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COMMENTARY

KDOQI US Commentary on the 2009 KDIGO Clinical Practice Guideline for the Diagnosis, Evaluation, and Treatment of CKD–Mineral and Bone Disorder (CKD-MBD)

Katrin Uhlig, MD, MS,[1] Jeffrey S. Berns, MD,[2] Bryan Kestenbaum, MD, MS,[3] Raj Kumar, MBBS,[4] Mary B. Leonard, MD,[5] Kevin J. Martin, MB, BCh,[6] Stuart M. Sprague, DO,[7] and Stanley Goldfarb, MD[8]

This commentary provides a US perspective on the 2009 KDIGO (Kidney Disease: Improving Global Outcomes) *Clinical Practice Guideline for the Diagnosis, Evaluation, Prevention, and Treatment of Chronic Kidney Disease–Mineral and Bone Disorder (CKD–MBD)*. KDIGO is an independent international organization with the primary mission of the promotion, coordination, collaboration, and integration of initiatives to develop and implement clinical practice guidelines for the care of patients with kidney disease. The National Kidney Foundation's Kidney Disease Outcomes Quality Initiative (KDOQI), recognizing that international guidelines need to be adapted for each country, convened a group of experts to comment on the application and implementation of the KDIGO guideline for patients with CKD in the United States. This commentary puts the KDIGO guideline into the context of the supporting evidence and the setting of care delivered in the United States and summarizes important differences between prior KDOQI guidelines and the newer KDIGO guideline. It also considers the potential impact of a new bundled payment system for dialysis clinics.

The KDIGO guideline addresses the evaluation and treatment of abnormalities of CKD-MBD in adults and children with CKD stages 3-5 on long-term dialysis therapy or with a kidney transplant. Tests considered are those that relate to laboratory, bone, and cardiovascular abnormality detection and monitoring. Treatments considered are interventions to treat hyperphosphatemia, hyperparathyroidism, and bone disease in patients with CKD stages 3-5D and 1-5T. Limitations of the evidence are discussed. The lack of definitive clinical outcome trials explains why most recommendations are not of level 1 but of level 2 strength, which means weak or discretionary recommendations. Suggestions for future research highlight priority areas.

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From ¹*Tufts Medical Center, Tufts University School of Medicine, Boston MA;* ²*University of Pennsylvania School of Medicine, Philadelphia, PA;* ³*University of Washington Kidney Research Institute, Seattle, WA;* ⁴*Mayo Clinic College of Medicine, Rochester, MN;* ⁵*The Children's Hospital of Philadelphia, University of Pennsylvania School of Medicine, Philadelphia, PA;* ⁶*Division of Nephrology, Saint Louis University, St. Louis, MO;* ⁷*North Shore University Health System University of Chicago Pritzker School of Medicine, Chicago, IL; and* ⁸*University of Pennsylvania School of Medicine, Philadelphia, PA.*

KDIGO (Kidney Disease: Improving Global Outcomes) is an international initiative with a key mission of developing clinical practice guidelines in the area of chronic kidney disease (CKD). KDIGO recently published an evidence-based clinical practice guideline for the prevention, diagnosis, evaluation, and treatment of metabolic bone disease in individuals with CKD.[1] Because an international guideline needs to be adapted for the United States, the National Kidney Foundation's Kidney Disease Outcomes Quality Initiative (KDOQI) convened a multidisciplinary group to comment on the applicability and implementation of the KDIGO guideline for patients with CKD in the United States. This commentary presents the KDIGO guideline recommendation and statements, provides a succinct discussion and annotation of the supporting rationale, and comments on their applicability in the context of practice in the United States.

KDIGO was established in 2003 as an independent nonprofit foundation governed by an international board of directors, with its stated mission to "improve the care and outcomes of kidney disease patients worldwide through promoting coordination, collaboration, and integration of initiatives."[2] Mineral abnormalities and renal osteodystrophy in CKD and, more recently, linkage of these with extraosseous calcification have been areas of intense interest and controversy. In 2005, KDIGO sponsored a controversies conference, "Definition, Evaluation and Classification of Renal Osteodystrophy." The resulting 2006 KDIGO position statement proposed a definition for CKD–mineral and bone disorder (CKD-MBD) and for renal osteodystrophy, shown in Box 1.[3]

Both initial bone formation during growth (bone modeling) and changes in bone structure and function during adulthood (bone remodeling) are severely disrupted in patients with CKD. This results from disturbances in mineral metabolism, and a number of abnormalities in levels of hormones and cytokines that regulate blood levels of calcium, phosphorus, and various other ionic species, as well as bone, directly. Abnormal

Box 1. Definitions of CKD-MBD and of Renal Osteodystrophy

Definition of CKD-MBD

A systemic disorder of mineral and bone metabolism due to CKD manifested by either one or a combination of the following:
◇ Abnormalities of calcium, phosphorus, PTH, or vitamin D metabolism
◇ Abnormalities in bone turnover, mineralization, volume, linear growth, or strength
◇ Vascular or other soft-tissue calcification

Definition of renal osteodystrophy

Renal osteodystrophy is an alteration of bone morphology in patients with CKD.
It is one measure of the skeletal component of the systemic disorder of CKD-MBD that is quantifiable by histomorphometry of bone biopsy.

Abbreviations: CKD, chronic kidney disease; CKD-MBD, chronic kidney disease–mineral and bone disorder; PTH, parathyroid hormone.

Adapted from Moe et al[3] with permission of Nature Publishing Group.

bone structure and function is a common finding in patients with CKD requiring dialysis (stage 5D) and many patients with CKD stages 3-5. In addition, extraskeletal calcification is a feature, at least in part, of deranged mineral and bone metabolism of CKD and may even be exacerbated by some of the therapies used to correct mineral and bone changes in CKD. Interactions among abnormal mineral metabolism, abnormal bone, and extraskeletal calcification may contribute to the morbidity and mortality of patients with CKD. Hence, this guideline is needed to help define best practices based on current disease concepts and best available research evidence.

KDIGO GUIDELINE PROCESS

A KDIGO Work Group of international experts and an Evidence Review Team defined pertinent questions related to the clinical management of CKD-MBD and developed study inclusion criteria. Target populations for the KDIGO guideline and this commentary are adults and

Table 1. Strength of a Recommendation

Grade for Strength	Implications for		
	Patients	Clinicians	Policy Makers
Level 1 Strong "We recommend . . . should"	Most people in your situation would want the recommended course of action and only a small proportion would not	Most patients should receive the recommended course of action	The recommendation can be evaluated as a candidate for developing a policy or a performance measure
Level 2 Weak or discretionary "We suggest . . . might"	Most people in your situation would want the recommended course of action, but many would not	Different choices will be appropriate for different patients. Each patient needs help to arrive at a management decision consistent with her or his values and preferences	The recommendation is likely to require substantial debate and involvement of stakeholders before policy can be determined

Note: In addition to graded recommendations, the KDIGO Work Group could also issue statements that were not graded (see text).

Abbreviation: KDIGO, Kidney Disease: Improving Global Outcomes.

Based in part on Guyatt et al.[6]

children with CKD stages 3-5, those on long-term dialysis therapy, and kidney transplant recipients. The target audience is practitioners caring for these patients.

For treatment questions, outcomes of interest were grouped into 3 categories: outcomes with direct importance to patients (eg, mortality, cardiovascular disease events, hospitalizations, fracture, and quality of life), intermediate outcomes (eg, vascular calcification, bone mineral density [BMD], and bone biopsy), and biochemical outcomes (eg, serum calcium, phosphorus, alkaline phosphatase, and parathyroid hormone [PTH] levels). Clinical outcomes were considered to be of critical or high importance, whereas intermediate and laboratory outcomes were considered to be of moderate importance. Thus, the work group acknowledged that these intermediate and biochemical outcomes currently are not sufficiently validated surrogates for hard clinical events.

The KDIGO Work Group agreed a priori to include only randomized controlled trials (RCTs) of 6 months' duration with a sample size of at least 50 patients in systematic reviews. Exceptions were made for studies with bone biopsy outcomes (minimum sample size, 20 per study). Studies of smaller sample size involving children were tabulated in overview tables.

The grading approach followed in the KDIGO bone guideline is adopted from the Grading of Recommendations Assessment, Development and Evaluation (GRADE) approach.[4,5] The strength of each recommendation is rated as level 1, which means strong, or level 2, which means weak or discretionary. Wording corresponding to a level 1 recommendation is "We recommend . . . should" and implies that most patients should receive the course of action. Wording for a level 2 recommendation is "We suggest . . . might," which implies that different choices will be appropriate for different patients, with the suggested course of action being a reasonable choice in many patients. Usually, level 1 but not level 2 recommendations are candidates for developing a performance measure.[6] In addition, each statement is assigned a grade for the quality of the supporting evidence: A (high), B (moderate), C (low), or D (very low). Furthermore, for topics that cannot be subjected to systematic evidence review, the work group could issue statements that are not graded. Typically, these provide guidance based on common sense; for example, reminders of the obvious or recommendations that are not specific enough to allow direct application of evidence. Table 1 lists implications of the guideline grades and describes how the strength of the recommendations should be interpreted by guideline users. With the evolution in grading,

grades between KDOQI and KDIGO recommendations are not directly comparable.

KDOQI PROCESS FOR ADAPTATION OF THE KDIGO BONE GUIDELINE

Certain organizational, legislative, and cultural issues may affect the applicability of evidence to a specific context.[7] Variability in values and judgments also may legitimately impact on interpretation of evidence and its translation into recommendations.[6] This highlights the need for a process of adapting an existing guideline, in this case, the global KDIGO guideline, to the US setting. A large amount of evidence reviewed for the KDIGO guidelines was generated in the United States or settings similar to the United States with regard to the epidemiologic characteristics of CKD-MBD, resources, and health care delivery systems. In addition, 6 members of the KDIGO guidelines work group were US based. Therefore, it can be expected that many recommendations generally are applicable to the United States. However, this commentary provides an opportunity for additional summary and reflection regarding their appropriateness for implementation in the US health care system. KDOQI convened a multidisciplinary group to comment on the application of the KDIGO CKD-MBD clinical practice guidelines in the United States. After the authors approved a commentary draft, the KDOQI Chair and Vice Chairs for Guidelines and Commentary, Research, Education, and Public Policy, as well as the National Kidney Foundation's Scientific Advisory Board, reviewed the commentary and their recommendations were incorporated into the final article.

Explicit cost considerations of the recommendations warrant detailed analysis and are beyond the scope of this report; however, the potential impact of a newly proposed bundled payment system for dialysis clinics is considered in the first section of this commentary. In the following section the original KDIGO guideline recommendations for CKD-MBD are presented with the strength that originally was assigned to them. KDIGO guideline chapters 3 and 4 relate to the evaluation and treatment of CKD-MBD in patients with CKD stages 3-5 and 5D, and chapter 5, to CKD stages 1-5T. For ease of referencing with the KDIGO guideline, we retained the original sequential number assigned to each statement. After each set of recommendations, we provide a commentary regarding their rationale and a statement regarding their applicability to the United States. Table 2 shows a summary of KDIGO recommendations on evaluation for CKD-MBD in patients with CKD stages 3-5D, and Table 3 shows this for patients with CKD stages 1-5T. Because the KDIGO guideline builds on more recent evidence, its recommendations should replace those published previously by the KDOQI.[8] Table 4 juxtaposes pertinent KDIGO and KDOQI recommendations. Our commentary provides additional information guiding clinical practice in the United States and should be used in conjunction with careful reading of the KDIGO clinical practice guideline.

CONSIDERATIONS FOR IMPLEMENTATION: POTENTIAL IMPACT OF A NEW BUNDLED PAYMENT SYSTEM FOR DIALYSIS CLINICS

Implementation of the guideline recommendations in outpatient dialysis patients is likely to be affected greatly by the introduction of new payment policies created through the Medicare Improvements for Patients and Providers Act of 2008 (MIPPA). Beginning in 2011, the Centers for Medicare & Medicaid Services (CMS) plans to implement an updated prospective payment system including an expanded bundle. In a draft regulation published in the Federal Register on September 29, 2009, the CMS proposed that the expanded bundle include all drugs and biologics formerly reimbursed under either Medicare Part B or Part D that are used to treat patients with end-stage renal disease (ESRD), regardless of the administration route.[10,11] The health care reform legislation passed by the US House of Representatives (HR 3962) includes a similar requirement. The proposal would make the dialysis unit responsible for provision of the following items under the bundle:

- Services included in the composite rate as of 2010
- Injectable biologics used to treat anemia; erythropoiesis-stimulating agents and any oral form of such agents
- Other injectable medications that are furnished to ESRD beneficiaries and paid

Table 2. KDIGO Recommendations on Evaluation for CKD-MBD in CKD Stages 3-5D

| CKD Stage (GFR [mL/min/1.73 m^2]) | Biochemical Components[a] | | | | Bone | | | Blood Vessels |
	Ca, P	PTH	ALP	25(OH)D	Bone-specific ALP	Bone Biopsy	BMD	Calcification Testing
Stage 3 (30-59)	Once (1C)[b]; then every 6-12 mo (NG)	Once (1C)[b]; then based on level and CKD progression (NG)	Once (1C)[b]	Once (2C); then based on level and treatments (2C)	Can be used to evaluate bone disease (2B)	In various settings[c] and before treatment with bisphosphonates (NG)	No routine testing in the presence of CKD-MBD (2B)	No recommendation for routine screening
Stage 4 (15-29)	Every 3-6 mo (NG)	Every 6-12 mo (NG)	Every 12 mo[d] (NG)					
Stage 5 (<15 or dialysis)	Every 1-3 mo (NG)	Every 3-6 mo (NG)						

Note: Number and letters in parentheses refer to strength of recommendation and quality of evidence (see Table 1 for grades).

Abbreviations and definitions: 25(OH)D, 25-hydroxyvitamin D (calcidiol); ALP, alkaline phosphatase; BMD, bone mineral density; Ca, calcium; CKD, chronic kidney disease; CKD-MBD, chronic kidney disease-mineral and bone disorder; D, dialysis (when referring to CKD stage); GFR, glomerular filtration rate; KDIGO, Kidney Disease: Improving Global Outcomes; NG, statement not graded; P, phosphorus; PTH, parathyroid hormone.

[a]Base the frequency of laboratory measurements on the presence and magnitude of abnormalities and rate of CKD progression. Increase frequency intervals as needed to monitor for trends, treatment efficacy, and side effects (NG).

[b]In children, monitoring of Ca, P, and ALP levels is suggested beginning in CKD stage 2 (2D).

[c]Various settings include unexplained fractures, persistent bone pain, unexplained hypercalcemia, unexplained hypophosphatemia, and possible aluminum toxicity.

[d]More frequently in presence of increased PTH levels.

Table 3. KDIGO Recommendations on Evaluation for CKD-MBD in CKD Stages 1-5T

CKD Stage (GFR [mL/min/1.73 m²])	Biochemical Components[a]				Bone	
	Ca, P	PTH	ALP	25(OH)D	Bone Biopsy	BMD
Immediate posttransplant	At least every wk until stable (1B)					
Stage 1T (>90) Stage 2T (60-89) Stage 3T (30-59)	Every 6-12 mo (NG)	Once and then based on level and CKD progression (NG)	Every 12 mo[b] (NG)	Once and then based on level and treatments (2C)	Consider to guide treatment, specifically before treatment with bisphosphonates (NG)	In first 3 mo post-transplant if patient receives corticosteroids or has risk factors for osteoporosis (2D)
Stage 4T (15-29)	Every 3-6 mo (NG)	Every 6-12 mo (NG)				No routine testing (2B)
Stage 5T (<15)	Every 1-3 mo (NG)	Every 3-6 mo (NG)				

Note: Number and letters in parentheses refer to strength of recommendation and quality of evidence (see Table 1 for grades).

Abbreviations and definitions: 25(OH)D, 25-hydroxyvitamin D (calcidiol); ALP, alkaline phosphatase; BMD, bone mineral density; Ca, calcium; CKD, chronic kidney disease; CKD-MBD, chronic kidney disease–mineral and bone disorder; GFR, glomerular filtration rate; KDIGO, Kidney Disease: Improving Global Outcomes; NG, statement not graded; P, phosphorus; PTH, parathyroid hormone; T, transplant (when referring to CKD stage).

[a]Base the frequency of laboratory measurements on the presence and magnitude of abnormalities and rate of CKD progression. Increase frequency intervals as needed to monitor for trends and treatment efficacy and side effects (NG).

[b]More frequently in presence of increased PTH levels.

Table 4. Comparison of Key KDIGO 2009 and KDOQI 2003 Recommendations on Testing and Treatment Targets

KDIGO 2009	Grade	KDOQI 2003	Grade	Comment
		CKD Stages 3-5 and 5D		
In adults, recommend monitoring serum calcium, phosphorus, PTH, and ALP levels beginning in CKD stage 3 [KDIGO recommendation 3.1.1]	1C	Same, except no recommendation for ALP [KDOQI guideline 1.1]	E	Suggestion for using ALP as adjunct test
In children, suggest monitoring serum calcium, phosphorus, PTH, and ALP levels beginning in CKD stage 2 [3.1.1]	2D	Same, but also recommendation for total CO_2 [1.1P]	O	
In CKD stages 3-5D, suggest measuring 25(OH)D levels [3.1.3]	2C	In CKD stages 3-4, measure 25(OH)D, if PTH is above target range for stage of CKD [7.1]	E	Suggestion for expanded testing of 25(OH)D
Suggest that vitamin D deficiency and insufficiency be corrected using treatment strategies recommended for the general population [3.1.3]	2C	If serum 25(OH)D level <30 ng/mL (<75 nmol/L), supplementation with vitamin D_2 (ergocalciferol) should be initiated [7.2]	O	Suggestion for expanded treatment with vitamin D_2 or D_3 given suggestions for expanded testing
Suggest using individual serum calcium and phosphorus values, rather than the mathematical construct of Ca × P [3.1.5]	2D	Ca × P <55 mg^2/dL^2 recommended in CKD stages 3-5 [6.5]	E	Suggestion against product as mostly driven by phosphorus and not more informative than both components individually
Recommend clinical laboratories report assay methods used and any change in methods, sample source, and handling specifications. For appropriate interpretation of biochemistry data in CKD stages 3-5D, clinicians need to understand assay characteristics and limitations [paraphrased from 3.1.6] Rationale recommends use of second-generation assay for PTH [3.1.6]	1B	Evidence and recommendations for adults based mostly on PTH measured using second-generation Allegro assay from Nichols, which is not currently available [background to guideline 1] Evidence and recommendation in children mostly based on use of first-generation immunometric PTH assay [1.1P]	—	Reflects evolution in PTH assays
In patients with CKD stages 3-5D, suggest that measurements of serum PTH or bone-specific ALP can be used to evaluate bone disease because markedly high or low values predict underlying bone turnover [3.2.3]	2B	Bone-specific ALP not specifically recommended Unexplained increases in bone ALP activity together with increases in PTH is indication for considering bone biopsy in CKD stage 5D [2.2.b]	— / O	Suggestion for testing bone-specific ALP in certain individuals
In CKD stages 3-5D, reasonable to perform bone biopsy in various settings and before therapy with bisphosphonates in patients with CKD-MBD [3.2.1]	NG	Bone biopsy should be considered in CKD stage 5D in various settings [2.2]	O	Expanded indication for bone biopsy including before treatment with bisphosphonates
In CKD stages 3-5D with biochemical abnormalities of CKD-MBD, suggest that BMD testing not be routinely performed [3.2.2]	2B	DXA should be used in patients with fractures and those with known risks for osteoporosis [2.4]	O	Suggestion for restricted testing of BMD
No recommendation given for routine screening for vascular calcification [rationale for 3.3]	—	Same	—	

(Continued)

Table 4 (Cont'd). Comparison of Key KDIGO 2009 and KDOQI 2003 Recommendations on Testing and Treatment Targets

KDIGO	Grade	KDOQI	Grade	Comment
In CKD stages 3-5, suggest maintaining serum phosphorus in the reference range [4.1.1]	2C	In CKD stages 3-4, maintain serum phosphorus at [3.1]: ≥2.7 mg/dL ≤4.6 mg/dL	 E O	Suggestion for same target range in CKD stages 3-4, lower in CKD stage 5
In CKD stage 5D, suggest lowering increased phosphorus levels toward the reference range [4.1.1]	2C	In CKD stages 5 and 5D, maintain serum phosphorus at 3.5-5.5 mg/dL [3.2]	E	No prescriptive phosphorus target range. Suggestion to lower toward reference permits greater flexibility based on assessment of risk-benefit and patient preferences
In CKD stages 3-5D, suggest maintaining serum calcium in reference range [4.1.2]	2D	In CKD stages 3-4, same for corrected total calcium [6.1] In CKD stages 5 and 5D, same for corrected total calcium, but preference for aiming toward lower end of reference range (8.4-9.5 mg/dL) [6.2]	E O	Suggestion not specific for corrected total calcium
In CKD stages 3-5 not on dialysis therapy, suggest evaluating patients with PTH levels above the upper reference limit of the assay for hyperphosphatemia, hypocalcemia, and vitamin D deficiency [4.2.1]	2C	PTH target ranges: [1.4] CKD stage 3, 35-70 pg/mL CKD stage 4, 70-110 pg/mL CKD stage 5, 150-300 pg/mL	 O O E	No prescriptive PTH target range. Suggestion for lower PTH threshold in CKD stages 4-5 to prompt evaluation, correction of modifiable factors and possibly treatment
In CKD stage 5D, suggest maintaining PTH level in the range of ~2-9 times the upper reference limit for the assay [4.2.3]	2C	In CKD stage 5D, PTH target range is 150-300 pg/mL [1.4]	E	No prescriptive PTH target range. Suggestion for wider target range, corresponding to PTH of ~130-600 pg/mL
Suggest that marked changes in PTH within this range prompt initiation or change in therapy [4.2.3]	2C			
		CKD Stages 1-5T		
In patients in the immediate post–kidney transplant period, recommend measuring serum calcium and phosphorus at least weekly until stable [5.1]	1B	During the first week after kidney transplant, serum phosphorus level should be measured daily [16.2]	O	
In patients after the immediate post–kidney transplant period, monitor serum calcium, phosphorus, PTH, and ALP levels. Reasonable to base frequencies on the presence and magnitude of abnormalities and rate of CKD progression [paraphrased from 5.2]	NG	Also recommendation for monitoring total CO_2 [16.1] No recommendation for ALP	O —	Suggestion for using ALP as an adjunct test
Suggest that 25(OH)D levels might be measured and repeated testing determined by baseline values and interventions [5.3]	2C	No recommendation	—	Suggestion for expanded testing of 25(OH)D
Reasonable to manage abnormalities of CKD-MBD as for patients with CKD stages 3-5 [5.2]	NG	Similar [16.5]	O	
Suggest that vitamin D deficiency and insufficiency be corrected [5.4]	2C	No recommendation	—	Suggestion for expanded treatment with vitamin D_2 or D_3

(Continued)

Table 4 (Cont'd). Comparison of Key KDIGO 2009 and KDOQI 2003 Recommendations on Testing and Treatment Targets

KDIGO	Grade	KDOQI	Grade	Comment
In patients with eGFR >30 mL/min/1.73 m² and treatment with corticosteroids or risk factors for osteoporosis, suggest measuring BMD in the first 3 mo after kidney transplant [5.5]	2D	Kidney transplant recipients should have BMD measured using DXA [16.4]	O	Suggestion for more restricted testing of BMD
In CKD stages 4-5T, suggest that BMD testing not be routinely performed [5.7]	2B			
In patients in first 12 mo after kidney transplant with eGFR >30 mL/min/1.73 m² and low BMD, suggest consideration of treatment with vitamin D, calcitriol/alfacalcidiol, or bisphosphonates	2D	If BMD T score is −2 or less at or after transplant, consider treatment with parenteral bisphosphonates [16.4b]	O	Expanded indication for bone biopsy including before treatment with bisphosphonates
Consider a bone biopsy, specifically before use of bisphosphonates [5.6]	NG	No recommendation	—	

Note: Recommendations may be paraphrased, abbreviated, or summarized from KDIGO CKD-MBD,[1] KDOQI bone,[8] and KDOQI nutrition in children[9] guidelines. For verbatim KDIGO recommendations, see text.

Abbreviations and definitions: 25(OH)D, 25-hydroxyvitamin D (calcidiol); ALP, alkaline phosphatase; BMD, bone mineral density; Ca × P, calcium-phosphate product; CKD, chronic kidney disease; CKD-MBD, chronic kidney disease–mineral and bone disorder; D, dialysis (when referring to CKD stage); DXA, dual-energy x-ray absorptiometry; E, graded as evidence in KDOQI guideline; eGFR, estimated glomerular filtration rate; KDIGO, Kidney Disease: Improving Global Outcomes; KDOQI, Kidney Disease Outcomes Quality Initiative; NG, statement not graded; O, graded as opinion in KDOQI guideline; P, pediatric (ie, guideline from KDOQI nutrition in children guideline[51]); PTH, parathyroid hormone.

for separately under Part B and any oral equivalent to such medications

- Laboratory tests and other items and services furnished to beneficiaries for the treatment of ESRD

Currently, this definition has been interpreted broadly by the CMS to include all medications given in the dialysis unit, as well as any laboratory test prescribed by a physician providing dialysis regardless of the site of service and even if not entirely related to ESRD care.

This proposal aims to reduce total Medicare payments for dialysis services by 2% both during the 4-year phase-in period and after the bundled payment system is fully implemented. Facilities will have the opportunity to opt out of the phase-in and be paid under the new bundled system starting in 2011.

Therefore, access to medications by patients receiving hemodialysis treatments in outpatient centers may change. Because Medicare Part D most likely will no longer cover medications now considered by the CMS to be a part of renal dialysis services, patients may no longer have access to the same medications they do now. Dialysis clinics would receive payment from Medicare for dialysis-related medications and be responsible for ensuring patients' access to the prescribed medications. Many clinics are not set up to dispense these medications that patients now receive through a pharmacy. Also, there is real concern that clinics could discourage physicians from prescribing certain brands of medications that are more costly, particularly if the CMS do not adequately reimburse for the cost of these drugs in the bundle. Additionally, it is unclear how the cost for new drugs would be factored.

With regard to the KDIGO CKD-MBD guideline, the additional medications that dialysis clinics would be paid for as part of the proposed bundled payment include phosphate binders, oral or intravenous vitamin D analogues, and calcimimetics. Additionally, laboratory tests including, for example, vitamin D or bone-specific alkaline phosphatase levels, would be included in the expanded bundle if ordered by a dialysis provider or sent from the dialysis unit. It is expected that the CMS will reimburse $14 per treatment on average above and beyond the current composite rate for the new items going into the bundle that were previously covered under Part D. With fixed bundle reimbursement, providers will have to trade off costs for different treatments, for

example, treatment with erythropoietin in one patient versus treatment with a calcimimetic in another, or treatment with calcium-based versus non–calcium-based phosphorus binders. Given the overall low quality of evidence for clinical benefit from treatments for CKD-MBD and the corresponding weak guideline recommendations, it is likely that the cost of a drug will directly impact on decision making and access to more expensive drugs will be restricted. More global inclusion of laboratory tests also has the potential to impact on the frequency of testing, as well as selection of tests related to MBD care.

Currently, the US nephrology community is responding to the proposed rule (eg, see editorials[12-16] in the February 2010 issue of the *American Journal of Kidney Diseases*). A final rule by the CMS is expected later in 2010. How practice patterns and outcomes related to CKD-MBD care may be influenced by the proposed changes in the payment system in the United States will require careful scrutiny by the CMS, providers, and researchers.

COMMENTARY ON KDIGO BONE GUIDELINE

Recommendations in Chapter 3.1: Diagnosis of CKD-MBD: Biochemical Abnormalities

3.1.1 We recommend monitoring serum levels of calcium, phosphorus, PTH, and alkaline phosphatase beginning in CKD stage 3 (1C). In children, we suggest such monitoring beginning in CKD stage 2 (2D).

In adults, changes in levels of biochemical markers of CKD-MBD may begin in CKD stage 3; however, the rate of change and severity of abnormalities are highly variable among patients. The strong recommendation indicates that assessment of CKD-MBD should begin in stage 3. In children, PTH level increases occur as early as CKD stage 2,[17] and the Work Group thus made a weak recommendation suggesting assessment of calcium, phosphorus, PTH, and alkaline phosphatase in children starting in CKD stage 2.

The rationale for this recommendation addresses the issue of whether calcium should be measured as total calcium, ionized calcium, or total calcium corrected for measured albumin. The work group did not recommend that corrected calcium measurement be abandoned at present, although recent data did not show supe-

riority over total calcium alone.[18] It considered measurement of ionized calcium to be more specific, but presently not practical or cost-effective. These recommendations are applicable to the United States.

3.1.2 In patients with CKD stages 3-5D, it is reasonable to base the frequency of monitoring serum calcium, phosphorus, and PTH on the presence and magnitude of abnormalities and rate of progression of CKD (not graded).
Reasonable monitoring intervals would be:
- In CKD stage 3: For serum calcium and phosphorus, every 6-12 months; and for PTH, based on baseline level and CKD progression
- In CKD stage 4: For serum calcium and phosphorus, every 3-6 months; and for PTH, every 6-12 months
- In CKD stage 5, including 5D: For serum calcium and phosphorus, every 1-3 months; and for PTH, every 3-6 months
- In CKD stages 4-5D: For alkaline phosphatase activity, every 12 months or more frequently in the presence of increased PTH levels (see chapter 3.2)

These statements provide guidance for testing intervals. The frequency of repeated testing needs to take into account whether and what abnormalities were identified, their severity and duration, and level of kidney function and rate of kidney disease progression. The KDIGO Work Group recommends using total alkaline phosphatase activity as an adjunct test. It may provide supplemental information in the assessment of bone turnover, particularly in the setting of increased PTH levels and in the assessment of response to therapy for increased PTH levels if liver disease is not likely to be the cause of increased total alkaline phosphatase levels.[19,20] Bone-specific alkaline phosphatase derives more specifically from bone and can be used when the clinical situation is more ambiguous; however, the test is not readily available. High total alkaline phosphatase levels have been associated with higher mortality,[21-23] but it is not known whether therapies aimed at decreasing these levels improve patient outcomes. The KDOQI bone guideline also discussed that concomitant consideration of alkaline phosphatase levels can increase the predictive power of PTH levels,[24,25] although data were insufficient to determine the sensitivity and specificity of alkaline phosphatase levels for renal osteodystrophy alone or together with PTH levels.[8] The value of alkaline phosphatase for clinical decision making remains to be proved,

especially in the present era with different PTH assays and a lower prevalence of osteomalacia. These statements are applicable to the United States. The practitioner can individualize as needed.

3.1.2 (continued)	In patients with CKD 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).

There are no data to directly support a specific testing frequency. This statement provides the necessary flexibility for more frequent measurement when levels are changing rapidly and to monitor the effects of treatments, including potential adverse effects. This statement is applicable to the United States.

3.1.3	In patients with CKD stages 3-5D, we suggest that calcidiol (25[OH]D) might be measured, with 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).

The serum vitamin D level that represents "sufficiency" is the subject of an ongoing debate and is complicated by variability in measurements of vitamin D compounds.[26-28] Substrate vitamin D deficiency has been variably defined as 25(OH)D level <10-20 ng/mL, and insufficiency has been variably defined as 25(OH)D level higher than the limits for deficiency but <32-35 ng/mL.[29,30] There are no data about whether vitamin D levels should vary between those with or without CKD. In patients with CKD, vitamin D deficiency or insufficiency may be a cause of increased PTH levels. Observational studies show an association between low vitamin D levels and adverse clinical outcomes,[24,30-33] and link treatment with vitamin D or its analogues to improvements in surrogate or clinical outcomes.[23,34-37] However, data from clinical trials with vitamin D for important clinical outcomes are lacking at this time. The potential risks of vitamin D repletion are minimal; therefore, although the benefits of this have not been proved, the work group believed that measurement and treatment of deficiency might be beneficial, making weak recommendations for measuring vitamin D and correcting deficiency

and insufficiency. This represents a change from the KDOQI guidelines, in which the recommendation to measure 25(OH)D was limited to patients with CKD stages 3-4 and elevated PTH level.

These recommendations are applicable to the United States. Ultimately, the practitioner in the United States needs to individualize the decision for whether, when, and how often to measure vitamin D and below what threshold and to what target range to treat. A reasonable approach is to periodically measure 25-hydroxyvitamin D in patients with CKD and initiate treatment if the level is low. Recommendations for vitamin D repletion in the general population specify a cholecalciferol dose of 1,000-2,000 IU/d because lower doses minimally impact on 25-hydroxyvitamin D level.[38-40] However, a more aggressive dosing regimen may be used in patients with CKD. The KDOQI bone guideline provided a recommendation for supplementation in patients with CKD stages 3-4 with ergocalciferol, 50,000 IU, orally dosed weekly or monthly based on serum 25-hydroxyvitamin D level.[8] This has not been tested in patients with CKD stage 5, 5D, or T. Monitoring calcium, phosphorus, vitamin D, and PTH levels can guide subsequent dose adjustments.

3.1.4	In patients with CKD stages 3-5D, we recommend that therapeutic decisions be based on trends, rather than a single laboratory value, taking into account all available CKD-MBD assessments (1C).

This statement recommends assessing all parameters of CKD-MBD together and each parameter over time, rather than one value in isolation. Thus, the practitioner needs to review patterns and temporal trends to make clinical decisions. Furthermore, the practitioner needs to know what assays are used. PTH and phosphorus levels are subject to diurnal variation and vitamin D levels are subject to seasonal variation. Testing for PTH and phosphorus should be performed at similar times during the day and week. To eliminate between-assay variability, the same assay should be used for monitoring changes over time. This recommendation is applicable to the United States. This recommendation has significant implications for dialysis provider performance measures that typically focus on laboratory values at

a single point in time and do not consider trends over time.

> 3.1.5 In patients with CKD stages 3-5D, we suggest that individual values of serum calcium and phosphorus, evaluated together, be used to guide clinical practices rather than the mathematical construct of calcium-phosphorus product (2D).

Despite epidemiologic data linking increased calcium-phosphorus product with poorer patient outcomes,[41,42] the work group suggests using the individual components rather than the mathematical construct of calcium-phosphorus product, which is driven largely by serum phosphorus. The product generally does not provide additional clinical information beyond that provided by its components.[43-45] Thus, the KDIGO Work Group advised against relying on the product in clinical decision making. This recommendation is applicable to the United States.

> 3.1.6 In reports of laboratory tests for patients with CKD stages 3-5D, 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 appropriate interpretation of biochemistry data (1B).

This recommendation is addressed to clinical pathologists performing the measurement of the laboratory components of CKD-MBD. Given the variability within and across assays, especially for PTH and vitamin D compounds, clinical laboratories should assist clinicians in interpretation of test results by reporting assay characteristics and methods used. Clinicians need to standardize within their outpatient clinical practices and dialysis units the methods of sample collection, processing, and assays used.

Analytic problems with PTH measurement include: (1) poor standardization among different PTH assays, (2) high biological variation within individuals, and (3) uncertainty about the role of unmeasured PTH fragments.[27,46] The widely used second-generation "intact" PTH (iPTH) assays measure not only full-length active PTH, but also different types and amounts of circulating fragments.[47-49] Despite these limitations, the work group favored the continued use of second-generation iPTH assays in clinical practice rather than the more recently introduced "bioactive" or "biointact" third-generation PTH assays, which have not yet been shown to have

better test performance. To assist interpretation of values obtained using different PTH assays, the reader is referred to the article by Souberbielle et al,[46] which suggests conversion factors for many currently used PTH assays using the Allegro iPTH assay as a reference. Although this provides a practical tool to reduce some of the interassay discrepancies in the absence of a true reference standard, it has not been externally validated and does not overcome the problem of variable assay reactivity with PTH fragments.

For measurement of 25-hydroxyvitamin D, immunoassays have reasonably good precision and many clinical laboratories now routinely measure 25-hydroxyvitamin D using liquid chromatography-mass spectroscopy, which has excellent precision.[26-28,50] This recommendation is applicable to the United States. Readers are referred to Section 3.1.6 of the KDIGO guidelines for discussion of issues related to measurement of calcium, phosphorus, PTH, vitamin D, and alkaline phosphatase.

Recommendations in Chapter 3.2: Diagnosis of CKD-MBD: Bone

> 3.2.1 In patients with CKD stages 3-5D, 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 before therapy with bisphosphonates in patients with CKD-MBD (not graded).

Renal osteodystrophy is a complex disorder. Biochemical laboratory and imaging tests do not adequately predict the underlying bone histology. Thus, although bone biopsy is invasive and cannot be performed easily in all patients, it is the gold standard for the diagnosis of renal osteodystrophy. Bone biopsy should be considered in patients for whom the cause of clinical symptoms and biochemical abnormalities is not certain and for whom the effect of treatment on bone needs to be assessed. As detailed in the KDOQI bone and mineral guidelines, aluminum bone disease also requires bone biopsy for diagnosis. However, this is less common in the current era. The KDIGO position statement suggested that tissue from bone biopsies in patients with CKD should be characterized by determin-

ing bone turnover, mineralization, and volume (TMV).[3]

The statement that bone biopsy is reasonable before initiating treatment with bisphosphonates applies to only those with evidence of CKD-MBD. Although there is a large number of elderly with CKD stage 3 and low BMD in the United States, this statement applies to only those who also have CKD-MBD, which in practical terms means increased PTH or phosphate level. Bone biopsy is the most accurate test for the diagnosis of adynamic bone disease, and the presence of adynamic bone disease is a contraindication to bisphosphonate treatment.

The preferred site for a bone biopsy is the iliac crest, and the biopsy is undertaken with a trocar or a drill. Assessment of turnover requires double labeling with tetracycline according to a protocol, and reading of the biopsy specimen requires particular expertise and resource. The procedural risk is low; however, discomfort and pain at the biopsy site are common. Although biopsy is the gold standard test for renal osteodystrophy, the natural history of renal bone disease shows great variability and different types of osteodystrophy have at best only modest relationships with clinical outcomes. Future studies need to evaluate the merit of the TMV classification for informing clinical treatment decisions and ultimately improving bone and other clinical outcomes.

In the United States, bone biopsies currently are not widely undertaken for the evaluation of renal osteodystrophy. In some centers, this service is provided by a specialist in bone health, such as an endocrinologist or nephrologist. Wide implementation of this statement would require a greater pool of individuals with proficiency in the performance and interpretation of bone biopsies. In addition to addressing the barriers to getting a bone biopsy, future research is needed to evaluate the usefulness of bone biopsy results for the selection of therapies. Regarding the use of bisphosphonates in patients with CKD stage 3 with CKD-MBD, see the commentary on recommendation 4.3.3.

3.2.2   In patients with CKD stages 3-5D 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 popula-

tion, and BMD does not predict the type of renal osteodystrophy (2B).

In the general population, low BMD measured using dual-energy x-ray absorptiometry (DXA) predicts fracture and mortality; however, evidence for its ability to predict fractures or other clinical outcomes in patients with CKD stages 4-5 is limited.[51] In patients with CKD stage 5D, evidence linking low BMD and fracture risk is weak, inconsistent, and varies by site.[52] Volumetric BMD, measured predominantly using quantitative computed tomography (CT), correlated with fractures in 1 small study of hemodialysis patients.[53] Also, determination of BMD, whether measured using DXA or quantitative CT, does not distinguish among types of renal osteodystrophy. Patients with CKD-MBD and osteoporosis cannot be assumed to benefit from therapies such as bisphosphonates. Thus, the work group issued this suggestion against routine BMD testing in individuals with laboratory evidence of CKD-MBD, ie, individuals with CKD and increased phosphorus or PTH levels. This recommendation is applicable to the United States.

3.2.3   In patients with CKD stages 3-5D, we suggest that serum PTH or bone-specific alkaline phosphatase measurement can be used to evaluate bone disease because markedly high or low values predict underlying bone turnover (2B).

Circulating PTH or bone-specific alkaline phosphatase levels correlate with some histomorphometric measurements in bone biopsy specimens. However, the positive predictive value for both tests is only modest for detection of high and low bone turnover states, especially for detecting adynamic bone.[19,20,54-56] Nevertheless, because bone biopsy is not feasible in most patients, the work group issued a weak recommendation suggesting measurement of these serum markers because they may be useful to estimate bone turnover, especially when values are very abnormal. This recommendation is applicable to the United States.

3.2.4   In patients with CKD stages 3-5D, we suggest not to routinely measure bone-derived turnover markers of collagen synthesis (such as procollagen type I C-terminal pro-peptide) and breakdown (such as type I collagen cross-linked telopeptide, crosslaps, pyridinoline, or deoxypyridinoline) (2C).

The markers mentioned in this recommendation do not predict clinical outcomes or bone histologic states any better than do circulating PTH or bone-specific alkaline phosphatase levels. Therefore, the work group issued a weak recommendation against their routine measurement. Although they currently are not sufficiently validated to be recommended for wide use, some of these markers appear promising for monitoring the treatment of osteoporosis in patients with earlier stages of CKD. This recommendation is applicable to the United States.

> 3.2.5 We recommend that infants with CKD stages 2-5D have length measured at least quarterly, whereas children with CKD stages 2-5D should be assessed for linear growth at least annually (1B).

Children with CKD stages 2-5D commonly have defects in linear growth. The text accompanying this KDIGO recommendation provides additional age-specific monitoring intervals, which are at least monthly in infants (ie, children aged <1 year), at least quarterly in children younger than 2 years, and at least annually in older children and adolescents. Linear height should be plotted accurately on the appropriate growth chart for either height, velocity, or ideally both. These intervals and age groups are not entirely consistent with those provided in the KDOQI guideline on nutrition in children with CKD.[9] The latter KDOQI guideline recommends more frequent monitoring, as often as monthly in infants with CKD stage 5D and every 6 months in older children. However, taken together, the KDIGO and KDOQI recommendations emphasize that growth is a sensitive indicator of bone health in children. Children with CKD therefore require more frequent monitoring than healthy children. Beyond the minimum frequency recommended, frequency needs to be individualized based on the degree of abnormal height and velocity observed. Delays in growth should prompt evaluation for causes of growth failure. This recommendation is applicable in the United States.

Recommendations in Chapter 3.3: Diagnosis of CKD-MBD: Vascular Calcification

> 3.3.1 In patients with CKD stages 3-5D, 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 calcifica-

tion as reasonable alternatives to CT-based imaging (2C).

Extraosseous calcification is one of the components of CKD-MBD (Box 1). The prevalence and severity of extraosseous calcification, including calcification of arteries and cardiac valves, increase as kidney function decreases. Calcification is more severe and follows an accelerated course in people with CKD compared with healthy people.[57,58] CT-based tests, such as electron beam (EBCT) or multislice CT (MSCT), can measure coronary artery and valvular calcifications, but other more widely available tests also can measure calcifications in other vessels, for example, lateral abdominal x-ray and echocardiography (valvular calcification). In the general population, the magnitude of coronary artery calcification imaged using either EBCT or MSCT is a strong predictor of cardiovascular event risk. In patients with CKD, the presence and severity of cardiovascular calcification also predict cardiovascular morbidity and mortality.[58]

Ongoing investigation centers on the question whether calcification in patients with CKD is located in the intima and thus is similar to that found in non-CKD patients, for whom it correlates with calcified atherosclerotic plaque, or in the media as an expression of arteriosclerosis, which possibly is related to CKD-MBD. In addition to the uncertainty regarding the pathologic correlate of calcification in patients with CKD, it has not been shown that measurement of calcifications using any technique has clinical utility for stratification into distinct risk groups, which then might derive benefit from modification of their treatment. Thus, most of the work group believed that indiscriminate screening for calcification in patients with CKD-MBD could not be recommended.[59] This weak recommendation indicates the work group's suggestion that if a practitioner still wants to test for calcification in a patient with CKD, lateral abdominal radiography and echocardiography can be used as alternatives to the more costly CT-based imaging.

In the United States, screening of asymptomatic patients with CKD for calcification is not recommended. The clinical utility of testing specific patients for calcification also is not clear. If a practitioner still wants to perform untargeted testing for calcification, using lateral abdominal

radiography and echocardiography provides as much or as little useful information as the more costly tests using EBCT or MSCT.

> 3.3.2 We suggest that patients with CKD stages 3-5D with known vascular/valvular calcification be considered at highest cardiovascular risk (2A). It is reasonable to use this information to guide management of CKD-MBD (not graded).

The work group made a discretionary recommendation that a patient who is known to have vascular or valvular calcification might be considered to be at highest cardiovascular risk and an ungraded statement about incorporation of information about calcification into the selection of CKD-MBD treatments. This recommendation rests on epidemiologic data showing higher mortality in those with some or more severe calcification (see online Supplementary Tables 12 and 13 for chapter 3.3 of the KDIGO guideline). However, as discussed, how information about calcification improves the precision of predicting relative or absolute risk in an individual patient is unclear. Furthermore, it has not been shown that modification of treatment strategies based on calcification tests can achieve better patient outcomes. Recommendation 4.1.5 provides a discretionary recommendation suggesting that the amount of calcium-based phosphate binders might be restricted in the presence of arterial calcification. The rationale for this is discussed under recommendation 4.1.5. The work group found no prospective clinical studies addressing the effects of vitamin D, vitamin D analogues, and calcimimetics on vascular calcification.

Recommendations in Chapter 4.1: Treatment of CKD-MBD Targeted at Lowering High Serum Phosphorus and Maintaining Serum Calcium

> 4.1.1 In patients with CKD stages 3-5, we suggest maintaining serum phosphorus levels in the reference range (2C). In patients with CKD stage 5D, we suggest decreasing increased phosphorus levels toward the reference range (2C).

Many patients with CKD stages 4-5D have high serum phosphorus levels. Observational data for patients with CKD stage 5D show an association of higher serum phosphorous levels with mortality and cardiovascular events.[41,60] In dialysis patients, the positive relationship of hyperphosphatemia with mortality is robust, but the threshold above which risk is increased varies across studies and ranges from 5.0 to 7.0 mg/dL.[23,42,45,60-62] In patients with CKD stages 3-5, the risk relationship between phosphorus level and poor outcome is not found consistently; however, in some studies, high-normal levels are associated with increased risk, as also seen in individuals without CKD.[63,64]

Laboratory experimental data show that hyperphosphatemia may directly cause or exacerbate other aspects of CKD-MBD, including secondary hyperparathyroidism (HPT), decreased serum calcitriol levels, abnormal bone remodeling, and soft-tissue calcification. However, it has not been examined in placebo-controlled RCTs whether treating hyperphosphatemia to specific treatment goals improves clinical outcomes of patients with CKD. Thus, the work group made a discretionary recommendation for treating hyperphosphatemia, acknowledging that despite the robust risk relationships, observational data do not prove a causal relationship and laboratory experimental data may not be directly applicable to patients. For CKD stages 3-5, the work group issued a discretionary recommendation suggesting to maintain phosphorus levels in the reference range, and for CKD stage 5D, it issued a discretionary recommendation suggesting to decrease phosphorus levels toward the reference range.

Treatments for patients with hyperphosphatemia include phosphate binders, limiting dietary phosphate intake, and/or increasing the frequency or duration of dialysis. Use of phosphate-restricted diets in combination with oral phosphate binders has become well established in the management of patients with CKD stages 3-5 and 5D. However, use of phosphate binders is associated with side effects, most commonly of gastrointestinal origin. In dialysis patients, phosphate binders make up 50% of the high pill burden.[65] Thus, in some patients, treatment to achieve a serum phosphorus level within the reference range may not be possible, the number of pills necessary may be too large, or the degree of dietary restriction may impact on quality of life. Furthermore, in many patients, mobilization of phosphorus from the skeleton (or perhaps other tissues) may contribute to hyperphosphatemia, and this cannot be treated using dietary phosphate binders. This discretionary recommendation allows clinicians to discuss the

potential benefits and harms of drug therapy with their patients and individualize decision making based on differing clinical circumstances and patient preferences.

This recommendation is applicable to the United States.

> 4.1.2 In patients with CKD stages 3-5D, we suggest maintaining serum calcium levels in the reference range (2D).

The threshold above which calcium level becomes significantly associated with increased relative risk for all-cause mortality varies among studies from 9.5 to 11.4 mg/dL.[23,45,60-62] It is unclear at what level of low serum calcium the risk increases. It also is unknown whether treatment-related hypocalcemia, for example, from calcimimetics, confers a risk similar to that with identical calcium levels that is not related to treatment with this class of drugs. This weak recommendation suggests using the laboratory reference range as the treatment target. A calcium level outside the reference range requires evaluation for treatment effects or other causes. This recommendation is applicable to the United States.

> 4.1.3 In patients with CKD stage 5D, we suggest using a dialysate calcium concentration of 1.25-1.50 mmol/L (2.5-3.0 mEq/L) (2D).

Studies that have measured calcium in spent dialysate to determine net calcium flux with hemodialysis have found near-neutral calcium flux in patients with a dialysate calcium concentration of 2.5 mEq/L, although there was variability among patients.[66-68] Although maintenance of neutral calcium balance probably is desirable in most adult dialysis patients (with slightly negative calcium balance perhaps being preferable in patients with extensive vascular calcification), overall calcium balance is influenced by diet, vitamin D level, use of vitamin D or its analogues, dialysate calcium concentration, and other factors. It is not possible to assess overall calcium balance in routine clinical care. It also generally is not feasible or likely to be safe to use widely varying and individualized dialysate calcium concentrations within a dialysis unit. The weak recommendation based on a majority vote of the work group suggests calcium dialysate concentration of 2.5-3.0 mEq/L (1.25-1.50 mmol/L) for both hemodialysis and peritoneal

dialysis patients. Others have argued that in many patients, hemodialysate calcium concentration may need to be lower to achieve a neutral calcium mass balance.[69] A higher dialysate calcium concentration may be needed in patients on nocturnal hemodialysis therapy.[70,71] The rationale accompanying the KDIGO recommendation emphasizes the need to individualize dialysate calcium concentration for both hemodialysis and peritoneal dialysis patients. Thus, the US practitioner needs to use judgment.

Selecting dialysate calcium concentration requires consideration of the patient's calcium levels and other laboratory components of CKD-MBD; concomitant therapies with phosphate binders, calcitriol, vitamin D analogues, or calcimimetics; and treatment goals. However, in the absence of robust clinical data regarding the optimal dialysate calcium concentration, the practitioner in the outpatient dialysis setting also needs to weigh safety concerns in prescribing individualized dialysate calcium concentrations.

> 4.1.4 In patients with CKD stages 3-5 (2D) and 5D (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).

These weak recommendations suggest using phosphate binders for the treatment of hyperphosphatemia in patients with CKD. The recommendations are weak because there are no placebo-controlled randomized trials that show that decreasing hyperphosphatemia with a phosphate binder decreases patient mortality or morbidity. Phosphate binders are effective in decreasing phosphorus levels. A body of RCT evidence focuses on the comparative effectiveness of non–calcium-containing phosphate binders versus calcium-containing binders.[72] There is no proven superiority of any one drug or class for clinical outcomes. Commonly used phosphate binders and their potential advantages and disadvantages are listed in Table 5, which is reproduced from the KDIGO guideline.[1]

In children with CKD, calcium-based phosphate binders have been effective for decreasing phosphate levels.[79] Evidence comparing newer non–calcium-containing binders with calcium-

Table 5. Phosphate-Binding Compounds

Binder Source	Rx	Forms	Content (mineral/metal/element)	Potential Advantages	Potential Disadvantages
Aluminum hydroxide	No	Liquid, tablet, capsule	Aluminum content varies from 100 to >200 mg/tablet	Very effective phosphate-binding capacity; variety of forms	Potential for aluminum toxicity; altered bone mineralization, dementia; GI side effects
Calcium acetate	Yes/No	Capsule, tablet	Contains 25% elemental Ca^{2+} (169 mg elemental Ca^{2+} per 667-mg capsule)	Effective phosphate binding, potential for enhanced phosphate-binding capability over $CaCO_3$, potentially less calcium absorption	Potential for hypercalcemia-associated risks, including extraskeletal calcification and PTH suppression; more costly than $CaCO_3$; GI side effects
Calcium carbonate	No	Liquid, tablet, chewable, capsule, gum	Contains 40% elemental Ca^{2+} (200 mg elemental Ca^{2+} per 500 mg $CaCO_3$)	Effective, inexpensive, readily available	Potential for hypercalcemia-associated risks, including extraskeletal calcification and PTH suppression; GI side effects
Calcium citrate	No	Tablet, liquid, capsule	Contains 22% elemental Ca^{2+}	Not recommended in CKD	Enhancement of aluminum absorption; GI side effects
Calcium ketoglutarate	—	—	—	—	Similar to other calcium salts, costly, GI side effects, potentially less hypercalcemic than calcium carbonate or acetate, not well studied
Calcium gluconate	—	Tablet, powder	—	—	Similar to other calcium salts, not well studied
Ferric citrate	—	—	—	—	GI side effects, not well studied
Magnesium/calcium carbonate	No	Tablet	~28% elemental Mg^{2+} (85 mg) per total $MgCO_3$ and 25% elemental Ca^{2+} (100 mg) per total $CaCO_3$	Effective; potential for lower calcium load than pure calcium-based binders	GI side effects, potential for hypermagnesemia, not well studied
Magnesium carbonate/calcium acetate	Yes	Tablet	—	—	Lack of availability worldwide; assumed to have similar effects of its components
Sevelamer-HCl	Yes	Caplet	None	Effective; no calcium/metal; not absorbed; potential for reduced coronary/aortic calcification compared with calcium-based binders in some studies; reduces plasma concentration of LDL-C	Cost; potential for decreased bicarbonate levels; may require calcium supplement in presence of hypocalcemia; GI side effects
Sevelamer carbonate	Yes	Caplet, powder	None	Effective; no calcium/metal; not absorbed; assumed to have similar advantages as sevelamer HCl; potentially improved acid-base balance	Cost; may require calcium supplement in presence of hypocalcemia; GI side effects
Lanthanum carbonate	Yes	Wafer, chewable	Contains 250, 500, or 1,000 mg elemental lanthanum per wafer	Effective; no calcium; chewable	Cost, potential for accumulation of lanthanum due to GI absorption, although long-term clinical consequences unknown; GI side effects

Abbreviations: $CaCO_3$, calcium carbonate; CKD, chronic kidney disease; CKD-MBD, chronic kidney disease–mineral and bone disease; GI, gastrointestinal; KDIGO, Kidney Disease: Improving Global Outcomes; LDL-C, low-density lipoprotein cholesterol; PTH, parathyroid hormone; Rx, prescription.
Reproduced from the KDIGO CKD-MBD guideline[1] with permission of Nature Publishing Group.

containing binders is limited and insufficient to support specific recommendations.

This recommendation is applicable to the United States. It allows practitioners to initiate phosphate-binder treatment based on their and their patients' judgments for phosphorus targets. It also provides flexibility to choose a binder based on its profile of effects and side effects and allows combining binders to minimize side effects from high doses of one agent.

> 4.1.5 In patients with CKD stages 3-5D and hyperphosphatemia, we recommend restricting the dose of calcium-based phosphate binder and/or the dose of calcitriol or vitamin D analogue in the presence of persistent or recurrent hypercalcemia (1B).
> In patients with CKD stages 3-5D 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).

Hypercalcemia is a recognized side effect of calcium-containing phosphate binders and vitamin D analogues. Severe or persistent hypercalcemia necessitates the reduction or cessation of either or both drugs. A weak recommendation suggests exercising restraint in prescribing high doses of calcium-based phosphorus binders in the presence of arterial calcification. In aggregate, studies comparing calcium carbonate or calcium acetate against the non–calcium-based binder sevelamer are inconclusive in showing superiority for clinical outcomes.[72] However, some studies showed less progression of calcification in sevelamer-treated patients, although this effect was inconsistent across studies.[72] Trials of lanthanum versus calcium-containing binders have not examined clinical outcomes.

A dose reduction of calcium-based phosphate binders also is suggested in the presence of adynamic bone disease or suppressed PTH level. Data from trials comparing noncalcium binders with calcium-based binders are inconclusive regarding effects on bone histologic states, and clinical bone fracture has not been examined as an outcome.

Any discretionary recommendation depends on the work group's judgments to a large degree and the suggested course of action allows individualization of therapy. Following these suggestions is discretionary for the US practitioner. The

recommendations do not provide a specific amount for the upper limit of a safe amount of calcium intake because there are no trial data to support one. The KDOQI guidelines provided an opinion-based suggestion to limit daily calcium intake from phosphate binders to 1,500 mg/d for elemental calcium and 2,000 mg/d for total intake of elemental calcium including dietary calcium regardless of the presence of calcification.[8] Higher calcium intake may be considered when serum calcium level is low or PTH level is high. However, dialysate calcium and administration of vitamin D analogues also may contribute to a net positive calcium balance.

> 4.1.6 In patients with CKD stages 3-5D, we recommend avoiding long-term use of aluminum-containing phosphate binders, and in patients with CKD stage 5, avoiding dialysate aluminum contamination to prevent aluminum intoxication (1C).

This recommendation reflects the opinion of the work group that because numerous alternative phosphate binders are available and there is no ability to predict a safe aluminum dose, long-term use of aluminum-based phosphate binders should be avoided. This recommendation is applicable to the United States and reflects current practice in the United States. Short-term treatment with aluminum-containing phosphate binders may be used when clinically appropriate.

> 4.1.7 In patients with CKD stages 3-5D, we suggest limiting dietary phosphate intake in the treatment of hyperphosphatemia alone or in combination with other treatments (2D).

Data are insufficient to strongly endorse dietary phosphate restriction as the primary intervention for the management of CKD-MBD. However, dietary phosphorus restriction may help keep phosphorus levels normal in patients with CKD stages 3-5 and serve as an adjunct to phosphate binders and dialytic phosphorus removal in dialysis patients. This requires attention to maintaining adequate protein intake. In the United States, a significant portion of phosphorus intake may derive from phosphate salts used as additives and preservatives, especially in processed and fast foods.[73-75] Thus, dietary counseling to avoid food with high phosphorus content while ensuring adequate protein intake may help with management of increased serum phosphorus concentrations, particularly in long-term di-

alysis patients. In the United States, most practitioners will rely on dialysis unit dieticians to counsel patients regarding dietary phosphorus and protein intake. In other settings for patients with CKD not on dialysis therapy, such dietary counseling often is more difficult to obtain.

> 4.1.8 In patients with CKD stage 5D, we suggest increasing dialytic phosphate removal in the treatment of persistent hyperphosphatemia (2C).

How modification of dialysis prescription can improve phosphorus removal is an area of interest. Despite the absence of evidence supporting specific phosphorus target levels in patients on dialysis therapy, better dialytic control of serum phosphorus levels has the potential to reduce the need for phosphate binders and allow more liberal dietary phosphorus intake. One study comparing nocturnal prolonged-duration hemodialysis 6 times weekly with standard thrice-weekly hemodialysis found lower phosphorus levels and a lower amount of required oral phosphate binder.[76]

Control of hyperphosphatemia may be factored in as a treatment goal when choosing a modality or prescription for a hemodialysis patient. However, thrice-weekly hemodialysis, typically 3.5-4 hours per session in a dialysis center, is the most common prescription in the United States, and any deviation from this delivery model encounters logistic, administrative, and financial challenges. Because dialysis dose and intensity affect not only serum phosphate levels, it will require studies of clinical outcomes comparing conventional with more extended or more frequent dialysis to support the need for changing the status quo. There is no evidence that there are clinically meaningful differences in phosphorus removal among different dialysis membranes or dialyzers in current routine use that would enable increasing phosphorus removal.

Recommendations in Chapter 4.2: Treatment of Abnormal PTH Levels in CKD-MBD

> 4.2.1 In patients with CKD stages 3-5 not on dialysis therapy, the optimal PTH level is not known. However, we suggest that patients with iPTH levels higher than the upper reference limit of the assay first are evaluated for hyperphosphatemia, hypocalcemia, and vitamin D deficiency (2C).
> It is reasonable to correct these abnormalities with any or all of the following: decreasing dietary phosphate intake and administering phosphate binders, calcium supplements, and/or native vitamin D (not graded).

As the recommendation states, the optimal PTH level for patients with CKD stages 3-5 who are not on dialysis therapy is not known. The recommendation suggests evaluating those with PTH levels higher than the upper limit of the reference range for potentially modifiable factors, such as hyperphosphatemia, hypocalcemia, and vitamin D deficiency, that may have led to secondary HPT. Treatment of these factors may decrease PTH levels into the reference range or prevent further increase. The suggested course of action is discretionary for US practitioners.

> 4.2.2 In patients with CKD stages 3-5 not on dialysis therapy in whom serum PTH levels are progressively increasing and remain persistently higher than the upper reference limit for the assay despite correction of modifiable factors, we suggest treatment with calcitriol or vitamin D analogues (2C).

If PTH levels progressively increase and remain higher than the reference range, treatment with calcitriol or vitamin D analogues is suggested. In the absence of placebo-controlled trials showing clinical benefit from treatment of HPT, this weak recommendation is based on the decrease in PTH levels in response to active vitamin D compounds.[77] The suggested course of action is discretionary for US practitioners. Caution should be exercised to avoid hypercalcemia and increases in serum phosphorus levels. The work group did not recommend use of calcimimetics in patients with stages 3-5 CKD because of insufficient data for efficacy and safety.

> 4.2.3 In patients with CKD stage 5D, we suggest maintaining iPTH levels in the range of approximately 2-9 times the upper reference 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).

The suggested PTH level range for patients with CKD stage 5D is not supported by high-quality evidence. It takes into account wide inter-assay variability of values obtained with many of the commercial iPTH assays in use, likely because of variable reactivity with accumulating PTH fragments. Thus, it is important to know the

characteristics of the particular iPTH assay in use. See also discussion of recommendation 3.1.6. The KDOQI guidelines suggested a PTH level range of 150-300 pg/mL for patients with CKD stage 5D using a Nichols iPTH assay that is no longer available; iPTH levels within this range also are not uniformly predictive of bone histologic states, especially when considered alone. The point above which PTH level becomes significantly associated with increased all-cause mortality varies among studies from 400 to 600 pg/mL. The PTH level range suggested in the KDIGO guideline corresponds to approximately 130-600 pg/mL, taking into account the different iPTH assays in use commercially.[48] To date, no RCT has examined whether treatment to achieve a specific PTH target improves clinical outcomes.

It is important to recognize that treatments aimed at affecting PTH levels also invariably influence calcium and phosphorus levels and levels of other hormones, making it difficult to assess the therapeutic benefit of interventions based on PTH level changes. The recommendation suggests that marked changes in PTH levels within this PTH range should trigger a response to avoid a future level outside the range. This recommendation gives flexibility to US practitioners in using and adjusting treatments that are effective in decreasing PTH levels despite lack of proof for clinical benefit from a specific PTH range.

4.2.4 In patients with CKD stage 5D and increased or increasing PTH levels, we suggest that calcitriol, vitamin D analogues, calcimimetics, or a combination of calcimimetics and calcitriol or vitamin D analogues be used to decrease PTH levels (2B).

- It is reasonable that the initial drug selection for the treatment of increased PTH level be based on serum calcium and phosphorus levels and other aspects of CKD-MBD (not graded).
- It is reasonable that calcium- or non–calcium-based phosphate binder dosage be adjusted so that treatments to control PTH levels do not compromise phosphorus and calcium levels (not graded).
- We recommend that in patients with hypercalcemia, calcitriol or other vitamin D sterol be reduced or stopped (1B).
- We suggest that in patients with hyperphosphatemia, calcitriol or other 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 iPTH levels decrease to less than 2 times the upper reference limit for the assay, calcitriol, vitamin D analogues, and/or calcimimetics be reduced or stopped (2C).

These medical treatments are effective for decreasing PTH levels. Selection of an agent needs to consider the trends of calcium and phosphorus levels along with those of PTH, their degree of abnormality, and concomitant therapy with phosphorus binders. If serum calcium level is low, vitamin D sterols can be the mainstay. If serum calcium level is increased, a calcimimetic can be used. There are no data supporting the clinical superiority of any vitamin D analogues available in the United States compared with calcitriol or placebo.[77]

In children with CKD stages 3-5D, trial data were limited to comparisons of calcitriol with placebo, calcitriol in different frequency or through a different route, and paricalcitol with placebo. The evidence was insufficient to make specific recommendations in children. There were no studies evaluating calcimimetics in children. These recommendations are applicable in the United States.

4.2.5 In patients with CKD stages 3-5D with severe HPT who fail to respond to medical/pharmacologic therapy, we suggest parathyroidectomy (2B).

The number of parathyroidectomies in the United States has decreased in the past 10-15 years given the effectiveness of drugs for medical treatment of HPT and lack of evidence showing clear superiority of parathyroidectomy on meaningful clinical outcomes. However, severe HPT may be resistant to medical therapy. Subtotal or total parathyroidectomy with autotransplant performed by an expert surgeon effectively decreases PTH, calcium, and phosphorus levels. There is a lack of RCTs directly comparing medical with surgical therapy for HPT. Nevertheless, it should be remembered that surgical treatment is an option in patients with acceptable surgical risk in whom medical therapy has failed either because of lack of response of PTH or side effects from medical therapy. This recommendation is applicable to the United States.

Recommendations in Chapter 4.3: Treatment of Bone With Bisphosphonates, Other Osteoporosis Medications, and Growth Hormone

> 4.3.1 In patients with CKD stages 1-2 with osteoporosis and/or high risk of fracture, identified using World Health Organization (WHO) criteria, we recommend management as for the general population (1A).

Because CKD-MBD usually is not present in patients with CKD stages 1-2, these individuals should be treated for osteoporosis or high fracture risk as the general population. The narrative for this recommendation contains a link to a web-based tool (FRAX; www.shef.ac.uk/FRAX/index.htm), which provides a calculator to determine risk of fracture within the subsequent decade based on race/ethnicity. Given the high prevalence of early stages of CKD in elderly patients who are likely to have osteoporosis, this recommendation calls attention to the need to evaluate fracture risk in this population and treat accordingly. This recommendation is applicable in the United States.

> 4.3.2 In patients with CKD stage 3 with PTH levels in the reference range and osteoporosis and/or high risk of fracture identified using WHO criteria, we suggest treatment as for the general population (2B).

Although there are no trials of antiosteoporosis therapies specifically in individuals with designated CKD, there is some evidence from large trials with bisphosphonates, teriparatide, and raloxifene in women with postmenopausal osteoporosis. Given the trial inclusion criteria, these individuals did not have evidence of CKD-MBD because they excluded participants with manifest kidney disease, as well as those with increased PTH or abnormal calcium or phosphorus levels. Their vitamin D status at baseline is unknown. However, because the trials used a serum creatinine cutoff level to determine eligibility and included a large number of elderly women, they unknowingly included a substantial group of individuals with decreased estimated glomerular filtration rate (eGFR) corresponding to CKD stage 3 and even some individuals with eGFR corresponding to CKD stage 4.[78-81] Despite some uncertainty stemming from the method of estimating GFR and loss of precision in post hoc subgroup analyses, it appears that treatments with risedronate, alendronate, teriparatide, or ralox-

ifene had similar efficacy in those with moderately decreased eGFR as in those with a mildly decreased or normal eGFR, resulting in improved BMD and reduced fractures. This recommendation is applicable to the United States. It may apply to a large group of older patients with eGFRs in the upper range of CKD stage 3 (ie, GFR, 45-60 mL/min/1.73 m^2) who do not have laboratory evidence of CKD-MBD.

> 4.3.3 In patients with CKD stage 3 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 biochemical abnormalities and progression of CKD, with consideration of a bone biopsy (2D).

The narrative to this recommendation describes that in CKD stage 3, some patients have already developed abnormalities of CKD-MBD, in particular, secondary HPT. As kidney disease progresses, bone disease changes from idiopathic osteoporosis to renal osteodystrophy. Despite wide variability among patients regarding this transition, biochemical manifestations of CKD-MBD initially appear at an approximate GFR of 40-50 mL/min/1.73 m^2. The pathogenesis of bone disease in patients with CKD-MBD is different from that in patients with postmenopausal osteoporosis. Therefore, extrapolating effects from patients with osteoporosis that excluded individuals with abnormal PTH values to patients with CKD stages 3-5D may not be valid. Along with concerns about the applicability of treatment effects, there is increasing concern about long-term safety with drugs that are cleared by the kidneys.[82] The work group suggests that secondary HPT be addressed first, as outlined in recommendation 4.2.1.

In patients in whom HPT has been corrected, GFR is stable and risk of a fracture outweighs the potential long-term risk of inducing irreversible low bone turnover, therapy with bisphosphonates may be considered. However, because bisphosphonates are likely to prevent fractures only in patients who have increased bone resorption, the work group suggests a bone biopsy when feasible. If therapy with bisphosphonates is given, lower dose and shorter treatment duration should be considered. The suggested approach is applicable in the United States, although as discussed, bone biopsy availability may be limited.

4.3.4   In patients with CKD stages 4-5D with biochemical abnormalities of CKD-MBD and low BMD and/or fragility fractures, we suggest additional investigation with bone biopsy before therapy with antiresorptive agents (2C).

In individuals with CKD stages 4-5D and biochemical evidence of CKD-MBD, trial data for the efficacy and safety of antiresorptive agents are lacking. The work group thus could not recommend routine use of these agents. A bone biopsy is suggested before therapy with bisphosphonates, teriparatides, or raloxifene. This suggestion is applicable in the United States.

4.3.5   In children and adolescents with CKD stages 2-5D 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).

In children with CKD, linear growth abnormalities are common and can be corrected using recombinant human growth hormone.[83] Decisions to start growth hormone therapy should be based on height velocity and potential for linear growth (bone age and maturational stage), as well as height deficits. Treatment entails daily subcutaneous injection. Adverse events may include impaired glucose tolerance. The current pediatric KDOQI guideline for nutrition in children with CKD[9] specifies that "Recombinant human growth hormone therapy should be considered in children with CKD stages 2-5D, short stature [height SDS < -1.88 (height-for-age $<$ 3rd percentile)], and potential for linear growth if growth failure (height velocity-for-age SDS < -1.88) persist beyond 3 months despite treatment of nutritional deficiency and metabolic abnormalities." In the United States, preferences of the patient and his or her guardian about the value placed on accelerated linear growth versus the burden of daily injections and the potential for harm should be elicited.

RECOMMENDATIONS IN 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 phosphorus at least weekly until stable (1B).

During the immediate posttransplant period with usually rapidly changing GFRs, wide fluctuations in serum calcium and phosphorus levels may be seen and thus frequent monitoring is needed. Hypophosphatemia occurs in a large proportion of patients immediately after transplant, and serum calcium levels tend to increase after transplant; these changes usually stabilize after about 6 months.[84] PTH levels decrease significantly during the first 3 months after transplant, but typically stabilize at increased values after 1 year. This recommendation is applicable to the United States.

5.2   In patients after the immediate post–kidney transplant period, it is reasonable to base the frequency of monitoring serum calcium, phosphorus, and PTH on the presence and magnitude of abnormalities and rate of progression of CKD (not graded). Reasonable monitoring intervals would be:
  • In CKD stages 1-3T, for serum calcium and phosphorus, every 6-12 months, and PTH, once, with subsequent intervals dependent on baseline level and CKD progression
  • In CKD stage 4T, for serum calcium and phosphorus, every 3-6 months, and for PTH, every 6-12 months
  • In CKD stage 5T, for serum calcium and phosphorus, every 1-3 months, and for PTH, every 3-6 months
  • In CKD stages 3-5T, measurement of alkaline phosphatases annually or more frequently in the presence of increased PTH levels (see chapter 3.2)

In patients with CKD receiving treatments for CKD-MBD or in whom 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 stages 3-5 (not graded) (see chapter 4.1 and 4.2)

After the immediate posttransplant period, transplant function usually stabilizes. The above ungraded statements provide guidance for the frequency of monitoring for laboratory abnormalities at that time. They are extrapolated from those provided for nontransplant patients with corresponding CKD stage (see recommendation 3.1.2). Data directly supporting the utility of these measurements are limited in nontransplant CKD patients and even more limited in kidney transplant patients. However, CKD-MBD is common after kidney transplant. Furthermore, kidney transplant patients with normal or mildly decreased eGFRs are still considered to have CKD and may have residual bone disease from pretransplant CKD-MBD. Thus, in addition to suggesting monitoring serum calcium, phospho-

rus, and PTH levels in patients with CKD stage 3T (as for CKD stage 3), this is also suggested for CKD stages 1-2T. As for nontransplant patients with CKD-MBD, the frequency of measurements may be increased to monitor for trends and treatment efficacy and side effects (see identical statement under 3.1.2.). These frequencies provide a reasonable framework and apply to the United States.

The statement to follow the same principles for treatment of biochemical abnormalities of CKD-MBD in kidney transplant patients as outlined for patients with CKD stages 3-5 is reasonable. However, CKD-MBD in kidney transplant patients is an even more heterogeneous disease than in nontransplant patients. It is the consequence of many different factors, including pretransplant CKD-MBD, effects of immunosuppressive drugs, level of kidney function recovery, and risk factors for osteoporosis.

> 5.3 In patients with CKD stages 1-5T, we suggest that 25(OH) vitamin D (calcidiol) levels might be measured, with repeated testing determined by baseline values and interventions (2C).

This weak recommendation also is extrapolated from the recommendation for nontransplant patients with CKD (recommendation 3.1.3). It is supported by finding low vitamin D levels in some patients after kidney transplant. Avoidance of sunlight and wider use of sunscreen may contribute to low vitamin D levels in transplant patients. This discretionary recommendation is applicable in the United States.

> 5.4 In patients with CKD stages 1-5T, we suggest that vitamin D deficiency and insufficiency be corrected using treatment strategies recommended for the general population (2C).

This weak recommendation is extrapolated from the recommendation for nontransplant patients with CKD. See also commentary on recommendation 3.1.3. This discretionary recommendation is applicable in the United States.

> 5.5 In patients with eGFR greater than approximately 30 mL/min/1.73 m^2, we suggest measuring BMD in the first 3 months post–kidney transplant if they receive corticosteroids or have risk factors for osteoporosis, as in the general population (2D).

It is unclear whether low BMD in kidney transplant patients corresponds to fracture risk. Thus, the work group believed that DXA should be reserved for high-risk populations, including those receiving significant doses of corticosteroids or those with risk factors for osteoporosis in the general population (see recommendation 3.2). In addition, DXA screening is suggested only in individuals with a well-functioning transplant, in other words, CKD stages 1-3T. Those with more advanced CKD will be more likely to have abnormal bone quality from CKD-MBD, which is likely to compromise the ability of BMD to predict fractures. This discretionary recommendation is applicable in the United States.

> 5.6 In patients in the first 12 months post–kidney transplant with eGFR greater than approximately 30 mL/min/1.73 m^2 and low BMD, we suggest that treatment with vitamin D, calcitriol/alphacalcidiol, or bisphosphonates be considered (2D).
> - We suggest that treatment choices be influenced by the presence of CKD-MBD, indicated by abnormal levels of calcium, phosphorus, 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 because of the high incidence of adynamic bone disease (not graded)

There are insufficient data to guide treatment after the first 12 months.

As discussed, bone disease in kidney transplant patients is heterogeneous, with variable pathologic states resulting from an overlap of risk factors related to CKD, transplant, and osteoporosis. Thus, treatment data from the general population without CKD, patients with CKD without a kidney transplant, or other solid-organ transplant patients without CKD-MBD cannot be directly extrapolated. There are no RCTs in kidney transplant patients examining bone-specific therapies on clinical outcomes, such as fractures or cardiovascular disease events. Although loss of bone density occurs after kidney transplant,[85] particularly in the first year, and some trials have examined BMD as an outcome, this has not been validated as a surrogate outcome for fractures. The overall number of studies of kidney transplant patients and number of patients treated with vitamin D, calcitriol/alphacalcidiol, or bisphosphonates are low, both within and beyond the first 12 months after transplant. Thus, treatment recommendations are discretionary. Evaluation and selection of any treatments should consider the

constellation of abnormalities in calcium, phosphorus, PTH, and vitamin D levels. Bisphosphonates should not be used if there are abnormalities in calcium, phosphate, vitamin D, or PTH levels.

In children with CKD stages 1-5T, there is only one trial comparing placebo versus alfacacidiol versus calcitonin versus alendronate.[86] The evidence was deemed to be insufficient to support specific recommendations for treatments for bone disease in pediatric kidney transplant recipients.

Given the complexity of MBD in kidney transplant recipients, it is reasonable to consider a bone biopsy to guide bone-specific treatment. This would be particularly important before using bisphosphonates because these agents have better efficacy in high bone turnover and may lead to adynamic bone disease. These recommendations and statements are applicable in the United States.

> 5.7 In patients with CKD stages 4-5T, 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 type of kidney transplant bone disease (2B).

The uncertainty surrounding the value of BMD for predicting underlying bone disease, fracture, or other clinical outcomes in kidney transplant patients increases with more advanced stages of CKD because there is a higher likelihood of more severe underlying bone abnormalities of CKD-MBD. This recommendation is applicable to the United States.

> 5.8 In patients with CKD stages 4-5T with known low BMD, we suggest management as for patients with CKD stages 4-5 not on dialysis therapy, as detailed in chapter 4.1 and 4.2.(2C)

Although routine testing for BMD in patients with CKD stages 4-5T is discouraged, some patients may still undergo testing that shows low BMD. This discretionary recommendation suggests that these individuals be referred to as having low BMD rather than osteoporosis and that they be evaluated and managed for hyperphosphatemia and HPT as patients with CKD without a kidney transplant (as described in chapter 4.1 and 4.2 in the KDIGO guideline). It

seems prudent that treatment with bone-specific therapies other than those aiming at correcting abnormalities of calcium, phosphorus, PTH, and vitamin D levels would be guided by a bone biopsy (see recommendation 5.6).

RESEARCH RECOMMENDATIONS

The KDIGO guideline document summarizes our current knowledge regarding the management of CKD-MBD and highlights areas in need of future research. Each guideline chapter contains research recommendations at the end, and chapter 6 contains a short list of research questions deemed to have high priority for advancing the field. Research comparing therapeutic strategies for CKD-MBD admittedly is difficult to do because phosphate-lowering drugs, vitamin D and its analogues, calcimimetics, and dialysis calcium concentrations variably impact on the components of MBD. However, key questions are to what target phosphorus levels should be decreased in patients with CKD stages 3-5 and 5D and what the optimal treatment strategy is for this. Similarly, a key question is to what PTH target we should treat and with what strategy. In a population with a great burden of mortality and morbidity, treatment trials have to examine clinical end points. Future treatment trials also should examine surrogate outcomes along with clinical outcomes because reliance on surrogate end points requires validation by showing concordance with clinical outcomes in trials of similar agents or strategies in addition to robust risk relationships in observational studies.[87]

CONCLUSION

The KDIGO guideline is based on the newly created disease concept of CKD-MBD. KDIGO used an approach to guideline development that required stringent mapping of recommendations to the available evidence. It exposed the uncertainty surrounding a number of practice areas, as well as the lack of definitive evidence for clinical benefit from a range of currently widely used and advocated treatments. This prohibits the issuance of specific and directive recommendations, but allows for more flexibility in setting treatment goals and weighing benefits and harms in specific situations. Target ranges proposed by the 2003 KDOQI guideline for phosphorus and PTH

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levels in patients with CKD stage 5D are not supported by high-quality evidence and should not be used for performance measurement.

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