked to consider the need for a bone biopsy diagnosis of renal osteodystrophy type after assessment of the reversibility of CKD-MBD and the course of the patient's CKD. This is consistent with the notion that in the absence of CKD-MBD, low bone mass and/or fragility fractures may be treated as in the general population. However, in some patients, turnover type may influence treatment strategies. DXA BMD is widely available in the general community, and its results for adult patients with CKD are easily interpreted in the context of the WHO T scores.<sup>9,12</sup> Treatment of underlying biochemical abnormalities in CKD-MBD should be based on the KDIGO recommendations to mitigate the effects of vitamin D deficiency and secondary hyperparathyroidism on bone. However, levels of vitamin D metabolites and PTH that optimize bone quality across CKD stages remain to be defined. The decision to treat with either antiresorptive or anabolic agents needs to consider both the level of kidney function and underlying bone turnover, which may not be apparent from circulating biochemical markers of bone turnover. In this setting, a bone biopsy becomes useful. The lack of access to bone biopsy with histomorphometry for the diagnosis of underlying bone turnover will limit the applicability of this guideline recommendation. Given the importance of preventing fractures in patients with CKD, nephrologists could consider training in the bone biopsy procedure and incorporating bone biopsies into training programs. The lack of clinical trial data on the antifracture effectiveness of antiresorptive and anabolic agents needs to be addressed in patients with CKD-MBD. However, secondary analyses of the FDA registration trials for antiresorptive and anabolic agents suggest safety and antifracture efficacy in patients with CKD stages 3 to 4 without evidence of CKD-MBD.<sup>57</sup>

### Evaluation and Treatment of Kidney Transplant Bone Disease

- 5.5: In patients with CKD G1T-G5T with risk factors for osteoporosis, we suggest that BMD testing be used to assess fracture risk if results will alter therapy (2C).
- 5.6: In patients in the first 12 months after kidney transplant with an estimated glomerular filtration rate greater than approximately 30 mL/min/1.73 m<sup>2</sup> and low BMD, we suggest that treatment with vitamin D, calcitriol/alfacalcidol, and/or antiresorptive agents be considered (2D).
- We suggest that treatment choices be influenced by the presence of CKD-MBD, as indicated by abnormal levels of calcium, phosphate, PTH, alkaline phosphatases, and 25(OH)D (2C).
  - It is reasonable to consider a bone biopsy to guide treatment (Not Graded).
- There are insufficient data to guide treatment after the first 12 months.

### Commentary

Guideline statement 5.5 is similar to 3.2.1 and suggests use of BMD to assess fracture risk in the kidney transplant population. Guideline statement 5.6 recommends treating patients after a kidney transplantation who have an estimated GFR > 30 L/min/1.73 m<sup>2</sup> and low BMD. The statement also suggests the consideration of available therapies to treat patients with low BMD. Because bone mineral abnormalities that are present in the CKD population can persist after transplantation, the guideline recommends taking into account the said abnormalities while treating post-transplantation patients. The guideline also recommends a bone biopsy be considered to inform treatment decisions. It readily acknowledges the lack of data after the first year of transplantation.

### Clinical Utility

Low BMD heightens the risk for fractures after kidney transplantation.<sup>58</sup> This guideline update acknowledges that nutritional vitamin D, calcitriol, active vitamin D analogues, and antiresorptive agents (bisphosphonates and denosumab) prevent bone loss in the first year after transplantation.<sup>59</sup> However, the guideline recommendation cannot be graded higher because clinical trials of antiresorptive medications in posttransplantation patients were not powered to demonstrate that bone loss prevention with these agents prevents fractures. The clinician is asked to consider a bone biopsy to correctly classify the type of renal osteodystrophy when it is relevant for treatment decisions.

### Implementation and Challenges

The guideline recommendations imply that low BMD after transplantation is associated with fractures. Hence, BMD can be used to classify fracture risk. Although this may be true, there is a lack of prospective evidence showing that low BMD in transplant recipients predicts fracture risk. Much of the evidence in transplant recipients is extrapolated from the CKD population. In contrast, there are data on the use of vitamin D, calcitriol, and antiresorptive agents in transplant recipients with low BMD.<sup>60-63</sup> Therefore, the suggestion of treating transplant recipients with low BMD with the aforementioned therapies is appropriate with the caveat that the data for bisphosphonates are mixed in the transplantation population, with BMD improvement seen at some bone sites but not in others. It should also be noted that most of the studies were aimed at improving BMD and were not powered to detect reductions in fracture rates. Therefore, we do not know whether improving BMD in this population translates into lower fracture risk. Bone tissue-level safety for denosumab, bisphosphonates, and teriparatide remains an area of research

**Box 2. Suggested Areas for Future Investigation****Diagnosis and Treatment of Bone**

- Studies are needed to determine the cost-effectiveness of DXA BMD testing for CKD stages 3-5 and 5D
- Prospective studies are needed to establish the utility of DXA BMD testing for prediction of fractures in kidney transplant recipients and in children with CKD
- Randomized clinical trials are needed to assess antifracture efficacy and safety (including bone tissue safety) of antiresorptive and anabolic agents in patients with CKD of all stages and after transplantation
- Levels of 25(OH)D and PTH that optimize bone outcomes (ie, optimize mineralization and bone turnover status and minimize fracture risk) need to be defined in adult and pediatric patients with CKD and kidney transplant recipients
- Research is needed to develop sensitive and specific circulating bone turnover biomarkers for clinical and research use for patients across the spectrum of CKD

**Treatment of CKD-MBD Targeted at Lowering High Serum Phosphate and Maintaining Serum Calcium**

- A well-powered trial with ESRD, CVD events, and mortality as end points is needed to examine the safety and efficacy of phosphate-lowering interventions in individuals with CKD stages 3-4
- A well-powered trial with CVD events, hospitalizations, and mortality as end points is needed to examine the safety and efficacy of normalization of phosphate vs permissive mild to moderate hyperphosphatemia in hyperphosphatemic patients undergoing dialysis
- A well-powered trial with CVD, hospitalizations, and mortality as end points is needed to examine the comparative effectiveness of calcium acetate vs a non-calcium-containing binder in hyperphosphatemic patients undergoing dialysis
- A well-powered trial with CVD events, hospitalizations, and mortality as end points that accounts for calcium vs non-calcium-containing binder use is needed to examine the safety and efficacy of continued calcimimetic use in patients with mild hypocalcemia

**Treatment of Abnormal PTH Levels in CKD-MBD**

- Randomized clinical trials in children and adults that target different PTH levels across the spectrum of GFR with renal, bone, cardiovascular, and mortality end points would provide guidance on the optimal time of initiation of management and the optimal PTH level to be achieved at each CKD stage
- Prospective studies are needed to determine whether the combination of serum PTH with circulating biomarkers of bone turnover may provide improved prediction of bone health
- Randomized clinical trials with CVD events, hospitalizations, and mortality as end points are needed to examine the safety and efficacy of calcimimetics vs standard therapy in high-risk patients (eg, age > 60 years, known valvular or vascular calcification, wide pulse pressure, or presence of CHF)
- Randomized clinical trials of the parenteral calcimimetic agent etelcalcetide are needed to evaluate its effects on left ventricular mass, CVD events, mortality, hospitalizations, and other patient-centered end points

Abbreviations: 25(OH)D, 25-hydroxyvitamin D; CHF, congestive heart failure; CKD, chronic kidney disease; CKD-MBD, chronic kidney disease–mineral bone disorder; CVD, cardiovascular disease; DXA BMD, dual-energy x-ray absorptiometry bone mineral density; ESRD, end-stage renal disease; GFR, glomerular filtration rate; PTH, parathyroid hormone.

need. As described for guideline recommendations 3.2.2 and 4.3.3, bone biopsy availability is limited. Finally, levels of 25-hydroxyvitamin D and PTH that optimize bone outcomes in transplant recipients are not known and need to be defined.

**CONCLUSION**

Clinical providers in the nephrology care setting routinely encounter patients with CKD-MBD and struggle with an approach to management due to the complexity of the underlying pathophysiology, lack of evidentiary certainty, and a multimorbidity patient population. As is the case with other clinical practice guidelines, the KDIGO 2017 guideline update for CKD-MBD is intended to serve as a tool, along with clinical judgment, to facilitate clinical decision making and to implement high-quality care. Because most of the guideline recommendations are at the level of “we suggest” and are backed by a “low” or “very low” level of evidence, the language is often not definitive. The ambiguity and lack of unequivocally

actionable recommendations highlight potential challenges for implementation, remind us that clinical practice guidelines are to be used in conjunction with clinical judgement, and underscore the need for future research in this important area (see [Box 2](#) for suggested research topics).

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