

Executive summary of the 2017 KDIGO Chronic Kidney Disease–Mineral and Bone Disorder (CKD-MBD) Guideline Update: what's changed and why it matters



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The KDIGO 2017 Clinical Practice Guideline Update for the Diagnosis, Evaluation, Prevention, and Treatment of CKD-MBD represents a selective update of the prior CKD-MBD Guideline published in 2009. This update, along with the 2009 publication, is intended to assist the practitioner caring for adults and children with chronic kidney disease (CKD), those on chronic dialysis therapy, or individuals with a kidney transplant. This review highlights key aspects of the 2017 CKD-MBD Guideline Update, with an emphasis on the rationale for the changes made to the original guideline document. Topic areas encompassing updated recommendations include diagnosis of bone abnormalities in CKD–mineral and bone disorder (MBD), treatment of CKD-MBD by targeting phosphate lowering and calcium maintenance, treatment of abnormalities in parathyroid hormone in CKD-MBD, treatment of bone abnormalities by antiresorptives and other osteoporosis therapies, and evaluation and treatment of kidney transplant bone disease.

Kidney International (2017) **92**, 26–36; <http://dx.doi.org/10.1016/j.kint.2017.04.006>

KEYWORDS: bone mineral density; calcium; dialysis; hyperparathyroidism; hyperphosphatemia; KDIGO CKD-MBD Guideline; kidney transplantation
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The complete KDIGO 2017 Clinical Practice Guideline Update for the Diagnosis, Evaluation, Prevention, and Treatment of Chronic Kidney Disease–Mineral and Bone Disorder (CKD-MBD) is publishing simultaneously in *Kidney International Supplements*, volume 7, issue 1, 2017, which is available online at www.kisupplements.org.

Received 10 April 2017; accepted 17 April 2017

In 2009, Kidney Disease: Improving Global Outcomes (KDIGO) published the KDIGO Clinical Practice Guideline for the Diagnosis, Evaluation, Prevention, and Treatment of Chronic Kidney Disease–Mineral and Bone Disorder (CKD-MBD).¹ At that time, the Work Group acknowledged the lack of high-quality evidence on which to base recommendations. Over the years that followed, multiple randomized controlled trials (RCTs) and prospective cohort studies examined some of the key issues underlying the assessment, development, progression, and treatment of CKD-MBD. KDIGO recognizes the need to reexamine the currency of its guidelines on a periodic basis, and therefore convened a Controversies Conference in 2013, titled “CKD-MBD: Back to the Future.”²

The conference participants concluded that most of the 2009 recommendations¹ were still applicable in current practice; however, a total of 12 recommendations were identified for revision, based on new data. As a result, a Work Group was convened to undertake a “selective update”³ of the 2009 KDIGO CKD-MBD Guideline (Table 1).¹ Notably, despite the availability of results from several new key clinical trials, large gaps of knowledge still remained. Accordingly, many of the “opinion-based” recommendation statements from the 2009 Guideline¹ remain unchanged (see summary of KDIGO CKD-MBD recommendations).

Similar to the original 2009 KDIGO CKD-MBD Guideline,¹ development of the 2017 Update³ followed a rigorous process of evidence review and appraisal, based on systematic reviews of results from clinical trials. The structured approach was modeled after the GRADE system,⁴ which ascribes grades to the quality of the overall evidence and strength for each recommendation. Where appropriate, the Work Group issued “not graded” recommendations, based on general advice, that were not part of a systematic evidence review.

Despite the dearth of high-quality evidence identified in several areas pertaining to CKD-MBD, the Work Group was committed to developing a comprehensive guideline document that is of highest value to the nephrology community. The list of research recommendations in each chapter of the

Table 1 | Comparison of the 2017 and 2009 KDIGO CKD-MBD Guideline recommendations

2017 revised KDIGO CKD-MBD recommendations ³	2009 KDIGO CKD-MBD recommendations ¹	Brief rationale for updating
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).	3.2.2. In patients with CKD G3a–G5D with evidence of CKD-MBD, we suggest that BMD testing not be performed routinely, because BMD does not predict fracture risk as it does in the general population, and BMD does not predict the type of renal osteodystrophy (2B).	Multiple new prospective studies have documented that lower DXA BMD predicts incident fractures in patients with CKD G3a–G5D. The order of these first 2 recommendations was changed because a DXA BMD result might impact the decision to perform a bone biopsy.
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).	3.2.1. In patients with CKD G3a–G5D, it is reasonable to perform a bone biopsy in various settings including, but not limited to: unexplained fractures, persistent bone pain, unexplained hypercalcemia, unexplained hypophosphatemia, possible aluminum toxicity, and prior to therapy with bisphosphonates in patients with CKD-MBD (Not Graded).	The primary motivation for this revision was the growing experience with osteoporosis medications in patients with CKD, low BMD, and a high risk of fracture. The inability to perform a bone biopsy may not justify withholding antiresorptive therapy from patients at high risk of fracture.
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).		This new recommendation was provided in order to emphasize the complexity and interaction of CKD-MBD laboratory parameters.
4.1.2. In patients with CKD G3a–G5D, we suggest lowering elevated phosphate levels toward the normal range (2C).	4.1.1. In patients with CKD G3a–G5D, we suggest maintaining serum phosphate in the normal range (2C). In patients with CKD G5D, we suggest lowering elevated phosphate levels toward the normal range (2C).	There is an absence of data supporting that efforts to maintain phosphate in the normal range are of benefit to CKD G3a–G4 patients, including some safety concerns. Treatment should be aimed at overt hyperphosphatemia.
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).	4.1.2. In patients with CKD G3a–G5D, we suggest maintaining serum calcium in the normal range (2D).	Mild and asymptomatic hypocalcemia (e.g., in the context of calcimimetic treatment) can be tolerated in order to avoid inappropriate calcium loading in adults.
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).	4.1.3. 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) (2D).	Additional studies of better quality are available; however, these do not allow for discrimination of benefits and harm between calcium dialysate concentrations of 1.25 and 1.50 mmol/l (2.5 and 3.0 mEq/l). Hence, the wording is unchanged, but the evidence grade is upgraded from 2D to 2C.
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).	4.1.4. In patients with CKD G3a–G5 (2D) and G5D (2B), we suggest using phosphate-binding agents in the treatment of hyperphosphatemia. It is reasonable that the choice of phosphate binder takes into account CKD stage, presence of other components of CKD-MBD, concomitant therapies, and side effect profile (Not Graded).	Emphasizes the perception that early “preventive” phosphate-lowering treatment is currently not supported by data (see Recommendation 4.1.2). The broader term “phosphate-lowering” treatment is used instead of phosphate-binding agents since all possible approaches (i.e., binders, diet, dialysis) can be effective.
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).	4.1.5. In patients with CKD G3a–G5D and hyperphosphatemia, we recommend restricting the dose of calcium-based phosphate binders and/or the dose of calcitriol or vitamin D analog in the presence of persistent or recurrent hypercalcemia (1B).	New evidence from 3 RCTs supports a more general recommendation to restrict calcium-based phosphate binders in hyperphosphatemic patients across all severities of CKD.
In children with CKD G3a–G5D, it is reasonable to base the choice of phosphate-lowering treatment on serum calcium levels (Not Graded).	In patients with CKD G3a–G5D and hyperphosphatemia, we suggest restricting the dose of calcium-based phosphate binders in the presence of arterial calcification (2C) and/or adynamic bone disease (2C) and/or if serum PTH levels are persistently low (2C).	

(Continued on next page)

Table 1 | (Continued) **Comparison of the 2017 and 2009 KDIGO CKD-MBD Guideline recommendations**

2017 revised KDIGO CKD-MBD recommendations ³	2009 KDIGO CKD-MBD recommendations ¹	Brief rationale for updating
<p>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 (<i>Not Graded</i>).</p>	<p>4.1.7. 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).</p>	<p>New data on phosphate sources were deemed important to include as an additional qualifier to the previous recommendation.</p>
<p>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).</p>	<p>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 above the upper normal limit of the assay are first evaluated for hyperphosphatemia, hypocalcemia, and vitamin D deficiency (2C).</p> <p>It is reasonable to correct these abnormalities with any or all of the following: reducing dietary phosphate intake and administering phosphate binders, calcium supplements, and/or native vitamin D (<i>Not Graded</i>).</p>	<p>The Work Group felt that modest increases in PTH may represent an appropriate adaptive response to declining kidney function and has revised this statement to include “persistently above the upper normal PTH level as well as “progressively rising” PTH levels, rather than “above the upper normal limit.” That is, treatment should not be based on a single elevated value.</p>
<p>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 (<i>Not Graded</i>).</p>	<p>4.2.2. In patients with CKD G3a–G5 not on dialysis, in whom serum PTH is progressively rising and remains persistently above the upper limit of normal for the assay despite correction of modifiable factors, we suggest treatment with calcitriol or vitamin D analogs (2C).</p>	<p>Recent RCTs of vitamin D analogs failed to demonstrate improvements in clinically relevant outcomes but demonstrated increased risk of hypercalcemia.</p>
<p>In children, calcitriol and vitamin D analogs may be considered to maintain serum calcium levels in the age-appropriate normal range (<i>Not Graded</i>).</p>		
<p>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).</p>	<p>4.2.4. In patients with CKD G5D and elevated or rising PTH, we suggest calcitriol, or vitamin D analogs, or calcimimetics, or a combination of calcimimetics and calcitriol or vitamin D analogs be used to lower PTH (2B).</p> <ul style="list-style-type: none"> • It is reasonable that the initial drug selection for the treatment of elevated PTH be based on serum calcium and phosphate levels and other aspects of CKD-MBD (<i>Not Graded</i>). • It is reasonable that calcium or non-calcium-based phosphate binder dosage be adjusted so that treatments to control PTH do not compromise levels of phosphate and calcium (<i>Not Graded</i>). • We recommend that, in patients with hypercalcemia, calcitriol or another vitamin D sterol be reduced or stopped (1B). • We suggest that, in patients with hyperphosphatemia, calcitriol or another vitamin D sterol be reduced or stopped (2D). • We suggest that, in patients with hypocalcemia, calcimimetics be reduced or stopped depending on severity, concomitant medications, and clinical signs and symptoms (2D). • We suggest that, if the intact PTH levels fall below 2 times the upper limit of normal for the assay, calcitriol, vitamin D analogs, and/or calcimimetics be reduced or stopped (2C). 	<p>This recommendation originally had not been suggested for updating by the KDIGO Controversies Conference in 2013. However, due to a subsequent series of secondary and <i>post hoc</i> publications of the EVOLVE trial, the Work Group decided to reevaluate Recommendation 4.2.4 as well. Although EVOLVE did not meet its primary endpoint, the majority of the Work Group members were reluctant to exclude potential benefits of calcimimetics for G5D patients based on subsequent prespecified analyses. The Work Group, however, decided not to prioritize any PTH-lowering treatment at this time because calcimimetics, calcitriol, or vitamin D analogs are all acceptable first-line options in G5D patients.</p>

Table 1 | (Continued)

2017 revised KDIGO CKD-MBD recommendations ³	2009 KDIGO CKD-MBD recommendations ¹	Brief rationale for updating
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).	4.3.3. In patients with CKD G3a–G3b 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).	Recommendation 3.2.2 now addresses the indications for a bone biopsy prior to antiresorptive and other osteoporosis therapies. Therefore, 2009 Recommendation 4.3.4 has been removed and 2017 Recommendation 4.3.3 is broadened from CKD G3a–G3b to CKD G3a–G5D.
5.5. In patients with G1T–G5T with risk factors for osteoporosis, we suggest that BMD testing be used to assess fracture risk if results will alter therapy (2C).	5.5. In patients with an estimated glomerular filtration rate greater than approximately 30 ml/min/1.73 m ² , we suggest measuring BMD in the first 3 months after kidney transplant if they receive corticosteroids, or have risk factors for osteoporosis as in the general population (2D).	2009 Recommendations 5.5 and 5.7 were combined to yield 2017 Recommendation 5.5.
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 ² and low BMD, we suggest that treatment with vitamin D, calcitriol/alfacalcidol, and/or antiresorptive agents be considered (2D).	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 ² and low BMD, we suggest that treatment with vitamin D, calcitriol/alfacalcidol, or bisphosphonates be considered (2D).	The second bullet point is revised, consistent with the new bone biopsy recommendation (i.e., 2017 Recommendation 3.2.2).
<ul style="list-style-type: none"> 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 (<i>Not Graded</i>). 	<ul style="list-style-type: none"> 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, specifically before the use of bisphosphonates due to the high incidence of adynamic bone disease (<i>Not Graded</i>). 	
There are insufficient data to guide treatment after the first 12 months.	There are insufficient data to guide treatment after the first 12 months.	

25(OH)D, 25-hydroxyvitamin D; BMD, bone mineral density; CKD, chronic kidney disease; DXA, dual-energy X-ray absorptiometry; MBD, mineral bone disorder; PTH, parathyroid hormone, RCT, randomized controlled trial.

Changes to the above summarized recommendations resulted in renumbering of several adjacent guideline statements. Specifically, 2009 Recommendation 4.1.6 now becomes 2017 Recommendation 4.1.7; 2009 Recommendation 4.1.8 now becomes 2017 Recommendation 4.1.9; 2009 Recommendation 4.3.5 now becomes 2017 Recommendation 4.3.4; and 2009 Recommendation 5.8 now becomes 2017 Recommendation 5.7.

2017 CKD-MBD Guideline Update³ should guide future investigations, which in turn will help advance the evidence base in CKD-MBD.

CHAPTER 3.2: DIAGNOSIS OF CKD-MBD: BONE Bone mineral density testing

At the time of publication of the 2009 KDIGO CKD-MBD Guideline,¹ the literature addressing the ability to estimate

fracture risk in CKD from bone mineral density (BMD) measurements by dual-energy X-ray absorptiometry (DXA) was limited to cross-sectional studies that compared BMD in CKD patients with and without a prevalent fracture. These results were variable across studies and across skeletal sites. Due to the lack of evidence that DXA BMD predicted fractures in CKD patients as it does in the general population, and the inability of DXA to indicate the histological type of

bone disease, the 2009 Guideline¹ recommended that BMD testing not be performed routinely in patients with CKD G3a to G5D and CKD-MBD.

The evidence-based review for the 2017 KDIGO CKD-MBD Guideline Update³ identified 4 prospective cohort studies in adults demonstrating that DXA BMD predicted fractures across the spectrum from CKD G3a to G5D. These studies represent a substantial advance since the original 2009 Guideline was published.¹ Despite the fact that the studies were conducted across a range of CKD severity, the finding that hip BMD predicted fractures was consistent across studies, and 2 studies demonstrated associations comparable to those seen in the absence of CKD.

Based on these insights, the Work Group concluded that DXA BMD assessment is reasonable if a low or declining BMD will lead to additional interventions to reduce falls or use osteoporosis medications.

Renal osteodystrophy

Renal osteodystrophy is defined as abnormal bone histology and is 1 component of the bone abnormalities of CKD-MBD. Bone biopsy is the gold standard for the diagnosis and classification of renal osteodystrophy. The 2009 KDIGO CKD-MBD Guideline¹ noted that DXA BMD does not distinguish among types of renal osteodystrophy. Further, it concluded that the diagnostic utility of biochemical markers was limited by their poor sensitivity and specificity. Differences in parathyroid hormone (PTH) assays have also contributed to conflicting results across studies. For the 2017 Update,³ the Work Group encouraged the continued use of PTH trends, rather than 1-time values, to guide therapy. When PTH trends are inconsistent, a bone biopsy is a reasonable consideration if the results may lead to changes in therapy.

The 2009 Guideline¹ recommended a bone biopsy prior to antiresorptive therapy in patients with CKD G4 to G5D and evidence of biochemical abnormalities of CKD-MBD, low BMD, and/or fragility fractures. However, the Work Group is well aware that clinical experience concerning performance and evaluation of bone biopsies may be limited. There is growing evidence that antiresorptive therapies are effective in patients with CKD G3a to G3b and G4, and no robust evidence that these medications induce adynamic bone disease. Therefore, the 2017 Update³ no longer suggests performing a bone biopsy prior to initiation of these medications.

CHAPTER 4.1: TREATMENT OF CKD-MBD TARGETED AT LOWERING HIGH SERUM PHOSPHATE AND MAINTAINING SERUM CALCIUM

Phosphate-lowering therapy

Assessment. The previous Recommendation 4.1.1 from the 2009 KDIGO CKD-MBD Guideline¹ provided guidance regarding treatment based on serum phosphate levels in different glomerular filtration rate (GFR) categories of CKD. The accumulated evidence did not lead to a substantially different conclusion in that there is an increasing risk of all-cause mortality with increasing levels of serum phosphate

in a consistent and direct fashion. For GFR decline and cardiovascular event rate, results were less conclusive.

The Work Group considered it reasonable to take the context of therapeutic interventions into account when assessing values of phosphate, calcium, and PTH. Further, it is important to emphasize the interdependency of these biochemical parameters. Based on these assumptions, the Work Group also decided to split the previous 2009 Recommendation 4.1.1 into 2 new Recommendations: 4.1.1 (diagnostic recommendation based on accumulated observational evidence) and 4.1.2 (therapeutic recommendation based mostly on RCTs).

Treatment of hyperphosphatemia. Following the publication of the 2009 KDIGO CKD-MBD Guideline,¹ additional high-quality evidence now links higher concentrations of phosphate with mortality among patients with CKD G3a to G5 or after transplantation. However, there is still a lack of trial data demonstrating that therapeutic approaches to lower serum phosphate will improve patient-centered outcomes.

The 2009 Guideline¹ suggested maintaining serum phosphate in the normal range for patients with CKD G3a to G3b and G4. On reevaluating the evidence for the 2017 Update,³ the Work Group drew several conclusions: (i) the association between serum phosphate and clinical outcome is not monotonic; (ii) evidence is lacking to demonstrate the efficacy of phosphate binders for lowering serum phosphate in patients with CKD G3a to G4; (iii) the safety of phosphate binders in this population is unproven; and (iv) there is an absence of data showing that dietary phosphate restriction improves clinical outcomes.

Consequently, the Work Group has abandoned the previous suggestion to maintain phosphate in the normal range, instead suggesting that treatment be focused on patients with hyperphosphatemia. The Work Group recognizes that preventing, rather than treating, hyperphosphatemia may be of value in patients with CKD G3a to G5D, but acknowledges that current data are inadequate to support the safety or efficacy of such an approach.

Phosphate-lowering therapies. The 2009 KDIGO CKD-MBD Guideline¹ stated that available phosphate binders are all effective in the treatment of hyperphosphatemia, and there is evidence that calcium-free binders may favor halting the progression of vascular calcification compared with calcium-containing binders. Concerns about calcium balance and uncertainties about phosphate lowering in CKD patients not on dialysis, coupled with additional hard-endpoint RCTs and a systematic review, prompted the 2017 Update Work Group to reevaluate this recommendation. Based on the current evidence, the Work Group concluded that normophosphatemia may not be an indication to start phosphate-lowering treatments. Further, not all phosphate binders are interchangeable.

Particularly in the case of CKD patients not on dialysis, the 2017 Update Work Group clarified that phosphate-lowering therapies may only be indicated in the event of “progressive or persistent hyperphosphatemia,” and not to prevent hyperphosphatemia. When thinking about risk-benefit ratios,

even calcium-free binders may possess a potential for harm (e.g., due to side effects such as gastrointestinal distress and binding of essential nutrients). The Work Group also adopted the term “phosphate-lowering treatment” instead of “phosphate-binding agents,” because all possible approaches (i.e., binders, diet, and dialysis) can be effective.

New evidence suggested a need to revise the 2009 recommendation regarding the use of calcium-based phosphate binders. These recent RCTs added hard-end point data to the comparison of calcium-containing and calcium-free phosphate binders. Overall, the Work Group concluded that excess exposure to calcium through diet, medications, or dialysate may be harmful across all GFR categories of CKD, regardless of whether other candidate markers of risk (such as hypercalcemia, arterial calcification, adynamic bone disease, or low PTH levels) are also present. Therefore, the Work Group deleted these previous qualifiers in the 2009 recommendation, while acknowledging that they may still be valid in high-risk scenarios.

Some members of the Work Group felt the available evidence does not conclusively demonstrate that calcium-free agents are superior to calcium-based agents. In addition, none of the studies provided sufficient dose-threshold information about calcium exposure, nor did they give information on the safety of moderately dosed calcium-containing binders in combination therapies. Finally, because KDIGO guidelines are intended for a global audience and calcium-free agents are not available or affordable in all jurisdictions, recommending against the use of calcium-based binders would imply that no treatment is preferable to using calcium-based agents. Despite the understandable clinical desire to have numeric targets and limits, the Work Group could not make an explicit recommendation about a maximum dose of calcium-based binders, preferring to leave this to the judgment of individual physicians while acknowledging the potential existence of a safe upper limit of calcium dose.

Data are lacking on adverse effects of excess exposure to calcium through diet, medications, or dialysate in children. The Work Group concluded that there was insufficient evidence to change this recommendation in children, who may be uniquely vulnerable to calcium restriction.

Dietary phosphate. There was no general controversy regarding the 2009 KDIGO CKD-MBD Guideline¹ recommendation on dietary phosphate restriction to lower elevated phosphate levels. However, the Work Group acknowledged that the wording of the original statement was vague, especially with regard to new evidence on different phosphate and phosphoprotein sources. Within the 2017 Update,³ predefined criteria on study duration and cohort size prohibited inclusion of some study reports for full evidence review. Nevertheless, the Work Group felt that some of these reports raised safety issues that require further discussion.

There are 3 major sources of phosphates in the diet: (i) natural phosphates contained in raw or unprocessed foods, (ii) phosphates added to foods during processing, and (iii) phosphates in dietary supplements and medications. The

amount of phosphorus contributed by food intake is increasing with current processing practices that utilize phosphorus-containing ingredients. However, aggressive dietary phosphate restriction is difficult because it has the potential to compromise adequate intake of other nutrients, especially protein. Another consideration for modification of dietary phosphate and control of serum phosphate is the “bioavailability” of phosphorus in different foods based on the form: organic versus inorganic sources of phosphate. Animal- and plant-based foods contain the organic form of phosphate; food additives contain inorganic phosphate. Approximately 40% to 60% of animal-based phosphate is absorbed, while plant-based phosphate, mostly associated with phytates, is less absorbable (generally 20%–50%). The Work Group suggests including education about the best food choices as they relate to absorbable phosphate. Additionally, patients should be guided toward fresh and homemade foods, rather than processed foods, to avoid additives.

Studies reviewed by the Work Group showed that various types of nutrition education have had mixed results for controlling serum phosphate. Considering all aspects of dietary phosphate management, the Work Group decided not to change the principal recommendation on phosphate restriction. Instead, the Work Group added a qualifier statement suggesting that phosphate sources should be better substantiated and patient education should focus on best choices.

Maintaining serum calcium

As is the case for phosphate, novel epidemiological evidence linking higher calcium concentrations to increased mortality in adults with CKD has accumulated since the publication of the 2009 KDIGO CKD-MBD Guideline.¹ Additionally, new studies have associated higher concentrations of serum calcium with nonfatal cardiovascular events.

Because mild and asymptomatic hypocalcemia may well be harmless, especially in the presence of calcimimetic therapy, the Work Group emphasized an individualized approach to the treatment of hypocalcemia, rather than recommending the correction of hypocalcemia for all patients. However, significant or symptomatic hypocalcemia should still be addressed.

The 2009 Guideline¹ considered that a dialysate calcium concentration of 1.25 mmol/l (2.5 mEq/l) would yield neutral calcium balance. Based on new evidence, the 2017 Work Group felt that this recommendation remains valid as written in 2009. However, because additional studies of better quality are now available, the evidence grade has been changed from 2D to 2C.

CHAPTER 4.2: TREATMENT OF ABNORMAL PTH LEVELS IN CKD-MBD

Optimal PTH levels

Secondary hyperparathyroidism (SHPT) is characterized by a complex pathogenesis driven by several factors, including vitamin D deficiency, increasing fibroblast growth factor 23 levels, hypocalcemia, and hyperphosphatemia, which can lead to significant abnormalities in bone mineralization and turnover.

The 2009 KDIGO CKD-MBD Guideline¹ recommended addressing modifiable risk factors for all patients with a PTH level above the upper limit of normal for the assay used. Unfortunately, there is still an absence of RCTs that define an optimal PTH level for patients with CKD G3a to G5. The 2017 Update Work Group felt that modest increases in PTH may represent an appropriate adaptive response to declining kidney function, due to phosphaturic effects and increasing bone resistance to PTH. Therefore, the Update Work Group revised the 2009 Guideline recommendation to reflect the fact that treatment should not be based on a single elevated PTH value.

Further, the Work Group recognized an additional modifiable risk factor: high phosphate intake. Increasingly, studies have shown that excess phosphate intake does not always result in hyperphosphatemia (especially in early CKD), and that high phosphate intake may promote SHPT. Although dietary phosphate intake is modifiable, the Work Group also acknowledged that better methods for assessment of dietary phosphate intake and balance are required.

Calcitriol and vitamin D analogs

Nondialysis patients. Prevention and treatment of SHPT is important because imbalances in mineral metabolism are associated with CKD-MBD, and higher PTH levels are associated with increased morbidity and mortality in CKD patients. For many decades, calcitriol and other vitamin D analogs have been the primary therapeutic option for treating SHPT in individuals with CKD. The 2009 KDIGO CKD-MBD Guideline¹ summarized multiple studies demonstrating that administration of calcitriol or vitamin D analogs (such as paricalcitol, doxercalciferol, and alfacalcidol) resulted in suppression of PTH levels. However, there was a notable lack of trials demonstrating improvements in patient-centered outcomes.

Additional RCTs of calcitriol or vitamin D analog therapy have been published since the 2009 Guideline.¹ Two of these—the PRIMO and OPERA trials—demonstrated a significantly increased risk of hypercalcemia in patients treated with paricalcitol compared with placebo, in the absence of beneficial effects on surrogate cardiac endpoints. These results, combined with the opinion that moderate PTH elevations may represent an appropriate adaptive response, led the 2017 Update Work Group to conclude that the risk-benefit ratio of treating moderate PTH elevations was no longer favorable. Therefore, the Update Work Group recommended that the use of calcitriol or vitamin D analogs should be reserved only for severe and progressive SHPT.

Accordingly, the present Guideline³ no longer recommends routine use of calcitriol or its analogs in CKD G3a to G5. This change did not reach uniform consensus among the Work Group members. It should be noted that the participants in the PRIMO and OPERA trials only had moderately increased PTH levels; thus, therapy with calcitriol and vitamin D analogs may be considered in those with progressive and severe SHPT.

No RCTs were identified that demonstrated the beneficial effects of calcitriol or vitamin D analogs on patient-level

outcomes, such as cardiac events or mortality, and the optimal level of PTH in CKD G3a to G5 is not known. Further, therapy with these agents may have additional harmful effects related to increases in serum phosphate and fibroblast growth factor 23 levels. Therefore, the Work Group concluded that—if initiated for severe and progressive SHPT—calcitriol or vitamin D analogs should be started with low doses, independent of the initial PTH concentration, and then titrated based on the PTH response. Hypercalcemia should be avoided.

Dialysis patients. New data prompted the 2017 Update Work Group to reappraise the use of PTH-lowering therapies in patients with CKD G5D. A couple new trials evaluated treatment with cinacalcet versus placebo and 1 new trial evaluated calcitriol versus a vitamin D analog. There are still no new trials of calcitriol or vitamin D analogs that demonstrated clear benefits in patient-level outcomes.

The Update Work Group discussed the EVOLVE trial at length. Members were divided as to whether the EVOLVE data were sufficient to recommend cinacalcet as a first-line option for all patients with SHPT and CKD G5D who require PTH-lowering therapy.

One opinion is that the primary end point of the EVOLVE study was negative. The alternative opinion is that secondary analyses found effects on patient-level endpoints, while there are no positive data on mortality or patient-centered end points from trials with calcitriol or other vitamin D analogs.

Given the lack of consensus among the Work Group, coupled with the higher acquisition cost of cinacalcet, the 2009 recommendation for patients with CKD G5D was modified to list all acceptable treatment options in alphabetical order. The individual choice should continue to be guided by considerations about concomitant therapies and the patient's calcium and phosphate levels. In addition, the choice of dialysate calcium concentrations will impact serum PTH levels. Finally, it should be pointed out that parathyroidectomy remains a valid treatment option, especially when PTH-lowering therapies fail, as advocated in Recommendation 4.2.5 from the 2009 KDIGO CKD-MBD Guideline.¹

CHAPTER 4.3: TREATMENT OF BONE WITH BIPHOSPHONATES, OTHER OSTEOPOROSIS MEDICATIONS, AND GROWTH HORMONE

The current Recommendation 3.2.2 addresses the indications for a bone biopsy prior to antiresorptive and other osteoporosis therapies. Therefore, the original Recommendation 4.3.4 from the 2009 KDIGO CKD-MBD Guideline¹ was removed and Recommendation 4.3.3 was extended from CKD G3a through G3b to CKD G3a through G5D. Nevertheless, when such treatment choices are considered, their specific side effects must also be taken into account. For example, antiresorptives will exacerbate low bone turnover, and denosumab may induce significant hypocalcemia. The risk of administering antiresorptives must be weighed against the accuracy of the diagnosis of the underlying bone phenotype.

CHAPTER 5: EVALUATION AND TREATMENT OF KIDNEY TRANSPLANT BONE DISEASE

Assessment

The 2009 KDIGO CKD-MBD Guideline¹ recommended BMD testing in the first 3 months following transplantation in patients with an eGFR greater than 30 ml/min/1.73 m² if they receive corticosteroids or have risk factors for osteoporosis. However, it was recommended that DXA BMD not be performed in those with CKD G4T to G5T.

As detailed in the 2017 Recommendation 3.2.1,³ there is growing evidence that DXA BMD predicts fractures across the spectrum of CKD severity, including 4 prospective cohort studies in patients with CKD G3a to G5D. There are limited data suggesting that these findings extend to transplant recipients. Therefore, the current Guideline³ recommends BMD testing in transplant recipients, as in those with CKD G3a to G5D, if the results will impact treatment decisions.

Treatment

The current Recommendation 3.2.2 now addresses the indications for a bone biopsy prior to antiresorptive and other osteoporosis therapies. Therefore, the 2009 Recommendation 5.6 concerning bone biopsies in transplant recipients has been modified.

SUMMARY OF KDIGO CKD-MBD RECOMMENDATIONS UPDATED RECOMMENDATIONS ARE DENOTED IN BOXES

CHAPTER 3.1: DIAGNOSIS OF CKD-MBD: BIOCHEMICAL ABNORMALITIES

3.1.1: We recommend monitoring serum levels of calcium, phosphate, PTH, and alkaline phosphatase activity beginning in CKD G3a (1C).

In children, we suggest such monitoring beginning in CKD G2 (2D).

3.1.2: In patients with CKD G3a–G5D, it is reasonable to base the frequency of monitoring serum calcium, phosphate, and PTH on the presence and magnitude of abnormalities, and the rate of progression of CKD (Not Graded).

Reasonable monitoring intervals would be:

- In CKD G3a–G3b: for serum calcium and phosphate, every 6–12 months; and for PTH, based on baseline level and CKD progression.
- In CKD G4: for serum calcium and phosphate, every 3–6 months; and for PTH, every 6–12 months.
- In CKD G5, including G5D: for serum calcium and phosphate, every 1–3 months; and for PTH, every 3–6 months.
- In CKD G4–G5D: for alkaline phosphatase activity, every 12 months, or more frequently in the presence of elevated PTH (see Chapter 3.2).

In CKD patients receiving treatments for CKD-MBD, or in whom biochemical abnormalities are identified, it is reasonable to increase the frequency of measurements to monitor for trends and treatment efficacy and side effects (Not Graded).

3.1.3: In patients with CKD G3a–G5D, we suggest that 25(OH)D (calcidiol) levels might be measured, and repeated testing determined by baseline values and therapeutic interventions (2C).

We suggest that vitamin D deficiency and insufficiency be corrected using treatment strategies recommended for the general population (2C).

3.1.4: In patients with CKD G3a–G5D, we recommend that therapeutic decisions be based on trends rather than on a single laboratory value, taking into account all available CKD-MBD assessments (1C).

3.1.5: In patients with CKD G3a–G5D, we suggest that individual values of serum calcium and phosphate, evaluated together, be used to guide clinical practice rather than the mathematical construct of calcium-phosphate product (Ca × P) (2D).

3.1.6: In reports of laboratory tests for patients with CKD G3a–G5D, we recommend that clinical laboratories inform clinicians of the actual assay method in use and report any change in methods, sample source (plasma or serum), and handling specifications to facilitate the appropriate interpretation of biochemistry data (1B).

CHAPTER 3.2: DIAGNOSIS OF CKD-MBD: BONE

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).

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).

3.2.3: In patients with CKD G3a–G5D, we suggest that measurements of serum PTH or bone-specific alkaline phosphatase can be used to evaluate bone disease because markedly high or low values predict underlying bone turnover (2B).

3.2.4: In patients with CKD G3a–G5D, we suggest not routinely measuring bone-derived turnover markers of collagen synthesis (such as procollagen type I C-terminal propeptide) and breakdown (such as type I collagen cross-linked

telo peptide, cross-laps, pyridinoline, or deoxy-pyridinoline) (2C).

- 3.2.5: We recommend that infants with CKD G2–G5D have their length measured at least quarterly, while children with CKD G2–G5D should be assessed for linear growth at least annually (1B).

CHAPTER 3.3: DIAGNOSIS OF CKD-MBD: VASCULAR CALCIFICATION

- 3.3.1: In patients with CKD G3a–G5D, we suggest that a lateral abdominal radiograph can be used to detect the presence or absence of vascular calcification, and an echocardiogram can be used to detect the presence or absence of valvular calcification, as reasonable alternatives to computed tomography-based imaging (2C).

- 3.3.2: We suggest that patients with CKD G3a–G5D with known vascular or valvular calcification be considered at highest cardiovascular risk (2A).

It is reasonable to use this information to guide the management of CKD-MBD (*Not Graded*).

CHAPTER 4.1: TREATMENT OF CKD-MBD TARGETED AT LOWERING HIGH SERUM PHOSPHATE AND MAINTAINING SERUM CALCIUM

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

- 4.1.7: In patients with CKD G3a–G5D, we recommend avoiding the long-term use of aluminum-containing phosphate binders, and in patients with CKD G5D, avoiding dialysate aluminum contamination to prevent aluminum intoxication (1C).

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*).

- 4.1.9: In patients with CKD G5D, we suggest increasing dialytic phosphate removal in the treatment of persistent hyperphosphatemia (2C).

CHAPTER 4.2: TREATMENT OF ABNORMAL PTH LEVELS IN CKD-MBD

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).

4.2.2: In adult patients with CKD G3a–G5 not on dialysis, we suggest 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*).

4.2.3: In patients with CKD G5D, we suggest maintaining intact PTH levels in the range of approximately 2 to 9 times the upper normal limit for the assay (2C).

We suggest that marked changes in PTH levels in either direction within this range prompt an initiation or change in therapy to avoid progression to levels outside of this range (2C).

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).

4.2.5: In patients with CKD G3a–G5D with severe hyperparathyroidism who fail to respond to medical or pharmacological therapy, we suggest parathyroidectomy (2B).

CHAPTER 4.3: TREATMENT OF BONE WITH BIPHOSPHONATES, OTHER OSTEOPOROSIS MEDICATIONS, AND GROWTH HORMONE

4.3.1: In patients with CKD G1–G2 with osteoporosis and/or high risk of fracture, as identified by World Health Organization criteria, we recommend management as for the general population (1A).

4.3.2: In patients with CKD G3a–G3b with PTH in the normal range and osteoporosis and/or high risk of fracture, as identified by World Health Organization criteria, we suggest treatment as for the general population (2B).

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).

4.3.4: In children and adolescents with CKD G2–G5D and related height deficits, we recommend treatment with recombinant human growth hormone when additional growth is desired, after first addressing malnutrition and biochemical abnormalities of CKD-MBD (1A).

CHAPTER 5: EVALUATION AND TREATMENT OF KIDNEY TRANSPLANT BONE DISEASE

5.1: In patients in the immediate post-kidney transplant period, we recommend measuring serum calcium and phosphate at least weekly, until stable (1B).

5.2: In patients after the immediate post-kidney transplant period, it is reasonable to base the frequency of monitoring serum calcium, phosphate, and PTH on the presence and magnitude of

abnormalities, and the rate of progression of CKD (Not Graded).

Reasonable monitoring intervals would be:

- In CKD G1T–G3bT, for serum calcium and phosphate, every 6–12 months; and for PTH, once, with subsequent intervals depending on baseline level and CKD progression.
- In CKD G4T, for serum calcium and phosphate, every 3–6 months; and for PTH, every 6–12 months.
- In CKD G5T, for serum calcium and phosphate, every 1–3 months; and for PTH, every 3–6 months.
- In CKD G3aT–G5T, measurement of alkaline phosphatases annually, or more frequently in the presence of elevated PTH (see Chapter 3.2).

In CKD patients receiving treatments for CKD-MBD, or in whom biochemical abnormalities are identified, it is reasonable to increase the frequency of measurements to monitor for efficacy and side effects (Not Graded).

It is reasonable to manage these abnormalities as for patients with CKD G3a–G5 (see Chapters 4.1 and 4.2) (Not Graded).

- 5.3: In patients with CKD G1T–G5T, we suggest that 25(OH)D (calcidiol) levels might be measured, and repeated testing determined by baseline values and interventions (2C).
- 5.4: In patients with CKD G1T–G5T, we suggest that vitamin D deficiency and insufficiency be corrected using treatment strategies recommended for the general population (2C).

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 m² 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.

5.7: In patients with CKD G4T–G5T with known low BMD, we suggest management as for patients with CKD G4–G5 not on dialysis, as detailed in Chapters 4.1 and 4.2 (2C).

DISCLOSURE

Kidney Disease: Improving Global Outcomes (KDIGO) makes every effort to avoid any actual or reasonably perceived conflicts of interest that may arise as a result of an outside relationship or a personal, professional, or business interest of a member of the Work Group. All members of the Work Group are required to complete, sign, and submit a disclosure and attestation form showing all such relationships that might be perceived as or are actual conflicts of interest. This document is updated annually, and information is adjusted accordingly. All reported information can be found in the Work Group members' Biographic and Disclosure section of the complete *KDIGO 2017 Clinical Practice Guideline Update for the Diagnosis, Evaluation, Prevention, and Treatment of Chronic Kidney Disease–Mineral and Bone Disorder (CKD-MBD)* in *Kidney International*

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