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Canadian Society of Nephrology Commentary on the Kidney Disease Improving Global Outcomes 2017 Clinical Practice Guideline Update for the Diagnosis, Evaluation, Prevention, and Treatment of Chronic Kidney Disease-Mineral and Bone Disorder

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Abstract

Purpose of review: (1) To provide commentary on the 2017 update to the Kidney Disease Improving Global Outcomes (KDIGO) 2017 Clinical Practice Guideline Update for the Diagnosis, Evaluation, Prevention, and Treatment of Chronic Kidney Disease-Mineral and Bone Disorder (CKD-MBD); (2) to apply the evidence-based guideline update for implementation within the Canadian health care system; (3) to provide comment on the care of children with chronic kidney disease (CKD); and (4) to identify research priorities for Canadian patients.

Sources of information: The KDIGO 2017 Clinical Practice Guideline Update for the Diagnosis, Evaluation, Prevention, and Treatment of CKD-MBD.

Methods: The commentary committee co-chairs selected potential members based on their knowledge of the Canadian kidney community, aiming for wide representation from relevant disciplines, academic and community centers, and different geographical regions.

Key findings: We agreed with many of the recommendations in the clinical practice guideline on the diagnosis, evaluation, prevention, and treatment of CKD-MBD. However, based on the uncommon occurrence of abnormalities in calcium and phosphate and the low likelihood of severe abnormalities in parathyroid hormone (PTH), we recommend against screening and monitoring levels of calcium, phosphate, PTH, and alkaline phosphatase in adults with CKD G3. We suggest and recommend monitoring these parameters in adults with CKD G4 and G5, respectively. In children, we agree that monitoring for CKD-MBD should begin in CKD G2, but we suggest measuring ionized calcium, rather than total calcium or calcium adjusted for albumin. With regard to vitamin D, we suggest against routine screening for vitamin D deficiency in adults with CKD G3-G5 and G1T-G5T and suggest following population health recommendations for adequate vitamin D intake. We recommend that the measurement and management of bone mineral density (BMD) be according to general population guidelines in CKD G3 and G3T, but we suggest against routine BMD testing in CKD G4-G5, CKD G4T-5T, and in children with CKD. Based on insufficient data, we also recommend against routine bone biopsy in clinical practice for adults with CKD or CKD-T, or in children with CKD, although we consider it an important research tool.

Limitations: The committee relied on the evidence summaries produced by KDIGO. The CSN committee did not replicate or update the systematic reviews.

Abrégé

Justification: (1) Commenter les recommandations du KDIGO 2017 (Kidney Disease Improving Global Outcomes) sur les bonnes pratiques cliniques pour le diagnostic, l'évaluation et le traitement des troubles du métabolisme minéral osseux

associés aux maladies rénales chroniques (TMO-MRC); (2) appliquer les lignes directrices actualisées et fondées sur les données probantes en vue de leur mise en œuvre dans le système de soins de santé canadien; (3) commenter les soins prodigués aux enfants atteints d'insuffisance rénale chronique (IRC) et (4) définir les priorités de recherche des patients Canadiens.
Sources: Les recommandations du KDIGO 2017 (Kidney Disease Improving Global Outcomes) sur les bonnes pratiques cliniques pour le diagnostic, l'évaluation et le traitement des troubles du métabolisme minéral osseux associés aux maladies rénales chroniques (TMO-MRC).
Méthodologie: Les coprésidents du comité ont sélectionné les membres potentiels sur la base de leur connaissance du secteur de la santé rénale au Canada, tout en visant une bonne représentation de toutes les disciplines concernées, des centres universitaires et communautaires et des différentes régions géographiques.
Principaux commentaires: Nous approuvons un grand nombre des recommandations du KDIGO. Cependant, compte tenu de la rareté des anomalies du calcium et du phosphate et de la faible probabilité d'anomalies graves de la PTH (hormone parathyroïde), nous déconseillons le dépistage et la surveillance des taux de calcium, de phosphate, de PTH et de phosphatase alcaline chez les adultes atteints d'IRC de stade G3. Nous suggérons de mesurer ces paramètres chez les adultes de stade G4 et nous le recommandons pour les patients de stade G5. Chez les enfants, nous appuyons la recommandation de commencer la surveillance des TMO-MRC dès le stade G2, mais nous suggérons de mesurer le calcium ionisé plutôt que les taux de calcium total ou de calcium corrigé en fonction de l'albumine. En ce qui concerne la vitamine D, nous déconseillons le dépistage de routine des carences chez les adultes atteints d'IRC de stade G3 à G5 et G1T à G5T; nous suggérons plutôt de suivre les recommandations visant la population générale pour un apport adéquat en vitamine D. Nous recommandons que la mesure et la prise en charge de la densité minérale osseuse (DMO) se fassent en suivant les recommandations pour la population générale chez les adultes atteints d'IRC de stade G3 et G3T, mais nous déconseillons les tests de DMO de routine chez les adultes de stades G4-G5 et G4T-G5T, de même que chez les enfants atteints d'IRC. En raison de données insuffisantes, nous déconseillons également la pratique systématique d'une biopsie osseuse chez les adultes atteints d'IRC ou d'IRC-TMO, ainsi que chez les enfants atteints d'IRC, bien que nous la considérions comme un important outil de recherche.
Limites: Le comité s'est appuyé sur le résumé des preuves rédigé par le KDIGO. Le comité de la SCN n'a pas reproduit ou mis à jour les revues systématiques.

Keywords
CKD (chronic kidney disease), mineral bone disease, KDIGO, Canada, guidelines

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Introduction

KDIGO (Kidney Disease: Improving Global Outcomes) was established in 2003 with its stated mission "to improve the care and outcomes of kidney disease patients worldwide through promoting coordination, collaboration, and integration of initiatives to develop and implement clinical practice guidelines." The first KDIGO Clinical Practice Guideline for the Diagnosis, Evaluation, Prevention, and Treatment of Chronic Kidney Disease-Mineral and Bone Disorder (CKD-MBD) was published in 2009. In the intervening years, the evidence base increased substantially, and therefore KDIGO recognized the need to determine whether sufficient data had accumulated to support a reassessment of the 2009 guidelines. Accordingly, a Controversies Conference in 2013 titled "CKD-MBD: Back to the Future" identified 12 recommendations for reevaluation based on new data, and KDIGO commissioned an update to the 2009 CKD-MBD guidelines.

The focus of this Canadian Society of Nephrology (CSN) commentary is on the 2017 update to the KDIGO CKD-MBD guideline; however, commentary is also provided for guidelines that remained unchanged from 2009. The goal was to apply the evidence base of the KDIGO CKD-MBD guideline update for implementation within the Canadian health care system recognizing issues pertaining to cost and efficient use of health resources. Comments are made on the care of children with chronic kidney disease (CKD) where appropriate. We also aimed to identify research priorities for Canadian patients. This commentary is relevant to nephrologists, including pediatric nephrologists and transplant physicians, primary care physicians, nursing and pharmacy specialists, and nephrology dieticians who care for patients with CKD-MBD.

Review and Approval Process for CSN Commentaries

The commentary committee co-chairs selected potential members based on their knowledge of the Canadian kidney community, aiming for wide representation from relevant disciplines, academic and community centers, and different geographical areas in Canada. Once the commentary committee was determined, we followed the general methodology of the CSN guidelines and commentary development.[1-4] We considered the evidence, in general, as understood by the international community, and also sought to provide guidance and insight specifically directed to health care providers in Canada who care for patients with CKD-MBD.

An initial teleconference was held to discuss the guideline, to divide the committee into subcommittees based on the KDIGO guideline subsections, and to discuss the working plan. Each committee member reviewed the KDIGO guideline and provided comments on the whole document in general and on the section assigned to them specifically. The comments were then collated and circulated before another teleconference was scheduled. During the second teleconference, the chairs facilitated discussion to highlight the various issues about the evidence supporting the recommendations, its quality, and the members' agreement with each of the recommendations. They also facilitated discussion around the implementation of these guidelines in the Canadian context. This includes consideration of resources required and opportunity cost, contextualization to our publicly funded health care system, and recognition of specific factors such as funding models that differ by province.

Using notes from the teleconferences, a representative for each subcommittee, selected for their expertise in the area, wrote the first draft of the commentary and received feedback from other members in the subcommittee, and from the co-chairs. Subsequent drafts received feedback from all committee members. Then, a final teleconference was held to discuss differences in opinion and generate consensus around the final wording of the commentary. The committee maintained documentation of the process and decisions.

The CSN commentary is intended for health care providers in primary, secondary, or tertiary care who manage patients with kidney disease, recognizing that some of the issues are more specialized than others, and may be less relevant at the level of primary care. The committee used the Grading of Recommendations Assessment, Development and Evaluation (GRADE) framework to highlight the criteria that led to disagreement with the original recommendations or their strength.[5-7] The committee specifically considered the following criteria based on the GRADE framework when determining their agreement with the recommendations: balance of desirable and undesirable consequences of the proposed intervention, diagnosis or management strategy compared with the alternative option, the certainty of evidence (also described as quality of evidence), patients' values, resources implications, equity, acceptability, and feasibility.[8-11] The committee relied heavily on the evidence summaries produced by KDIGO. We recognized that we needed to balance the inclusion of evidence published since the KDIGO search dates and maintaining the unbiased nature of a systematic review. The CSN committee did not replicate or update the systematic reviews conducted by KDIGO. However, the committee accepted the inclusion of new evidence that is potentially practice changing based on members' knowledge and awareness of published articles.

We believe that the multidisciplinary nature of our committee would mitigate against bias in finding and including new work. In incorporating this additional evidence, we did not use formal GRADE methodology, but, instead, informally considered the certainty of the evidence and used GRADE language to determine where we judged it to fail. We expressed and discussed our ideas initially through shared documents and conference calls, and the final deliberations were made by rounds of feedback on the actual text. We tried to avoid "no recommendation," in keeping with the GRADE idea of landing on 1 of the 4 categories: "recommend," "suggest," "suggest against," and "recommend against." We deviated from this language only when no consensus could be reached on 1 of the

4 categories. It also became clear to the committee that in some instances, there is a need to separate CKD categories that were combined in 1 recommendation in KDIGO, specifically to highlight that the evidence supporting specific actions for different CKD categories may have a different certainty, and thus lead to differences in the strength of recommendations.

The KDIGO guideline includes a number of statements that are ungraded, or, where there is a mismatch between the strength of the statement and the assessed certainty of the evidence. A recent commentary by Guyatt and colleagues provided us with insight and an approach to this,[6] defining ungraded statements, often thought of as "good practice recommendations" or "motherhood statements," as "good practice statements." The commentators suggest that such statements are allowable when the evidence is actually very strong, and confidence in it is high, but the evidence is indirect and summarizing it would result in an unacceptable opportunity cost; evidence that is akin to our certainty that parachutes should be used when jumping from airplanes. When all of these conditions are met, they should not be graded. Otherwise, they should not be used, particularly, not as a substitute for gathering evidence. We thought that many of the ungraded KDIGO guideline recommendations could have been graded based on the evidence collected. We did not find any ungraded statements that met the rigorous criteria suggested by Guyatt and colleagues for the appropriate use of good practice statements. None of our statements meet these criteria: They should not be considered good practice statements where GRADE is unnecessary, but rather, our attempt to summarize literature without having the resources to formally GRADE or re-GRADE each KDIGO statement.

Structure of This Commentary

The structure of this commentary aligns with the structure of the KDIGO guideline. Numbered text within horizontal rules is quoted directly from the KDIGO document, using the same numbering scheme as in the original (all material is reproduced with permission of KDIGO). The text that follows, written by the commentary committee, comments on key guideline recommendations, discusses special implications for Canadian practice, and makes focused and selective recommendations for the most important future research. The focus will be on the guideline statements that the working group "do not concur" with or "concur with comments," and in instances where implications within the Canadian health care system warrant explanation.

Chapter 3.1: Diagnosis of CKD-MBD: Biochemical Abnormalities

3.1.1 KDIGO:

We recommend monitoring serum levels of calcium, phosphate, parathyroid hormone (PTH), and alkaline phosphatase (ALP) activity beginning in CKD G3a (*1C*).

3.1.1 CSN:

The CSN committee recommends against screening or monitoring serum levels of calcium, phosphate, PTH, and ALP activity for patients with CKD G3.

The CSN committee suggests monitoring serum levels of calcium, phosphate, PTH, and ALP activity for patients with CKD G4.

The CSN committee recommends monitoring serum levels of calcium, phosphate, PTH, and ALP activity for patients with CKD G5.

Commentary

There is strong epidemiological evidence that abnormalities in calcium and phosphate are uncommon, and that abnormalities in PTH are unlikely to be severe in CKD G3.[12,13] Because of this, in addition to the absence of any evidence-based strategy to improve outcomes based on these data, we recommend against screening or monitoring of these levels in patients with CKD G3. We suggest monitoring of these levels in patients with CKD G4 and recommend monitoring of these levels in patients with CKD G5. Frequency of testing will be determined by the level of glomerular filtration rate (GFR), patient-specific risk factors, and the results of tests to date (ie, less frequent testing in patients with higher GFR, with stable GFR, and those who have persistently not had abnormalities in their testing to date).

Implications Within Canadian Health Care

In Canada, the large majority of patients with CKD G3 are managed in a primary care setting. We did not think it reasonable, or a good use of resources, for primary care practitioners to undertake screening and monitoring activities in CKD G3, or to expect that primary care practitioners would manage clinically significant abnormalities detected in CKD G4 and G5. In CKD G5, hypocalcemia is more prevalent than at higher levels of GFR; because of the known adverse consequences of severe hypocalcemia and the availability of strategies to prevent or manage it, we recommend screening and monitoring in patients at this level of kidney function.[12,13]

3.1.3: KDIGO:

In patients with CKD G3a-G5D, we suggest that 25(OH)D (calcidiol) levels might be measured, and repeated testing determined by baseline values and therapeutic interventions (*2C*). We suggest that vitamin D deficiency and insufficiency be corrected using treatment strategies recommended for the general population (*2C*).

3.1.3 CSN:

The CSN committee suggests against routine screening or monitoring of 25(OH)D (calcidiol) levels. The CSN committee suggests following the population health recommendation of adequate vitamin D dietary intake.

The CSN committee recommends against routine supplementation for patients with CKD G3. We suggest case finding or empiric supplementation in people at high clinical risk of deficiency.
The CSN committee makes no recommendation for CKD G4-5D as we were unable to reach consensus.

Commentary

It is important to differentiate vitamin D insufficiency (levels 50 to <75 nmol/L) from deficiency (levels <50 nmol/L). Vitamin D deficiency is highly associated with development of bone mineralization defects in patients with CKD, which are corrected by vitamin D supplementation.[14-16] In patients at high risk of developing vitamin D deficiency (malnutrition, chronic malabsorption, severe nephrotic syndrome, vegan diet),[17] and in patients with chronic hypocalcemia or/and hypophosphatemia,[18] there is a rationale to test vitamin D levels and replete if deficiency is diagnosed.

Implications Within Canadian Health Care

Vitamin D insufficiency, by serum testing of 25 hydroxyvitamin D, is prevalent in Canada: overall, 32% and 40% in the winter,[19] with some studies suggesting that it may be more prevalent in patients with CKD.[20] There is lack of consensus as to what level of vitamin D justifies supplementation.[21] We suggest that health care workers recommend dietary vitamin D intake, in keeping with general population recommendations for Canada, of 600 IU (international unit) in children and adults to age 70 years, and 800 IU in adults above 70 years.[22] In coming to this suggestion for patients with G3 CKD, we applied the results of a 2019 large randomized controlled trial (RCT) and a 2018 meta-analysis, both of which showed no benefit from routine supplementation.[23,24] Outcomes were cardiovascular events, incident cancer, falls and fractures. In the RCT, the prevalence of vitamin D deficiency was 13%, comparable with data from patients with CKD G3.[13,25] We judged this to be high quality and direct evidence for patients with CKD G3, and recommend against routine supplementation in this group. However, in patients with CKD G3 who are at high risk of not meeting dietary requirements for vitamin D (malnutrition, chronic malabsorption, severe nephrotic syndrome, vegan diet), we suggest either empiric treatment or case finding through serum measurement, according to clinical assessment and judgment. We note that Health Canada continues to recommend that people over the age of 50 years take a daily vitamin D supplement of 400 IU (10 μg),[22] a recommendation that is unlikely to do harm. In patients with G4 and 5ND CKD, the prevalence of vitamin D deficiency may be higher, and in incident patients on hemodialysis, prevalence as high as 50% has been reported.[20,26] Because of the complexity of these issues and the absence of direct evidence, we make no recommendation for CKD G4-G5. Again, patients at high risk of deficiency might benefit from vitamin D measurement and supplementation, or from empiric supplementation, according to clinical assessment and judgment. In patients with kidney transplants who have CKD G1T-G3T, because of the higher prevalence of deficiency, we suggested, in addition to recommended dietary intake as above, following the population health recommendation of vitamin D supplementation of 400 IU daily for people over 50 years (section 5.4); G4T and G5T, like G4 and G5, have no recommendation because of the complexity of the issues.

Research Recommendations

The CSN workgroup thought that a large pragmatic trial of safety and efficacy of vitamin D supplementation in patients with CKD G4-G5 was a research priority and that patients with G3-G5 CKD should be included in future studies of calcium and vitamin D supplementation.

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

3.1.5 CSN:
The CSN committee recommends against using the mathematical construct of calcium-phosphate product.
The CSN committee recommends using the total calcium, rather than calcium adjusted for albumin, and suggests using ionized calcium only in situations where knowing the absolute value will greatly alter management.

Commentary

The calcium-phosphate product was a proposed measure of calcification tendency: Its construct validity was never established and the workgroup thought it of historical interest only.

In this measurement context, we considered another widespread practice: the adjustment, normalization, or "correction" of measured serum calcium for albumin using mathematical formulae. We recognized that no validation study demonstrating a clinically important improvement in agreement (κ) with the criterion measure of ionized calcium has been reported. A widely used formula is that suggested by Payne: Corrected calcium = total calcium + (0.025 × [40 – albumin]) (calcium in mmol/L, albumin in g/L). In unselected hospitalized patients with and without CKD, agreement between ionized calcium and unadjusted total calcium, and with calcium adjusted using the Payne formula was 0.78 and 0.73, respectively, with similar data in the subgroup whose albumin was lower than 30 g/L.[27,28] In patients with CKD, the agreement between ionized calcium and total calcium, and with calcium corrected by 2 formulae was 0.29 (95% confidence interval [CI] = 0.20-0.38), 0.28 (95%

CI = 0.19-0.37) and 0.25 (95% CI = 0.16-0.34), respectively, with no improvements in specificity or sensitivity from either formula in the detection of hypo- or hypercalcemia.[29] In patients on dialysis, the agreement between ionized calcium and unadjusted total calcium and with calcium adjusted according to the formulas of Payne, Berry, and Orrell were 0.78, 0.68, 0.45, and 0.84, respectively.[27] In clinical practice in Canada (and elsewhere), 2 different assays for albumin are in widespread use (bromocresol green and bromocresol purple); these methods correlate, but the mean difference between them is clinically relevant at 6.4 g/L.[30] This creates additional, clinically important measurement error when using an adjustment formula.[31,32] We concluded that the practice of adjusting calcium for albumin was unsupported by evidence.

Implications Within Canadian Health Care

Measuring albumin in addition to calcium adds to the resources required and costs of testing. No outcome studies comparing different strategies have been reported. For these reasons, we recommend that calcium be assessed by the measurement of total calcium; if the albumin is severely low, or there are other reasons to require a more precise measure of serum calcium status, we suggest measuring ionized calcium.

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

3.1.6 CSN:
The CSN committee recommends calibration of assays. Clinical laboratories should inform clinicians of the actual assay method in use and report any change in methods, sample source (plasma or serum), or handling specifications to facilitate the appropriate interpretation of biochemistry data.

For PTH, the workgroup thought it important to highlight the high level of between-assay and intraindividual variability. In a study of 37 patients on hemodialysis, differences between assays that would have led to alterations in guideline-based treatment recommendations were observed in 21% of patients.[33] Within a single assay, high levels of within-patient variability have also been reported: intraindividual coefficient of variation of intact PTH was 26% in hemodialysis patients and 19% in healthy volunteers.[34] These issues have a profound impact on the interpretation of PTH and reinforce the workgroup's recommendations that prescribing decisions based on PTH should be limited to extreme and persistent values, and that it is not possible to provide threshold values for specific interventions.

Chapter 3.2: Diagnosis of CKD-MBD: Bone

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

3.2.1 CSN:
The CSN committee suggests against routine BMD testing in patients with CKD G4-G5.

Commentary

Patients with CKD G3 have been included in general studies of the measurement properties of BMD assessment and in trials of prophylactic drug treatments that have shown efficacy for patient-important outcomes; the workgroup thought that CKD G3 patients at high risk of fracture or with low BMD should be treated with anti-osteoporotic therapy as in the general population. For G4-G5 CKD, we agreed that new data have shown that BMD predicts fracture in these patients. However, evidence is lacking that BMD results can inform an evidence-based prophylactic strategy in this population. For pharmacological prophylaxis of fractures, trials have included very few patients with severe kidney disease. Several other factors mitigate against generalizing from higher levels of GFR to CKD G4 to G5: The structural problem in bone at this level of GFR reflects metabolic bone disease as well as osteoporosis. There is a biological rationale that the type of bone disease (high or low bone turnover) should influence the type of anti-osteoporotic treatment (antiresorptive or bone-forming agent), yet there is empiric evidence for severe and temporally unpredictable hypocalcemia with some antiresorptive drugs (ie, denosumab) in patients with G4 to G5 CKD,[35] and bisphosphonates have been associated with low turnover bone lesion.[36] For a more detailed discussion of risks and benefits of pharmacotherapy for osteoporosis, see 4.3.3 below. We recommend exercise, regardless of BMD for all patients, because of the numerous health benefits produced.

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

3.2.2 CSN:
The CSN committee recommends against routine bone biopsy in clinical practice.

Commentary

We consider bone biopsy an important research tool. However, we cannot recommend or suggest bone biopsy in routine

clinical practice as there are currently insufficient data on which to base recommendations for use. It is reasonable for experienced health care workers seeking the optimal strategy for individual patients to continue to include bone biopsy, when they think it will usefully alter their management, and for bone biopsy to continue to be performed in clinical research; however, we recognized that there is no clear evidence-based treatment strategy that includes bone biopsy as a decision point. The current limitations of bone biopsy include lack of widespread expertise in performing or interpreting bone biopsy results, within-patient heterogeneity between cortical bone at different sites, dynamic changes that complicate the choice of timing of biopsy, invasiveness, and the difficulty of monitoring response to treatment without re-biopsy.[37-39] Ultrasound-guided bone biopsy by interventional radiologists may be a way to facilitate access to this technique to improve clinical research and perhaps clinical use in the future.

3.2.4 KDIGO:
In patients with CKD G3a-G5D, we suggest not to routinely measure bone-derived turnover markers of collagen synthesis (such as procollagen type I C-terminal propeptide), and breakdown (such as type I collagen cross-linked telopeptide, cross-laps, pyridinoline, or deoxypyridinoline) (*2C*).

3.2.4 CSN:
The CSN committee recommends against routine measurement of bone-derived turnover markers.

Commentary

Because of lack of evidence of how levels of these markers should change clinical practice, we agreed that bone-derived turnover markers of collagen synthesis (such as procollagen type 1 C-terminal propeptide) and breakdown (such as type 1 collagen cross-linked telopeptide, cross-laps, pyridinoline, or deoxypyridinoline) should not be measured in routine clinical practice, and, because of the resource implications attached to testing novel biomarkers, strengthened the wording.

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

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

4.1.1 CSN:
With respect to treatment of CKD-MBD:

The CSN committee recommends against screening, monitoring, or treating for patients with CKD G3.
CSN committee suggests monitoring and basing treatment decisions on serial assessments of phosphate, calcium, and PTH levels considered together, for patients with CKD G4-5.

Commentary

Based on the very low prevalence of calcium and phosphate abnormalities, or severe hyperparathyroidism (HPT), at GFR above 30 mL/min/1.73 m^2,[12,13] in addition to the lack of evidence supporting normalization of these parameters, our working group did not endorse routine measurement of phosphate, calcium, and PTH in patients with either CKD G3a or G3b. In a large, unselected population, serum calcium and phosphate remained normal at an estimated GFR (eGFR) >40 mL/min/1.73 m^2, suggesting that the likelihood of encountering abnormal levels at this level of eGFR would be low.[13] In patients with CKD G4 and G5ND, the working group felt that it was reasonable to measure phosphate, calcium, and PTH levels every 3 to 12 months. The working group agreed that the actual frequency of testing should be individualized, and consequent treatment decisions should be made while considering patient-specific trends for any given parameter while accounting for the concentrations of the other 2 parameters. In patients with G5D receiving hemodialysis, sampling frequency for calcium and phosphate is often monthly, although recent data suggest that less frequent assessments may be acceptable.[40] The optimal sampling frequency for patients on peritoneal dialysis is undefined.

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

4.1.2 CSN:
The CSN committee recommends against screening, monitoring, or treating with a view to lowering elevated phosphate levels toward the normal range, for patients with CKD G3.
The CSN committee suggests lowering phosphate levels toward the normal range for patients with CKD G4-5D.

Commentary

The 2009 KDIGO guidelines recommended maintaining serum phosphate in the normal range in patients with CKD G3a-G5ND, and lowering elevated phosphate levels *toward* the normal range in CKD G5D. Highlighting the challenge of consistently achieving normal values for serum phosphate, especially in more advanced CKD, and the lack of evidence for achieving uniformly normal values, the 2017 update suggests that attempts should be made to shift serum phosphate concentration toward the normal range across the spectrum of CKD (ie, CKD G3a to G5D). As outlined above,

the CSN working group did not endorse the routine measurement of serum phosphate in patients with either CKD G3a or G3b making these recommendations essentially moot for these patients. In CKD G4-G5D, the working group agreed with the suggestion that elevated phosphate levels should be lowered toward the normal range, acknowledging that this reflects usual clinical practice that is largely driven by associations linking hyperphosphatemia with adverse outcomes in large epidemiological studies. Furthermore, in light of the absence of strong evidence to support phosphate lowering, the working group acknowledged that the priority assigned to lowering serum phosphate should be individualized. A decision to recommend phosphate lowering should always take into account patient-specific factors such as patient values, age, comorbidity, nutritional status, preferred diet, and prognosis, as well as the degree of hyperphosphatemia. For patients receiving conservative management, dietary changes may be helpful in relieving symptoms and this should be the focus.[41] Patients who are willing to adopt a guideline-supported strategy of phosphate lowering toward the normal range should be informed that these efforts may not ultimately translate into concrete clinical benefits. Moreover, given the absence of strong evidence to guide practice, in addition to the intrusiveness, potential toxicity, and costs of phosphate binders, the Canadian nephrology community should endorse clinical trials that test the benefits of intensive phosphate lowering.

4.1.3 KDIGO:
In patients with CKD G3a-G5D, we suggest avoiding hypercalcemia (*2C*).

4.1.3 CSN:
The CSN committee recommends against screening or monitoring to identify calcium abnormalities for patients with CKD G3.
The CSN committee suggests avoiding hypo- and hypercalcemia for patients with CKD G4-5D.

Commentary

The working group agrees with the uncontroversial recommendation of maintaining normocalcemia given the well-known physiological effects of both hypercalcemia and hypocalcemia. The working group recognized that hypercalcemia in CKD G3-5 could reflect other causes (ie, primary HPT and malignancy) in addition to the harmful effects of therapies used to lower phosphate and PTH (ie, calcium-based phosphate binders and vitamin D analogs). The updated guideline for hypocalcemia was based on the EVOLVE trial where hypocalcemia occurred relatively frequently in the cinacalcet arm, yet was asymptomatic in all cases.[42,43] Nonetheless, the working group felt that there was inadequate data to support leaving asymptomatic hypocalcemia untreated.

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

4.1.5 CSN:
The CSN committee recommends against monitoring phosphate for patients with CKD G3.
The CSN committee recommends that, for patients with CKD G4-5D, decisions about phosphate-lowering treatment should be based on progressively or persistently elevated serum phosphate.

Commentary

The 2009 KDIGO guidelines recommended using phosphate-binding agents in the treatment of hyperphosphatemia in patients with CKD G3a-G5 (*2D*) and G5D (*2B*). The 2017 update has changed to (1) reflect new evidence, based on a surrogate outcome, that does not support the routine use of phosphate binders in people with early stages of CKD and (2) to reflect that there are phosphate-lowering strategies beyond phosphate binders. The guideline remains ungraded given the paucity of evidence upon which to make recommendations. In an RCT, 148 CKD patients with essentially normal phosphate concentrations were randomized to lanthanum, sevelamer, calcium, or placebo.[44] Patients receiving 1 of the 3 phosphate binders experienced a marginal decline in serum phosphate. In a subset of 96 patients, those randomized to any phosphate binder combined versus placebo had *greater* progression of coronary artery calcification over 9 months. Although the findings of the trial need to be interpreted within the limitations of the small sample size and single-center design, the findings cast doubt on the role of phosphate binders in patients with CKD G4 and G5ND who have essentially normal serum phosphate concentrations. Pending the results of clinical trials that test whether the liberalization of phosphate targets is acceptable, conducted with specific binders, it may be reasonable to take steps to lower phosphate concentrations in some patients in whom phosphate concentrations are persistently high, taking into account the patient-specific factors listed in 4.1.2.

4.1.6 KDIGO:
In adult patients with CKD G3a-G5D receiving phosphate-lowering treatment, we suggest restricting the dose of calcium-based phosphate binders (*2B*).

4.1.6 CSN:
The CSN committee recommends against monitoring or treating phosphate for adult patients with CKD G3.
The CSN committee suggests that, for patients with CKD G4-5D, the dose of calcium-based phosphate binder should be restricted, but we were unable to reach consensus on a suggested maximum dose.

Commentary

The CSN working group acknowledges the potential for excessive calcium intake (both from dietary sources and phosphate binders) to exacerbate vascular calcification.[44,45] However, a precise ceiling for total calcium intake remains unclear. The benefits of using non-calcium-based phosphate binders instead of calcium-based binders were suggested in a study of coronary artery calcification, but not supported in large randomized trials examining important clinical outcomes.[46,47] Although avoidance of calcium may benefit individual patients (ie, those with concomitant hyperphosphatemia, and hypercalcemia), the substantial cost of non-calcium-based phosphate binders compared with that of calcium-based binders makes it difficult to support the widespread use of these agents without clear evidence of benefit and cost-effectiveness.[48]

Implications Within Canadian Health Care

Although there was general agreement that non-calcium-based phosphate binders have a role in reducing serum phosphate in certain patients, the working group was not able to reach consensus to address the practical question: "In the setting of persistent hyperphosphatemia, what is the highest dose of calcium that you would recommend?" This issue is further complicated by the fact that Canadian patients are subject to different rules and regulations regarding government funding for non-calcium-based phosphate binders across provincial and territorial jurisdictions. The ability to prescribe non-calcium-based phosphate binders varies in the extreme from the province of Alberta where non-calcium-phosphate binders are not paid for by the provincial drug plan to the province of Quebec where non-calcium-based phosphate binders are covered for patients in whom calcium is "contraindicated, not tolerated, or not sufficient to control hyperphosphatemia." The eastern provinces of Canada stipulate that to obtain coverage, patients must have hyperphosphatemia (phosphate >1.8 mmol/L) in addition to either hypercalcemia and/or calciphylaxis, while in Ontario, hyperphosphatemia must be accompanied by either hypercalcemia or either coronary artery calcification or calciphylaxis. Manitoba funds non-calcium-based phosphate binders for patients with "excessive calcium intake" defined as an intake that exceeds 4500 mg elemental calcium per day. First Nations and Inuit Canadians have access to a federal-based drug coverage program, which covers patients who have "elevated phosphate levels despite dietary restriction and use of calcium, hypercalcemia and for patients with presumed adynamic bone disease (PTH level < 0.9 pmol/L)." As a result, the maximum dose of calcium-based binders that clinicians are willing to prescribe may be dictated by the extent to which noncalcium binders are accessible in that jurisdiction.

Research Recommendations

The working group suggested that a placebo-controlled RCT designed to address different phosphate targets, not confounded by binder choice, is necessary in CKD G4 to G5D. The working group felt that RCTs evaluating novel binders and intestinal phosphate transport inhibitors would also be valuable.

4.1.8 KDIGO:

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

4.1.8 CSN:

The CSN committee recommends against monitoring or treating serum phosphate in patients with CKD G3.

The CSN committee suggests, for patients with CKD G4-5 who have progressive and persistent hyperphosphatemia, the avoidance of inorganic phosphate additives and low-value foods with high phosphate content.

The CSN committee suggests, for selected patients with CKD G4-5 with progressive and persistent hyperphosphatemia who can understand and implement the changes required, changing a proportion of protein intake from animal- to plant-based protein.

The CSN committee recommends against protein restriction for patients with all categories of CKD.

Commentary

Given the cultural centrality of food and the enjoyment that patients derive from eating, and the absence of convincing data that dietary restriction improves outcomes, we do not believe that we should be dogmatic about dietary phosphate restriction. The working group thought that one simple and achievable focus for limiting dietary phosphate across the spectrum of CKD would be a reduction in the consumption of food products containing inorganic phosphate additives. Inorganic phosphates are commonly added to meat, dairy, bread, and snack products, particularly highly processed products, and restructured meat, but may also be added to meat that superficially appears unprocessed, such as beef filet, steaks, and chicken breasts.[49] These "enhanced" products have a phosphate-to-protein ratio on average 28% higher than unadulterated products, with some products almost 100% higher.[49] Furthermore, most, but not all, studies have found these additives, unlike naturally occurring phosphate, to be close to 100% bioavailable, as summarized by St-Jules and colleagues.[50] Although there are approximately 25 approved phosphate-based food additives, Health Canada has yet to systematically review their use. At present, food labels in Canada are not required to include the amount of phosphate—either organic or inorganic—although their

presence must be indicated. In general, the use of food additives must comply with the specifications set by the Joint FAO/WHO Expert Committee on Food Additives. Inorganic phosphate additives fall under the category of GRAS—generally recognized to be safe—and as such, are not subject to significant premarket review.[51] Although this assumption may be reasonable for the general population, it does not adequately address the needs of patients with impaired kidney function who would benefit from knowing the type and quantity of phosphate in the food they consume. Future necessary steps include policy change to mandatory requirement for food manufacturers to include phosphate content on food labels and to disclose the amount of phosphate, both organic and inorganic.

In unadulterated food, protein and phosphate are highly correlated. In a randomized trial of 35 patients, protein restriction (0.6 g/kg/d of high-biological-value protein, compared with usual diet) was shown to reduce 24-hour phosphate excretion; serum phosphate levels were not reported.[52] The risks and benefits of protein restriction are beyond the scope of this work. The 2015 Canadian CSN commentary on the KDIGO guidelines concluded that "the available evidence does not support, and we do not recommend, routine protein restriction (<0.8 g/kg/day) in patients with CKD. Protein restriction may be reasonable for some patients if certain conditions are all met: a well-nourished patient who understands the risks and benefits and the uncertainty about them, who wishes and has the resources to comply with dietary prescription, and who has access to expert ongoing dietary supervision and nutritional assessment, preferably by a dietitian."[2] We felt that the same caveats would apply to protein restriction as a method of restricting phosphate intake. Further to this, a post hoc observational analysis of participants in the Hemodialysis (HEMO) study found that lower prescribed dietary phosphate intake was associated with poorer indices of nutritional status at baseline and predicted greater need for nutritional supplementation, but did not predict longitudinal changes in caloric or protein intake.[53] Compared with other levels of more stringent phosphate restriction, those prescribed 1001 to 2000 mg/d and those with no specified phosphate restriction experienced better survival with hazard ratios 0.73 (95% CI = 0.54-0.97) and 0.71 (95% CI = 0.55-0.92), respectively.[53]

The ratio of protein to phosphate is highly variable between different foods.[54] Phosphate in plant foods is often complexed with phytates, leading to lower bioavailability.[50] Many studies have shown that plant consumption is associated with reduced risk of clinically important outcomes, including an RCT showing that Mediterranean diet pattern decreases cardiovascular outcomes in a high-vascular-risk general population, observational data showing decreased risk of incident CKD, and observational data showing decreased risk of death from all causes in patients with CKD and on dialysis.[55-63] A 1-week cross-over randomized trial of highly controlled vegetarian vs meat-based diets with equivalent phosphate content, conducted in 9 patients, showed decreased 24-hour phosphate, decreased serum phosphate, and decreased FGF-23 during the vegetarian period.[64] These studies, and an increasing awareness of the general undesirability of a restrictive philosophy, have led to an approach to dietary prescription that describes dietary patterns rather than enumerates restrictions. For example, the dietary approaches to stop hypertension (DASH) diet, modified alternate healthy eating index (mAHEI) diet, and Mediterranean diet, all include an emphasis on plant-based products.[55,59,60,62,65] Because of the lower bioavailability of phosphate in plant foods, these ideas may also be helpful for phosphate restriction for selected, motivated patients with CKD, and may have additional health benefits. Our caveats about changing people's diets without careful education and supervision all apply here too. Boiling and discarding the water used in cooking is an established method of reducing the phosphate content of meat and vegetables by 38% to 51%, but many patients are unable to prepare food from scratch, and most socially and culturally acceptable food is cooked using a variety of methods. It may be a useful adjunct for selected patients.[66]

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

4.1.9 CSN:
The CSN committee suggests, for patients with CKD G5D who have persistent and progressive hyperphosphatemia, increasing dialytic phosphate removal, recognizing that this decision will be driven by many other dialysis- and patient-related factors.

Commentary

The working group agreed that intensifying hemodialysis frequency or duration would be an acceptable treatment option for some patients with persistently elevated phosphate levels; however, the decision to intensify dialysis would need to be driven by other factors beyond just phosphate control. In addition, dialysis intensification would need to be balanced against the potential quality of life implications and resource limitations.[67] In peritoneal dialysis, longer dwell times are associated with improved phosphate clearance for low transporters.[68] The working group also thought that phosphate lowering could be achieved with avoidance of any dry time in peritoneal dialysis patients.

Chapter 4.2: Treatment of Abnormal PTH levels in CKD-MBD

4.2.1 KDIGO:
In patients with CKD G3a-G5 not on dialysis, the optimal PTH level is not known. However, we suggest that

patients with levels of intact PTH progressively rising or persistently above the upper normal limit for the assay be evaluated for modifiable factors, including hyperphosphatemia, hypocalcemia, high phosphate intake, and vitamin D deficiency (*2C*).

4.2.1 CSN:
The CSN committee recommends against monitoring or treating serum PTH for patients with CKD G3.
The CSN committee suggests, for patients with CKD G4 and G5NDlevels of intact PTH that are progressively rising or persistently above the upper normal limit for the assay, evaluation for modifiable factors, including hyperphosphatemia, hypocalcemia, high phosphate intake, and vitamin D deficiency.

Commentary

There is strong epidemiological evidence that abnormalities in PTH are unlikely to be severe in CKD G3; therefore, we do not recommend screening or monitoring PTH for patients in this category. We agree with the move away from prescriptive suggestions or recommendations based on absolute values of PTH to a focus on considering trends over time and modifying known, reversible factors. We agree that the focus should remain on patients with abnormalities of PTH that are marked and either progressive or persistent. There is a lack of clear evidence around both optimal targets and treatment impact on important clinical outcomes. This working group supports an overall strategy of monitoring trends in PTH and making clinical decisions incorporating this information as well as the individual patient's risk factors and comorbidities rather than focusing on any one laboratory value in isolation. In Canada, where 32% of the population has insufficient vitamin D levels (40% in winter), whether to routinely assess for vitamin D deficiency or to treat empirically with nutritional vitamin D requires an individualized approach.[19] Patients at high risk of deficiency might benefit from vitamin D measurement and supplementation, or empiric supplementation, according to clinical assessment and judgment.

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

4.2.2 CSN:
The CSN committee recommends against monitoring or treating serum PTH for patients with CKD G3.
The CSN committee suggests, for patients with CKD G4-5D, against the *routine* use of alfacalcidol, calcitriol, and vitamin D analogs.
The CSN committee suggests using alfacalcidol, calcitriol, and other vitamin D analogs for patients with CKD G4-5D who have severe and progressive HPT or who have hypocalcemia.

Commentary

The working group agreed that alfacalcidol, calcitriol, and other vitamin D analogs should not be routinely used in patients not on dialysis based on the lack of evidence of benefit in the PRIMO and OPERA studies as well as the risk of hypercalcemia observed in those trials.[69,70] The working group felt that there are certain situations where these agents might be appropriate to use (1) in patients with CKD G4 and G5 and severe and progressive HPT and (2) in patients with persistent or severe hypocalcemia.

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

4.2.4 CSN:
The CSN committee suggests, for patients with CKD G5D in whom the risks and benefits of PTH-lowering therapy are thought to favor treatment, treating with calcimimetics, alfacalcidol, calcitriol or other vitamin D analogs, or a combination of the 2. Note that the ordering of these statements is alphabetical and does not reflect a hierarchy of preferences, and that calcimimetic funding varies by province.

Implications Within Canadian Health Care

Statement 4.2.4 requires further consideration in the Canadian context. It is worth restating that the ordering of these interventions in the KDIGO document was based on alphabetical order, no other scheme being as acceptable to members of that workgroup, and is not meant to represent a hierarchy of evidence or a pattern for use. There is variable access to calcimimetics across Canadian jurisdictions, and their use within a publicly funded health care system has resource implications. The workgroup's interpretation of the EVOLVE trial of cinacalcet versus placebo in 3883 patients with moderate HPT on hemodialysis is that it failed to show a benefit, based on the primary outcome: For the composite of myocardial infarction, hospitalization for angina, congestive heart failure and peripheral-vascular-disease events, the hazard ratio was 0.93 (95% CI = 0.85-1.02; $P = .11$).[71] On this basis, the CSN workgroup suggests that treatment with calcimimetics be reserved for more severe or refractory HPT and to advocate for policy that publicly funds their use in these situations rather than for wider use.

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

4.2.5 CSN:
The CSN committee recommends against monitoring or treating serum PTH in patients with CKD G3.
The CSN committee suggests, in patients with CKD G4-5D who have severe HPT and who fail to respond to medical therapy, considering parathyroidectomy. The CSN committee suggests it is reasonable to consider parathyroidectomy without having to first "fail" calcimimetics. The common practice of first considering parathyroidectomy and reserving calcimimetics for those who are not surgical candidates remains a reasonable one.

Commentary

Whereas the KDIGO working group suggested parathyroidectomy only when medical therapy fails, it is the CSN working group's opinion that with the limited evidence around calcimimetics, it is not mandatory to trial calcimimetics before considering parathyroidectomy. Although trials directly comparing these treatment strategies are lacking, there is observational evidence that parathyroidectomy results in improvement in biochemical parameters, BMD, fracture risk, and may offer a potential survival benefit in patients with severe HPT. Moreover, parathyroidectomy is cost effective, especially in comparison with the much costlier alternative of cinacalcet.[72-79] As such, it is the CSN working group's opinion that parathyroidectomy remains a useful treatment option in those who are surgical candidates.

Implications Within Canadian Health Care

In many Canadian jurisdictions, parathyroidectomy is considered before the use of calcimimetics, and calcimimetics are reserved for those who are not surgical candidates; in the context of the current evidence, this continues to be a reasonable practice. The decision to pursue parathyroidectomy should consider PTH values, but also patient-specific factors, including symptoms and operative risk, and the drug coverage or affordability of medical management.

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

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

4.3.3 CSN:
The CSN committee, for patients with CKD G3, recommends that BMD measurement and management be practiced according to general population guidelines for osteoporosis, taking into account fracture history, individual risk profiles for osteoporosis, and the renal excretion of some drugs.
The CSN committee, for patients with CKD G4-G5, recommends against routine BMD measurement, or routine treatment of osteoporosis. The CSN committee suggests management of metabolic bone disease (section 3 and sections 4.1 and 4.2), exercise, reduction of tobacco, and alcohol use, and fall-prevention strategies.

Commentary

The CSN working group did not concur that there was evidence to support screening for, and management of, metabolic bone disease in CKD G3. Population data show low prevalence of metabolic abnormalities at this level, and these patients are not well represented in studies of strategies to prevent clinical outcomes in patients with metabolic bone disease. For these patients, we recommended case finding and risk-factor-based screening, and pharmacological fracture prophylaxis guided by risk and patients' preferences.[80] For example, a trial of a specific strategy based on clinical risks using the validated FRAX tool demonstrated a reduction in hip fractures (but not all osteoporotic fractures or all fractures).[80]

The CSN working group did not concur that there was evidence to support screening for, and management of, osteoporosis in CKD G4 and G5.

Alendronate reduced vertebral fractures and all fractures and increased BMD in an RCT of 6458 women.[81] Of these, 581 had creatinine clearance less than 45 mL/min, and 2409 had creatinine clearance 45-59 mL/min. For these women with predominantly CKD G3, there was no evidence of interaction between level of renal function and efficacy of alendronate. However, women with creatinine greater than 112 µmol/L were excluded from the trial, and the number of women included whose creatinine clearance was less than 30 mL/min is estimated at around 30 (data from graph). Meta-analysis of individual patient data from 9 randomized trials of risedronate identified no differences in efficacy across CKD subgroups, and a reduction in vertebral fractures overall; there were 572 women with creatinine clearance less than 30 mL/min included.[82] These 9 trials excluded women with creatinine more than 1.1 times the upper limit of normal; because of this, the subgroup of patients with creatinine clearance less than 30 mL/min has mean age 83 years, mean body mass index 22 kg/m^2, and 75% of patients in this group had clearance in the range 25 to 30 mL/min.

Zoledronic acid led to biochemical acute kidney injury (defined as $>$ 44 µmol/L increase in serum creatinine at 9-11 days postinfusion) in 1.3% of those who received drug

compared with 0.4% of patients receiving placebo, although no effect on long-term kidney function was seen.[83] The trial specifically excluded patients with creatinine clearance less than 30 mL/min; evidence of safety and efficacy are lacking for G4-G5 CKD.

A systematic review and meta-analysis of pharmacotherapy for osteoporosis in subgroups with CKD, defined as CKD G3-G5, concluded that bisphosphonates may slow loss of BMD among transplant recipients (moderate strength of evidence), but their effects on fractures and safety in transplant recipients and others with CKD were unclear.[84] Very few patients with CKD G4 and G5 were included in the original studies, however.[85]

Denosumab was studied in 7868 women aged 60 to 90 years. Overall, denosumab prevented both vertebral and nonvertebral fractures.[86] When patients were categorized by creatinine clearance or MDRD GFR, there was no interaction between treatment and renal function subgroup.[86] In this study, 1078 women had CKD G3; only 17 had CKD G4. Subsequently, reports of severe hypocalcemia after denosumab infusion in patients with CKD G4 and G5 have appeared.[35] The systematic review and meta-analysis of CKD G3 to G5 subgroups (mostly CKD G3) concluded that the effects of denosumab on BMD and fractures are unclear (with very low strength of evidence), and that it may increase risk for some safety outcomes.[84]

Raloxifene reduced vertebral, but not nonvertebral fractures in women after menopause, with no evidence that G3 CKD affected efficacy compared with more normal kidney function; this study included only 55 women with creatinine clearance less than 30 mL/min.[87] The systematic review and meta-analysis of CKD G3 and G5 subgroups (mostly CKD G3) concluded that raloxifene may prevent vertebral fractures but may not increase BMD (low strength of evidence).[84]

In our review, therefore, we did not identify a pharmacological strategy known to provide safe and effective fracture prophylaxis for routine use in patients with CKD G4 and G5 with or without osteoporosis or previous fractures. We believe that prophylactic interventions should only be offered in the setting of clear benefit and known harms, and that these conditions are not met for drugs in the prevention of fractures in patients with CKD G4 and G5.[88] We have therefore recommended against both BMD testing and routine drug treatment for osteoporosis in CKD G4 and G5. However, we recognize bone fragility and fractures as important outcomes in advanced CKD population and that research based on pharmacological interventions should be undertaken. As these drugs work by lowering bone resorption or by stimulating bone formation, there is a rationale that they could potentially be effective in advanced CKD, if treatment is based according to the level of bone turnover. As stated in previous section, it is reasonable for experienced health care workers seeking the optimal strategy for individual patients to include bone biopsy for evaluation of bone turnover if antiresorptive or bone-stimulating agents are to be used. Future clinical studies using bone biopsies will provide more information on the potential validity of this strategy.

It is possible that resistance training or aerobic training may improve BMD, while balance training may reduce the risk of falls.[89-91] Taken together with the known general health benefits of exercise in patients with and without CKD,[92,93] we suggest that patients with CKD G3 to G5 exercise, formulating a plan adapting to their functional level and preferences.[94,95] Also by generalization from the general population, limiting tobacco[96] and alcohol use,[97] fall-prevention strategies,[98] and improving our understanding of frailty[99] may reduce fracture risk, are unlikely to be harmful, and may convey additional health benefits.[80]

Research Recommendations

RCTs of pharmacological strategies (including substudies that include bone biopsies) to prevent fractures in patients with G4 and G5 CKD are needed, examining drugs that affect osteoporosis and those that affect the metabolic bone disease associated with low GFR.

CSN Transplant Workgroup Commentary on Transplant Guidelines

Chapter 5: Evaluation and Treatment of Kidney Transplant Bone Disease

The recommendations for kidney transplant recipients focus on fracture prevention with the traditional approach of assessing fracture risk, assessing bone density in patients at increased risk with adequate kidney function at 3 months, and instituting preventative therapy based on bone density.

5.3 KDIGO:
In patients with CKD G1T-G5T, we suggest that 25(OH)D (calcidiol) levels might be measured, and repeated testing determined by baseline values and interventions (*2C*).

5.3 CSN:
The CSN committee, for patients with CKD G1T-G5T, suggests against routinely screening or monitoring 25(OH)D (calcidiol) levels.

5.4 KDIGO:
In patients with CKD G1T-G5T, we suggest that vitamin D deficiency and insufficiency be corrected using treatment strategies recommended for the general population (*2C*).

5.4 CSN:
The CSN committee, for patients with CKD G1T-G3T, suggests following the population health recommendation of vitamin D supplementation of 400 units daily for people older than the age of 50.

Commentary

The KDIGO guidelines recommend that 25(OH)D (calcidiol) levels might be measured, and recommend vitamin D deficiency and insufficiency be corrected using treatment strategies as in the general population.[100] Canadian Osteoporosis guidelines recommend that 25(OH)D levels be measured in subjects who will receive pharmacological therapy for osteoporosis, those who have sustained recurrent fractures or have bone loss despite osteoporosis treatment, and those with comorbid conditions that affect absorption or action of vitamin D. These recommendations are largely opinion based and only indirectly applicable to kidney transplant recipients.[80] Recent Canadian data demonstrate that at the time of transplant, 36% of patients are vitamin D deficient (<50 nmol/L), and 30% are vitamin D insufficient (50-75 nmol/L),[101] and it is likely that effects of such deficiency are pleomorphic; however, Canadian data show no association between vitamin D status and subsequent rejection.[101] Because the prevalence is known to be high, the costs are low, and harm is unlikely, we suggest routine supplementation rather than routine testing, in keeping with CSN working group's guideline 3.1.3. In CKD G4T and G5T, the prevalence of metabolic bone disease further complicates the issue and available evidence is highly indirect and uncertain, we therefore make no recommendation.

5.5 KDIGO:
In patients with CKD G1T-G5T with risk factors for osteoporosis, we suggest that BMD testing be used to assess fracture risk if results will alter therapy (*2C*).

5.5 CSN:
The CSN committee suggests against routine BMD testing for patients with CKD G1T-5T.
The CSN committee, for patients with CKD G1T to G3T only, suggests BMD testing in those at higher than average risk, or with osteoporotic fracture, or if it will influence prophylaxis decisions.
The CSN committee suggests against BMD testing for patients with CKD G4T to G5T.

Commentary

The fundamental change in the recommendations is the suggestion that BMD be measured (using dual-energy X-ray absorptiometry [DXA]), whereas in the 2009 report, DXA was not recommended.[100] This conditional recommendation is based on evidence that is low quality and indirect: A number of studies in patients with CKD showing that BMD predicts fracture and a single retrospective cohort study of 46 patients with fractures among 238 patients with kidney transplants.[102] No studies have examined the question of whether a strategy involving BMD is superior to a strategy not involving BMD for any clinically important outcome. We also noted that although steroid exposure is a well-known risk factor for osteoporosis, Osteoporosis Canada defines relevant steroid exposure as at least 3 months cumulative therapy in the previous year at a prednisone-equivalent dose of ≥7.5 mg daily.[80] This might encompass the short-term steroid induction regimens used by some transplant programs, but is higher than that used for maintenance immunosuppression protocols. Some Canadian centers withdraw steroids completely, early post transplantation. Furthermore, evidence to inform the management of patients with CKD G4T-5T with reduced BMD is lacking. We recognized that the absence of evidence in this area leads to troubling practice variation with the frequency of BMD testing varying between 16% and 92% across transplant centers in Ontario.[103] We therefore recommend against routine BMD testing as the costs of testing are high—estimated at $600,000 in Ontario between 1994 and 2012.[103] We suggest BMD testing only in those at high risk (ie, patients with greater than standard steroid exposure or other risk factors) or if it will influence prophylaxis decisions (patients with CKD G1T-3T who are prepared to take medications to reduce the risk of fracture, should their BMD be low).

5.6a KDIGO:
In patients in the first 12 months after kidney transplant with an eGFR greater than approximately 30 mL/min/1.73m^2 and low BMD, we suggest that treatment with vitamin D, calcitriol/alfacalcidol, and/or antiresorptive agents be considered (*2D*).

5.6a CSN:
The CSN committee suggests that, for patients in the first 12 months after kidney transplant who have CKD G1-3T and low BMD, fracture prophylaxis with vitamin D, alfacalcidol, calcitriol, and other vitamin D analogs, or antiresorptive agents be considered.

5.6b KDIGO:
In patients in the first 12 months after kidney transplant with an eGFR greater than approximately 30 mL/min/1.73m^2, we suggest that treatment choices be influenced by the presence of CKD-MBD, as indicated by abnormal levels of calcium, phosphate, PTH, alkaline phosphatases, and 25(OH)D (*2C*).

5.6b CSN:
The CSN committee suggests that, for patients in the first 12 months after kidney transplant who have CKD G1-3T and low BMD, prophylaxis decisions be influenced by markers of CKD-MBD (calcium, phosphate, PTH, alkaline phosphatase, and, if measured, 25[OH]D).

Commentary

We recognized that evidence in this area is largely indirect, derived from populations without kidney transplants and without advanced CKD. There are potentially bigger issues that should be addressed. Some of these problems can be mitigated

by better pretransplant care, especially to prevent moderate to severe HPT. Higher PTH levels in transplant recipients are associated with increased mortality and graft loss.[104] Although the mechanism for this increase in risk is unclear, patient and graft loss are of greater significance than fracture. Moreover, fracture risk may be lower in Canadian transplant recipients than previously thought (10-year cumulative incidence of hip fracture was 1.7% in a recent Canadian study, with ≥3% defined as high risk in clinical guidelines).[105]

HPT and hypercalcemia within the first 3 months are prevalent, and may be persistent and severe.[106-108] Treatment with vitamin D analogs to improve bone density may not be helpful, and is relatively contraindicated in those with hypercalcemia.

We noted that these are all decisions around prophylaxis of future fracture, not around treatment.

Implications Within Canadian Health Care

A significant management issue is whether patients with significant HPT should be offered parathyroidectomy pretransplant. This is a major issue in Canada as many provinces will not cover cinacalcet for kidney transplant patients. Pretransplant parathyroidectomy has been associated with better graft survival, whereas post transplant parathyroidectomy has been associated with graft dysfunction, although some of this is transient.[109,110] Even if available, cinacalcet may not prove to be as effective as surgical intervention long term.[111]

5.6c KDIGO:
It is reasonable to consider a bone biopsy to guide treatment (*Not Graded*).

5.6c CSN:
The CSN committee recommends against routine bone biopsy in clinical practice, for patients with CKD G1T-5T (in keeping with CKD G1-5D, section 3.2.2).

5.6d KDIGO:
There are insufficient data to guide treatment after the first 12 months.

5.6d CSN:
The CSN committee makes no recommendation about prophylaxis after the first 12 months. There are insufficient data to attempt to reach consensus.
Beyond the first 12 months of transplant, the workgroup recognized that direct evidence is lacking and that the application of evidence from the general population or the early posttransplant period is increasingly indirect. The working group suggested following the same principles as outlined for the earlier period.

Research Recommendations

The KDIGO research recommendations are reasonable but are focused on fracture risk. A research priority should include a prospective (ideally randomized) comparison between cinacalcet and parathyroidectomy for persistent posttransplant HPT. Outcomes should be patient-important (ie, not just calcium and PTH values); patient-reported outcome measures should be considered. Fracture incidence is important, but outcomes important to transplant patients should also be included: some measure of graft health, life participation, and pain.[112]

CSN Pediatric Workgroup Commentary on Pediatric Guidelines

The CSN pediatric workgroup noted that the overall objective of management of MBD in pediatrics is to optimize growth, which is particularly rapid in the neonate and infant, and during puberty. Given the skeletal growth which occurs throughout childhood, growth-related consequences of the MBD of CKD, including slipped capital femoral epiphysis, genu varum and genu valgus, are a primary consideration in the management of pediatric patients.

3.1.1 KDIGO:
In children, we suggest monitoring levels of calcium, phosphate, PTH, and ALP beginning in CKD G2 (*2D*).

3.1.1 CSN:
The CSN committee suggests monitoring levels of calcium, phosphate, PTH, and alkaline phosphatase, for children with CKD G2-5D or T.

Commentary

The number of pediatric patients with CKD is much smaller than the number of adults; therefore, the societal burden of testing is lower. Moreover, a further potential consequence of error in children includes short stature.[113,114] For these reasons, thresholds for monitoring differ from those suggested in the adult guidelines: CKD G2-G5D in children rather than CKD G4-5D in adults. We suggest monitoring PTH, calcium, phosphate, and ALP as well as growth, blood pressure, assessment of proteinuria, and GFR at least annually, and with increased frequency in patients with lower GFR.[115]

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

3.2.1 CSN:
The CSN committee recommends against routine BMD testing to assess fracture risk in children with CKD.

Commentary

We suggest that fractures, particularly if more numerous than expected for age or nontraumatic in origin, rather than BMD,

should guide therapy (opinion). We suggest that diagnostic testing should be considered only if treatment or prophylaxis (ie, bisphosphonates) is contemplated, in patients with fractures or at above average risk. Under these circumstances, we suggest that treatment decisions should consider sequential changes in DXA results and not be based on a single set of *z*-scores.[116] At present, there are insufficient data to support the use of hip and radius BMD to predict incident fractures in healthy children and adolescents,[117] and no data exist for children with CKD. Moreover, there is significant variability in the availability and interpretation of DXA scans across the country, particularly in children before the completion of puberty. Until there is better evidence and availability of pediatric expertise across the country, we recommend against routine screening of children with DXA. Consequently, the CSN working group does not recommend routine DXA scans in children with CKD.

Research Recommendations

Prospective studies are needed to examine the utility of routine DXA or other scanning modalities for pediatric patients with CKD. We support ongoing research into newer modalities such as microCT,[118] peripheral Quantitative Computed Tomography (pQCT),[119] and High-Resolution peripheral Quantitative Computed Tomography (HR-pQCT)[120] as they may demonstrate superior results in determining fracture risk in this high-risk pediatric population. Research into the utility of thoracolumbar spine radiography to diagnose vertebral fractures, particularly in patients exposed to glucocorticoids, is a priority.[121,122]

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

4.1.2 CSN:
The CSN committee recommends using age-appropriate normal ranges for serum phosphate.
The CSN committee suggests lowering elevated phosphate level toward the normal range for children with CKD G2-G5D.

Commentary

The CSN pediatric working group agrees with this statement for pediatric-aged patients extended to G2, for the reasons summary in 3.1.1, and for consistency with 4.1.1, 4.1.3, and 4.1.6. It is important to note that normal phosphate reference intervals change with age and to aim for an age-appropriate phosphate.[11]

Research Recommendations

The CSN working group agrees that RCTs, with adequate power and longitudinal follow-up, designed to address phosphate targets in pediatric patients with CKD G2-G5D should be conducted. These studies should evaluate the impact of phosphate-lowering strategies on the incidence of patient-important outcomes, including CKD progression in children, and include patient-reported outcomes. The SONG-Kids (Standardized Outcomes in Nephrology for children and adolescents with CKD) initiative, when completed, will be helpful in informing the selection of outcomes.[123]

4.1.3 KDIGO:
In children with CKD G2-G5D, we suggest maintaining serum calcium in the age-appropriate normal range (*2C*).

4.1.3 CSN:
The CSN committee suggests measuring ionized calcium, rather than total calcium or calcium adjusted for albumin, for children with CKD G2-G5D.
The CSN committee recommends using age-appropriate normal ranges for serum ionized calcium.
The CSN committee suggests maintaining the serum ionized calcium in the normal range, for children with CKD G2-G5D.

Commentary

We recommend against using total calcium levels adjusted to serum albumin (adjusted, normalized, or "corrected" calcium) in children with CKD. We suggest that ionized plasma calcium be used both to monitor calcium levels and to make treatment decisions. Levels of albumin are often low in children with CKD. There is strong evidence that calcium levels normalized to serum albumin levels does not improve on total calcium in adults with and without CKD (see guideline 3.1.5), and that it is inaccurate and assay dependent[31,124]; the formula has, to our knowledge, not been studied in children. The number of patients involved and resource implications are limited; while the consequences of error are potentially severe and long-lasting.

4.1.6 KDIGO:
In children with CKD G2-G5D, it is reasonable to base the choice of phosphate-lowering treatment on serum calcium levels (*Not Graded*).

4.1.6 CSN:
The CSN committee suggests, for children with CKD G2-G5D, basing the choice of phosphate-lowering treatment on ionized serum calcium levels.

Commentary

In children with CKD G2-G5D, the ionized serum calcium should be the primary consideration in the choice of phosphate-lowering therapy. Furthermore, when the dose of elemental calcium required to lower phosphate levels toward the normal range exceeds the Recommended Dietary Allowance (RDA) for calcium intake for the child's age

group, one should consider issues of nonadherence and the use of alternative phosphate-lowering strategies.

Research Recommendations

The CSN pediatric working group agrees in principal that RCTs in children and adolescents with CKD should be conducted to determine whether calcium-based phosphate binders, compared with calcium-free phosphate binders, promote bone accrual (as measured by bone density and structure, and rates of fractures), and to determine the impact of phosphate binders on arterial calcification in the context of the high calcium requirement of growing bones. The proposed studies should have sufficient calcium intake at the lower doses to prevent confounding assessments of bone accrual due to low calcium intake. Recent data suggest that increased magnesium in the dialysate decreases vascular calcification propensity.[125] The CSN pediatric working group agrees that prospective clinical and balance studies should examine the role of magnesium as a phosphate binder with regard to patient-centered outcomes, calcification, and long-term cardiovascular event rates.

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

4.2.2 CSN:
The CSN committee suggests that alfacalcidol, calcitriol and other vitamin D analogs may be considered to maintain serum *ionized* calcium levels in the age-appropriate normal range, for children with CKD G2-G5D.

Commentary

The CSN pediatric working group agrees that alfacalcidol, calcitriol, and vitamin D analogs should be used to maintain ionized serum calcium levels in the normal range in children with CKD G2-G5D. The role of vitamin D in growing bone must also be considered in the decision to use calcitriol in these patients. Children with proximal tubular disorders, such as cystinosis, will require monitoring and treatment of ionized calcium levels regardless of GFR.

Research Recommendations

The CSN pediatric working group agrees that multicentre RCTs should be conducted in children to determine the benefits or harm of calcitriol or vitamin D analogs in CKD G2 to G5D; patient-important outcomes, including falls, fractures, sarcopenia, muscle strength, physical function, progression to end-stage kidney disease, cardiovascular events, hospitalizations, life participation, and mortality, should be assessed. Growth, and the development of rickets and bone deformity, should be included as important endpoints in studies that involve children.

Commentary on Adult-Specific Guidelines in the Pediatric Context

3.2.2 KDIGO:
In patients with CKD G3a-G5D, it is reasonable to perform a bone biopsy if knowledge of the type of renal osteodystrophy will impact treatment decisions (*Not Graded*).
The CSN pediatric working group recommends against routine bone biopsy in children with CKD because of the paucity of expertise in both performing and interpreting bone biopsies across the country, particularly in pediatric patients. Moreover, the published pediatric data are not particularly supportive of using this procedure to guide treatment decisions in children.[126] However, if this diagnostic test is used in selected children, we suggest routine double-labeled tetracycline to aid histologic interpretation.

4.1.4 KDIGO:
In patients with CKD G5D, we suggest using a dialysate calcium concentration between 1.25 and 1.50 mmol/L (2.5 and 3.0 mEq/L) (*2C*).
The CSN pediatric working group agreed that this suggestion would also apply to pediatric patients recognizing that there are clinical situations that may be unique to the pediatric population, such as in children with hypocalcemia without significantly increased plasma phosphate, in whom a higher calcium bath might be more appropriate.

4.1.8 KDIGO:
In patients with CKD G3a-G5D, we suggest limiting dietary phosphate intake in the treatment of hyperphosphatemia alone or in combination with other treatments (*2D*). It is reasonable to consider phosphate source in making dietary recommendations (*Not Graded*).
The CSN pediatric working group prioritizes dietary phosphate restriction over other phosphate-lowering strategies for children with CKD. In keeping with the adult working group, we suggest, where possible, restricting inorganic phosphates found in processed foods preferentially over organic phosphate found in foods with minimal or no processing. This enables a diet with RDA of protein for age and, in children, permits growth.[127]

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

In addition to modifiable factors, including hyperphosphatemia, hypocalcemia, high phosphate intake and vitamin D deficiency, the CSN pediatric working group suggests that adequate calcium intake be considered an additional factor of consideration in children with CKD.[128]

4.2.4 KDIGO:
In patients with CKD G5D requiring PTH-lowering therapy, we suggest calcimimetics, calcitriol, or vitamin D analogs, or a combination of calcimimetics with calcitriol or vitamin D analogs (*2B*).
The CSN pediatric working group suggests that there is vastly greater clinical experience with calcitriol and other vitamin D analogs, than with calcimimetics, in children with CKD G2 to 5D. The CSN pediatric working group therefore suggests using calcitriol and vitamin D analogs primarily to lower PTH in children with CKD G2-5D. In children, we recommend against calcimimetics until the long-term effects on a growing skeleton are better understood.

4.3.3 KDIGO:
In patients with CKD G3a-G5D with biochemical abnormalities of CKD-MBD and low BMD and/or fragility fractures, we suggest that treatment choices take into account the magnitude and reversibility of the biochemical abnormalities and the progression of CKD, with consideration of a bone biopsy.
The CSN pediatric working group suggests that, in children, there are other important considerations, including achieving optimal bone growth/BMD and minimizing deformity. If BMD testing is used, we suggest serial, rather than single, BMD measurements should be used to guide therapy.[116]

5.5 KDIGO:
In patients with CKD G1T-G5T with risk factors for osteoporosis, we suggest that BMD testing be used to assess fracture risk if results will alter therapy (*2C*).
Consistent with the CSN transplant working group, the CSN pediatric working group suggests against routine BMD testing in pediatric transplant patients, and suggests using it selectively, for example, in patients with an increased fracture rate, or nontraumatic fractures.

5.6 KDIGO:
In patients in the first 12 months after kidney transplant with an estimated GFR greater than approximately 30 mL/min/1.73m^2 and low BMD, we suggest that treatment with vitamin D, calcitriol, and/or antiresorptive agents be considered (*2D*).

From the pediatric perspective, the CSN pediatric working group agrees with the use of vitamin D and/or calcitriol in children following kidney transplantation but would caution against the use of antiresorptives in this population given that standard steroid-tapering regimens are often sufficient for improvement in BMD in children.[129-131] The long-term effect of inhibiting bone reabsorption in a growing skeleton is currently not known. There are insufficient data to guide treatment recommendations in children with kidney transplants.

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