Canadian Society of Nephrology/
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CSN/SCN

CSN
COMMENTARY

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

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INTRODUCTION

Professional societies throughout the world, including the Canadian Society of Nephrology (CSN), agree there is a need for developing clinical practice guidelines for patients with chronic kidney disease (CKD). However, as illustrated by the case of the plethora of anemia guidelines for CKD that have been completed (and updated) by many national professional societies since 2000,[1-5] creation of guidelines by individual professional societies results in significant duplication of effort. In this context, 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."[6]

The *KDIGO Clinical Practice Guideline for the Diagnosis, Evaluation, Prevention, and Treatment of Chronic Kidney Disease–Mineral and Bone Disorder (CKD-MBD)* represents a 2-year comprehensive effort to review the relevant evidence in CKD-MBD.[6] The CSN congratulates KDIGO on an excellent review of the available evidence.

Although the CSN welcomes the KDIGO evidence synthesis and global clinical practice guidelines initiative, the CSN[1] and other professional societies, including Kidney Disease Outcomes Quality Initiative (KDOQI),[7] believe that local factors require consideration when making recommendations to guide care. As such, the CSN guidelines committee formed a work group to evaluate the KDIGO CKD-MBD guidelines and determine the extent to which they were relevant within a Canadian context. This CSN work group believes that any limitations of these guidelines relate not to the effort of the KDIGO work group, but to the lack of information for the significance of mineral metabolism abnormalities in early-stage CKD, and more specifically, to the lack of conclusive information about how to guide management throughout CKD stages 3-5.

The KDIGO CKD-MBD guidelines focus on the management of children and adults with nondialysis and dialysis CKD and patients with kidney transplants. Given that the focus of the CSN is adults with CKD and the Canadian Society of Transplantation is preparing a commentary on the transplant-specific CKD-MBD guidelines, this commentary focuses on KDIGO guidelines relevant to adults with nondialysis and dialysis CKD. While preparing this commentary, the CSN work group carefully considered 2 recent Canadian sets of guidelines that have addressed mineral metabolism in CKD. These include: (1) the 2006 CSN hemodialysis guidelines,[8] which had a

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target audience of Canadian nephrologists and addressed the management of mineral metabolism in dialysis patients with CKD; and (2) the 2008 CSN guidelines focusing on the overall management of patients with nondialysis CKD targeting general practitioners.[9] Although the present commentary focuses on the KDIGO guidelines, important differences between the KDIGO CKD-MBD recommendations and the relevant CSN guidelines, as well as the reasons for these discrepancies, are noted when applicable.

Although this commentary is most relevant to Canadian nephrologists and specialists who care for patients with dialysis and nondialysis CKD, some of the commentary may be relevant for general practitioners who care for patients with CKD. In general, the CSN work group is of the opinion that CKD-MBD care should not be undertaken by general practitioners; rather, their focus should continue to be on therapies that have proven efficacy in patients with CKD, including cardiovascular risk reduction.

Across the Canadian health care jurisdictions, there is variable but highly restricted access to public funding for expensive medications (including non–calcium-based phosphate binders and calcimimetics), reflecting their high cost and limited outcome data beyond putative surrogate end points.[10] Acknowledging this reality and to maintain consistency with previous CSN guidelines, the resource implications of guidelines were considered when preparing this commentary.[1] The rationale for this is as follows. Given that the budget for health care is finite, directing excessive resources toward expensive marginally effective therapies limits the resources available to be used for other effective therapies.[11,12] In many Canadian jurisdictions, renal programs are responsible for caring for a defined group of dialysis and selected nondialysis patients with CKD with a finite pool of resources.[10] Careful consideration of both an intervention's effectiveness (and the magnitude of effect) and cost is needed to deploy resources to maximize health outcomes for our patients. Because physicians often are in a position to compare the benefits and risks of specific therapies, they should take an active role in deciding which therapies should be made available, by reimbursement, to Canadian patients.

Having said that, an alternate point of view expressed within the CSN is that as nephrologists, we are advocates for our patients, and failure to champion promising therapeutic interventions will lead to inadequate access to novel strategies.[13,14] This viewpoint may be influenced by the poor outcomes for dialysis patients and the belief that strict adherence to principles of evidence-based medicine is limited by the paucity of well-performed randomized controlled trials.[15] In the opinion of this CSN workforce, the KDIGO guidelines in general considered these issues and crafted recommendations that generally were acceptable, avoiding overly prescriptive recommendations when evidence was not definitive. Although this approach may be criticized, the reality is that nephrology has the fewest randomized trials of any medical subspeciality,[15] leading to a slim evidence base available to guide therapy. There is a lack of definitive evidence for potentially promising therapies, and this has led to variation in perspectives of Canadian nephrologists, as well as variation in access to therapies in Canada. The workforce strongly believes that nephrology as a community needs to focus its academic pursuits on improving the nephrology evidence base, and this should be done in partnership with industry and nonindustry funding agencies.

REVIEW AND APPROVAL PROCESS FOR CSN GUIDELINES AND COMMENTARIES

The development and review of this commentary were consistent with CSN policies set out for the conduct of clinical practice guidelines. The CSN guideline committee determined that this commentary was of priority, and a Chair was selected to guide the commentary process. Individual members were selected based on their interest and expertise, taking into consideration relevant conflicts of interest. Commentary development took place during fall 2009 using the original KDIGO CKD-MBD guidelines,[6] as well as the primary documents referenced within this report; additional literature searching was left to the discre-

Box 1. KDIGO Recommendations Concerning Diagnosis of CKD-MBD: Biochemical Abnormalities

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

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 the 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). 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). [*see comments*]

3.1.3. In patients with CKD stages 3-5D, we suggest that 25(OH)D (calcidiol) 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). [*see comments*] 3.1.4. In patients with CKD stages 3-5D, we recommend that therapeutic decisions be based on trends rather than on a single laboratory value, taking into account all available CKD-MBD assessments (1C) [*CSN work group concurs*]

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 practice, rather than the mathematical construct of calcium-phosphorus product (2D).

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 the appropriate interpretation of biochemistry data (1B) [*CSN work group concurs*]

Abbreviations: CKD, chronic kidney disease; CKD-MBD, chronic kidney disease–mineral and bone disorder; CSN, Canadian Society of Nephrology; KDIGO, Kidney Disease: Improving Global Outcomes; PTH, parathyroid hormone.

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tion of individual members. After repeated teleconferences, all authors approved the final text of the commentary. Because this was a commentary rather than a guideline, consensus was sought, and when it could not be achieved, both perspectives are raised. The final document was sent out for peer review by the CSN guidelines committee. The reviews were considered and responded to, with incorporation of further revisions before ratification by the CSN guidelines committee and CSN executive.

STRUCTURE OF THIS COMMENTARY

This commentary does not seek to discuss all KDIGO recommendations; rather, it was our intent to focus commentary on recommendations that are based on better quality evidence (ie, level 1 in the guideline[6]) or are more controversial. The KDIGO recommendations are provided in boxes, with CSN concurrence indicated. Implications and commentary relevant for Canadian health care are offered in the text when appropriate. For some recommendations (typically those that are opinion based), specific comments are not provided in italics.

REVIEW OF KDIGO RECOMMENDATIONS

Diagnosis of CKD-MBD: Biochemical Abnormalities

Commentary on Chapter 3.1

In chapter 3.1, there are 3 level 1 recommendations (Box 1). Our work group believed that one recommendation deserved further discussion; namely, the statement "We recommend monitoring serum levels of calcium, phosphorus, PTH [parathyroid hormone], and alkaline phosphatase activity beginning in CKD stage 3 (1C)" and the suggested monitoring intervals of every 6-12 months in stage 3 CKD. Given that the frequency of abnormalities in serum calcium and phosphorus levels is rare at a glomerular filtration rate (GFR) >40 mL/min (almost no patients with GFR >40 mL/min in a cross-sectional analysis of more than 1,800 patients with CKD stages 3-5 patients had abnormal calcium or phosphorus levels[16]), it is difficult to present a substantive argument in favor of routine measurement of calcium and phosphorus in patients with stage 3 CKD. This is particularly true given that the impact of managing abnormalities in mineral metabolism in patients with stage 3 CKD is

unknown, and most patients will not go on to require dialysis, but instead will die of other causes.[17] Moreover, when one considers that >95% of Canadian patients with stages 3-5 nondialysis CKD have stage 3 CKD,[18] this recommendation may inadvertently direct attention to a cohort of patients without identifiable laboratory abnormalities.

Of note, one other recommendation (level 2C) suggested that "25(OH)D (calcidiol) levels might be measured, and repeated testing determined by baseline values and therapeutic interventions." It was noted that the cost of laboratory tests, particularly measurement of PTH and vitamin D, is significant, and given budget limitations within publicly funded Canadian health care, this could direct resources away from other treatments for which better evidence of benefit is available. For example, the cost of a serum 25-hydroxyvitamin D assay is Can $100 locally. Until the clinical benefit of correcting nutritional vitamin D "insufficiency" has been established within the dialysis population or for patients with stages 4 and 5 CKD, it would seem premature to suggest screening with vitamin D assays. For patients with stage 3 CKD without biochemical evidence of MBD, it is reasonable to expect that the overall benefits of vitamin D supplementation in the general population (800-2,000 U/d) would apply, and Osteoporosis Canada does not recommend screening 25-hydroxyvitamin D assays in the general population for individuals already using routine supplementation.[19]

Implications Within Canadian Health Care

1. Patients with stage 3 CKD usually are managed by primary care practitioners rather than nephrologists. Our work group believed that routine laboratory monitoring for calcium, phosphate, PTH, and alkaline phosphatase is not warranted in stage 3 CKD, particularly in patients being managed exclusively within a general practice. An initial evaluation of laboratory markers of mineral metabolism should occur as GFR approaches 30 mL/min and could occur upon referral to a nephrologist because referral is recommended at GFR of 30 mL/min. Abnormalities in mineral metabolism that are detected by general practitioners should prompt nephrology assessment.
2. Vascular risk reduction must remain the focus of all physicians, particularly primary care physicians, in patients with stage 3 CKD because cardiovascular risk reduction strategies have improved clinical outcomes in patients with stage 3 CKD. In contrast, assessment and management of mineral metabolism in this group of patients has not been shown to improve outcomes and might interfere with the primary focus on vascular risk reduction.

Diagnosis of CKD-MBD: Bone

Commentary on Chapter 3.2

Fractures are more prevalent in patients with CKD stage 5 contrasted with the nonuremic population.[6] This is particularly true of hip fractures in elderly dialysis patients, particularly those with diabetes. The KDIGO working group found little evidence that future fracture risk might be linked specifically to identifiable risk factors or modified by specific therapy. The CSN work group agrees that it is not possible to generalize the extensive epidemiologic characteristics of fractures (and evidence-based therapy) in the general population to patients with CKD.

The diverse spectrum of the metabolic bone disease associated with renal osteodystrophy ranges from extensive deposits of woven bone in hyperparathyroidism to excessive unmineralized osteoid associated with osteomalacia; "adynamic" bone is more normal in structure. Not surprisingly, both bone mass and bone quality within the skeleton can vary widely according to the underlying pathobiological process. For this reason, the KDIGO working group emphasized at several points that bone biopsy with histomorphometric evaluation is the only certain method of classifying the underlying bone disease.

Bone mineral density (BMD) measurements assume a stable ratio of calcium hydroxyapatite to organic matrix within bone to assess "bone mass." In the general population, this relationship is valid enough that a diagnosis of osteoporosis can be made using the World Health Organization T score of −2.5 standard

Box 2. KDIGO Recommendations Concerning 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 treatment with bisphosphonates in patients with CKD-MBD (not graded). [*see comments*]

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 population and BMD does not predict type of renal osteodystrophy (2B). [*see comments*]

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

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 propeptide) and breakdown (such as type I collagen cross-linked telopeptide, cross-laps, pyridinoline, or deoxypyridinoline) (2C). [*CSN work group concurs*]

Abbreviations: BMD, bone mineral density; CKD, chronic kidney disease; CKD-MBD, chronic kidney disease–mineral and bone disorder; CSN, Canadian Society of Nephrology; KDIGO, Kidney Disease: Improving Global Outcomes; PTH, parathyroid hormone.

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deviations less than "peak adult bone mass."[20] Moreover, the combination of age, BMD, and specific additional risk factors (particularly prevalent osteoporotic fractures) allows some prediction of the probability of future fractures in the next 10 years, as recommended by Osteoporosis Canada.[21] However, BMD generally is lower in the dialysis population, particularly at cortical measurement sites (distal radius and hip), and the ability of BMD to predict fractures or other clinical outcomes in dialysis patients is weak and inconsistent. Moreover, in patients with nondialysis CKD stages 3-5 associated with abnormalities in mineral metabolism and dialysis CKD, BMD measurements do not distinguish between histologic types of underlying renal osteodystrophy. For these reasons, we agree that BMD measurements should not be used as a diagnostic tool in CKD stages 3-5 (Box 2). However, it is reasonable to conclude that decreased BMD in patients with stage 3 CKD without biochemical evidence of MBD can still be used to diagnose underlying osteoporosis.

Implications Within Canadian Health Care

1. In clinical practice, bone biopsy in dialysis patients rarely is performed in Canada. In part, this is due to the very limited laboratory services with the ability to process undecalcified bone specimens. With the exception of severe osteomalacia associated with aluminum intoxication, which might still occur in the minority of patients using aluminum-based binders, bone histologic evaluation may provide little additional relevant information that will change management in a way known to improve clinical outcomes.
2. Except in patients with stage 3 CKD without biochemical evidence of MBD, bone densitometry should not be used routinely in CKD stages 3-5D by Canadian nephrologists to form the basis of diagnostic and therapeutic decisions.
3. Although opinion based, it is routine practice in Canada to measure both intact PTH and serum total alkaline phosphatase in dialysis patients, and many nephrologists measure these in nondialysis patients with CKD as well. It is likely that markedly high or low values predict underlying bone turnover.

Diagnosis of CKD-MBD: Vascular Calcification

Commentary on Chapter 3.3

The CSN work group noted that chapter 3.3 referred to patients with stages 3-5 nondialysis and dialysis CKD (Box 3).[6] However, it is important to emphasize that the level of evidence, prevalence, and therapeutic strategies are heterogeneous among the various CKD stages, and most evidence exists for dialysis CKD.

With respect to the first recommendation, it is true that a lateral abdominal radiograph and 2-dimensional echocardiogram may be used to

Box 3. KDIGO Recommendations Concerning 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 calcification as reasonable alternatives to computed tomography–based imaging (2C). [*see comments*]

3.3.2. We suggest that patients with CKD stages 3-5D with known vascular/valvular calcification be considered at highest cardiovascular risk (2A). [*see comments*]

Abbreviations: CKD, chronic kidney disease; CKD-MBD, chronic kidney disease–mineral and bone disorder; KDIGO, Kidney Disease: Improving Global Outcomes.

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detect vascular and valvular calcification. However, it is important to note that population screening is not recommended by KDIGO or existing CSN guidelines because there are many unanswered questions regarding the utility of screening and lack of therapies conclusively shown to improve clinical outcomes in patients with vascular calcification or even treat and/or prevent vascular and valvular calcification.

With regard to the second recommendation, we note that all patients with CKD have increased cardiovascular risk. We agree that patients with vascular/valvular calcification carry an added adverse cardiovascular risk, although there is a large range of risk profile in patients with nondialysis and dialysis stages 3-5 CKD.

Implications Within Canadian Health Care

1. The issue of vascular calcification, particularly given how common it is (as many as 70% of patients with CKD stage 5D have vascular calcification[6]), is important. Although it is associated with higher cardiovascular risk, all patients with CKD are at high cardiovascular risk and aggressive risk reduction should be undertaken. However, there presently is a lack of information to direct management in such patients (see commentary on chapter 4.1).
2. With respect to screening for vascular calcification, our work group believed there were 3 issues: (a) screening, (b) "intentional case finding" in groups believed to be at high risk of vascular calcification, and (c) incidental detection of vascular calcification:
   a) We agree that screening for vascular calcification is not recommended. This is especially true given that effective screening implies that appropriate and effective therapeutic strategies are available. At present, there is a lack of conclusive evidence in support of any therapeutic strategy that may regress vascular calcification or improve clinical outcomes in CKD.
   b) With respect to intentional case finding in patients believed to be at high risk of vascular calcification, this also is not recommended given that predicting vascular calcification accurately is not possible based on clinical characteristics.
   c) It is likely that vascular calcification will be detected incidentally in many patients who are evaluated with x-rays or echocardiography during routine care. Although the work group agrees that the presence of vascular calcification identifies patients who are at higher risk of mortality, the work group was unable to find consensus on whether management should be altered in these patients given the lack of unequivocal evidence of benefit for any management strategy (see commentary on chapter 4.1).

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

Commentary on Chapter 4.1

Most recommendations in Chapter 4.1 are opinion based (Box 4). With respect to the recommendation regarding dialysate calcium concentration, the work group believed there may be selected situations in which a lower or higher dialysate calcium concentration may be considered after careful assessment of risks and benefits. For example, a low (1.0 mmol/L) bath may be considered in selected patients with hypercalcemia, although the risks associated with hypercalcemia need to be balanced against the

Box 4. KDIGO Recommendations Concerning 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). [*see comments*]

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

4.1.3 In patients with CKD stage 5D, we suggest using a dialysate calcium concentration between 1.25 and 1.50 mmol/L (2.5 and 3.0 mEq/L) (2D). [*see comments*]

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). [*see comments*]

4.1.5 In patients with CKD stages 3-5D and hyperphosphatemia, we recommend restricting the dose of calcium-based phosphate binders 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). [*see comments*]

4.1.6 In patients with CKD stages 3-5D, we recommend avoiding the long-term use of aluminum-containing phosphate binders and, in patients with CKD stage 5D, avoiding dialysate aluminum contamination to prevent aluminum intoxication (1C). [*CSN work group concurs*]

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). [*CSN work group concurs*]

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

Abbreviations: CKD, chronic kidney disease; CKD-MBD, chronic kidney disease–mineral and bone disorder; CSN, Canadian Society of Nephrology; KDIGO, Kidney Disease: Improving Global Outcomes; PTH, parathyroid hormone.

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potential risks of intradialytic hypotension and propensity toward arrhythmia.[22] Also, higher calcium concentration could be considered in nocturnal dialysis patients, who are more likely to have a net negative calcium balance,[23] or after parathyroidectomy, when "hungry" bones can cause refractory hypocalcemia. It should be noted that the impact of these strategies on clinical outcomes and the safety of low calcium baths (<1.25 mmol/L) are uncertain (as for all strategies discussed next), although selecting a different calcium dialysate typically will have no impact on costs.

One level 1 recommendation (to restrict the dose of calcium-based phosphate binders and/or dose of calcitriol or vitamin D analogue in the presence of persistent hypercalcemia) stimulated much discussion (Box 4). Although level 1, this recommendation is based on more common sense and observational data than randomized trials. The CSN work group acknowledged that based on the available evidence, limiting calcium intake in the scenarios described is likely to be more beneficial than harmful, although there was no consensus about the best strategy to achieve such a recommendation (discussed next).

There is a clear epidemiologic association and biological plausibility among hyperphosphatemia, net calcium intake, and important negative health consequences for patients with CKD that was shown first in a study of pediatric dialysis patients.[24] However, there is a lack of randomized trial evidence to suggest that maintaining serum calcium and phosphorus levels within the reference range is associated with improvements in clinically important outcomes.[25] Additionally, randomized controlled trials and meta-analyses performed to date do not conclusively support the use of one type of phosphate binder in preference to another for important patient outcomes.[25-28]

Specifically, controversy exists about the efficacy of non–calcium-based phosphate binders (ie, sevelamer and lanthanum) on relevant clinical outcomes (cardiovascular events, mortality, and hospitalization). The largest clinical trial to date, the Dialysis Clinical Outcomes Revisited (DCOR) study, enrolled 2,103 prevalent dialysis patients, allocating patients to

sevelamer or calcium therapy.[25] Although follow-up lasted for 20 months on average, this study had significant method limitations, including a differential loss to follow-up of approximately 50% in both groups and lack of patient blinding. The primary analysis showed no difference in patient survival between study groups (hazard ratio, 0.93 [95% confidence interval, 0.79-1.10]), although secondary analyses suggested a decrease in mortality in patients older than 65 years.[25] Reanalysis of this data set using Medicare claims data (thus ensuring complete follow-up for the primary outcome) showed no difference in mortality overall or in any patient subgroup.[29] One small randomized study of incident dialysis patients suggested improved survival, although this was noted in only adjusted analyses and after extended follow-up after active treatment and the planned study period had ended.[30] Three meta-analyses have compared the impact of non–calcium-based phosphate binders and calcium-based phosphate binders on mortality. One found no difference in survival,[26] whereas 2 found a non–statistically significant 30% decrease in mortality.[27,28] Given the methodological limitations and therefore concern for study validity for the largest trials contributing weight to these meta-analyses (including significant loss to follow-up; ie, >50% in the largest sevelamer and lanthanum trials,[25,31] and lack of patient blinding), the impact of non–calcium-based binders on clinically relevant outcomes is uncertain.

Given how common vascular calcification is in dialysis patients, many cases are likely to be detected incidentally. In patients with arterial calcification and hyperphosphatemia, KDIGO recommends restricting the dose of calcium-based phosphate binders. Presumably, implementation of this recommendation may require the use of more frequent dialysis or of much longer duration or the use of non–calcium-based phosphate binders, which are more than 20-fold more expensive than calcium carbonate. If the cost of non–calcium-based phosphate binders was similar to that of calcium-based binders, our work group believed that use of such binders would be much less controversial. However, this is not the case.

The recommendation by KDIGO to limit the use of calcium-based binders in the scenarios outlined (and presumably use non–calcium-based binders) generated significant discussion, and our work group could not reach consensus. Given the lack of conclusive evidence of benefit, the lack of randomized trials that have assessed morbidity and mortality in patients with vascular calcification, and the expense of sevelamer and lanthanum, several members believed that use of these agents was not justified until further evidence of clinical benefit could be established in valid randomized trials. Moreover, these members believed that such a recommendation would make it less likely that the randomized trials needed to investigate the efficacy of these agents would be performed. Given the recent drawn-out experience with hemoglobin normalization in patients with end-stage renal disease,[32] largely supported by similar lines of observational evidence, this situation is far from optimal.

Alternatively, other members believed that the use of non–calcium-based binders in the situations recommended or suggested by KDIGO was justified on theoretical grounds, the existing randomized controlled trials were underpowered to show statistically significant benefit, recent meta-analyses suggest clinical benefit, and calcium-based phosphate binders are likely to cause positive calcium balance in late stages of CKD and have never been proven to be safe.

Implications Within Canadian Health Care

1. Although recommendations regarding the use of dialysate calcium concentrations of 1.25-1.5 mmol/L are reasonable, there may be scenarios in which higher or lower calcium concentrations may be considered.
2. The work group recommendations are similar to the recent Canadian guidelines noted previously,[8,9] with the exception that non–calcium-containing phosphate binders were not recommended within the CSN guidelines for nondialysis patients because of a lack of morbidity and mortality data.
3. Variation in access and practice currently exists in Canada with respect to the potential strategies mentioned, including nocturnal or extended-hours hemodialysis and use of non–calcium-based binders. Within Canada, other mechanisms to decrease serum phosphate levels and the amount of

Box 5. KDIGO Recommendations Concerning 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 are first 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). [*see comments*]

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

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). [*see comments*]

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

It is reasonable that the initial drug selection for the treatment of increased PTH levels be based on serum calcium and phosphorus levels and other aspects of CKD-MBD (not graded). It is reasonable that calcium-based or non–calcium-based phosphate-binder dosage be adjusted so that treatments to control PTH levels do not compromise levels of phosphorus and calcium (not graded). We recommend that in patients with hypercalcemia, calcitriol or another vitamin D sterol be reduced or stopped (1B). [*CSN work group concurs*]

We suggest that in patients with hyperphosphatemia, calcitriol or another vitamin D sterol be reduced or stopped (2D). [*CSN work group concurs*]

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). [*CSN work group concurs*]

4.2.5. In patients with CKD stages 3-5D with severe hyperparathyroidism that fail to respond to medical/pharmacologic therapy, we suggest parathyroidectomy (2B). [*see comments*]

Abbreviations: CKD, chronic kidney disease; CKD-MBD, chronic kidney disease–mineral and bone disorder; CSN, Canadian Society of Nephrology; iPTH, intact parathyroid hormone; KDIGO, Kidney Disease: Improving Global Outcomes; PTH, parathyroid hormone.

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calcium-containing phosphate binders in hypercalcemic patients with CKD stage 5D may need to be explored until better quality evidence in support of more expensive options is available. This might include intensive dietary intervention including avoidance of processed foods, lower dialysate calcium, longer dialysis duration (nocturnal, in center, or at home), use of magnesium-based phosphate binders, and parathyroidectomy.

Treatment of Abnormal PTH Levels in CKD–MBD

Commentary on Chapter 4.2

Within this section, there is only one relatively strong recommendation, that "vitamin D sterols or calcitriol be reduced or stopped in patients with hypercalcemia," with the rest of the recommendations being based on weak evidence (Box 5). In contrast to previous KDOQI guidelines on mineral metabolism,[33] these guidelines are much less prescriptive and do not provide specific targets for therapy other than to suggest an intact PTH level of 2-9 times the reference range. The KDIGO guidelines are similar to the CSN guidelines,[8] emphasizing the importance of increased phosphate and calcium levels rather than PTH levels.

Although some clinicians may believe that the present KDIGO guidelines are not helpful in patient management, the following points should be emphasized: (1) the level or range of intact PTH levels that are associated with or determine bone health or cardiovascular health are unknown; (2) increased PTH levels have been associated with cardiovascular events, but the association is not as strong as for hyperphosphatemia and there are no randomized trials that have shown decreasing PTH levels to be associated with better clinical outcomes; (3) low PTH levels seem to be as common, if not more common, than increased levels, and options for reversing this or the implications of such a reversal are not well worked out; and (4)

previous studies of vitamin D, vitamin sterols, and calcimimetics in patients with CKD have either been of poor quality and/or have used biomarkers as the study outcomes, rather than clinical end points.

Implications Within Canadian Health Care

1. The KDIGO intact PTH targets are similar to those recommended by the CSN (10.6-53 pmol/L)[8] and seem reasonable pending further evidence. Treatment when iPTH level increases to >53 pmol/L with symptoms of hyperparathyroidism should be considered.
2. The CSN work group believes that parathyroidectomy remains a reasonable alternative for patients with severe hyperparathyroidism that fails to respond to other therapy, although the work group believes that the indication for parathyroidectomy should be based on symptoms or signs associated with an increased PTH level, such as resistant anemia, intractable pruritis, or other manifestations, rather than PTH level alone. This decision needs to integrate information about the individual patient's perioperative risk because studies suggest a mean 30-day mortality risk after parathyroidectomy of 3.1%, which can be substantially greater in some patient subgroups (eg, those with diabetes).[34]
3. In current clinical practice, calcitriol, vitamin D analogues, calcimimetics, or a combination of calcimimetics and calcitriol or vitamin D analogues are used to medically decrease PTH levels. However, there is variable but highly restricted access to public funding for calcimimetics across Canada as a result of their high cost and limited outcome data beyond PTH lowering. As such, the options available to most Canadian patients with end-stage renal disease include dietary modification, phosphate binders, and vitamin D analogues alone.

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

Commentary on Chapter 4.3

Dialysis patients who present with intercurrent fractures present a particular therapeutic dilemma because fractures are common and there is no evidence to date that any therapy decreases the risk of fracture in dialysis patients. With respect to nondialysis CKD, the CSN work group noted that post hoc analyses of the pivotal clinical trials evaluating antiresorptive therapies allow some recommendations concerning these agents in managing osteoporosis in patients with impaired kidney function. In patients with CKD stages 1-2, there is good evidence that the efficacy of bisphosphonates and raloxifene is not impaired. The same can be said of these agents in patients with CKD stage 3, provided that these individuals have no underlying biochemical evidence of CKD-MBD. These recommendations follow from the post hoc analyses of pivotal phase 3 randomized clinical trials of these agents, in which patients were enrolled with various degrees of kidney disease (though all participants were required to have normal biochemical parameters of vitamin D and parathyroid function). Thus, the CSN work group agrees that management of future fracture risk reduction should be no different in these patients than for the general population (Box 6).

In patients with advanced stage 3 CKD with evidence of biochemical abnormalities in mineral metabolism, as for patients with stages 4 and 5 CKD, the work group could find little evidence on which to base therapeutic recommendations (Box 6). There are no data to support either the safety or the efficacy of bisphosphonates, estrogens, or selective estrogen receptor modulators to prevent fractures in this population.

Implications Within Canadian Health Care

1. In patients with stages 1 and 2 CKD, together with those with stage 3 CKD without evidence of abnormalities of mineral metabolism, it is reasonable to assess and treat patients for their risk of osteoporosis according to the current guidelines established for the general population by Osteoporosis Canada (www.osteoporosis.ca). Management would include assessment of future fragility fracture risk based on age, sex, prior osteoporotic fracture, BMD and other significant risk factors, including glucocorticoid use. Management would include routine supplementation with vitamin D (1,000-2,000 U/d)

Box 6. KDIGO Recommendations Concerning 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, as identified by World Health Organization criteria, we recommend management as for the general population (1A). [*CSN work group concurs*]

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 World Health Organization criteria, we suggest treatment as for the general population (2B). [*see comments*]

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 the biochemical abnormalities and progression of CKD, with consideration of a bone biopsy (2D).

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). [*see comments*]

Abbreviations: BMD, bone mineral density; CKD, chronic kidney disease; CKD-MBD, chronic kidney disease–mineral and bone disorder; CSN, Canadian Society of Nephrology; KDIGO, Kidney Disease: Improving Global Outcomes; PTH, parathyroid hormone.

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and calcium (1,000-15,00 mg/d total elemental calcium intake) and specific pharmacotherapy, including bisphosphonates when appropriate.

2. For patients with stage 3 CKD who have abnormalities in mineral metabolism and those with more advanced CKD stages, there is no evidence to support the safety or therapeutic efficacy of the therapies currently used to reduce the risk of fractures in the general population. Although nutritional vitamin D insufficiency/deficiency is common in the dialysis population, the clinical harm resulting from this has not been defined, and there is no evidence for benefits resulting from supplementation to "sufficient" levels of serum 25-hydroxyvitamin D (>75 nmol/L). It is not reasonable to generalize the clear benefits of bisphosphonates to reduce fracture risk in the nonuremic population to the dialysis population.

CONCLUSION

In many ways, nephrologists should be chagrined by the situation we find ourselves in when attempting to care for dialysis patients in general and in particular with respect to mineral metabolism. It is clear that abnormalities in mineral metabolism are associated with adverse clinical outcomes. However, our management is driven largely by results of observational trials because the number of clinical trials is limited and existing clinical trials often are underpowered or use nonclinical outcomes.

Future changes in care should be driven by adequately powered randomized trials with clinical end points. The challenge is to create an environment that promotes advances in CKD care, stimulates randomized trials, increases evidence-based nephrology practice, and encourages industry and public research funders to support this. Moreover, it important to satisfy provincial health ministries that nephrologists are reasonable in terms of balancing access to promising new treatments while acknowledging that resources directed to therapies with an incomplete evidence-base might direct resources away from other effective therapies. Perhaps a more general discussion of how to accomplish these goals for our data-impoverished discipline should take priority over the production of specific guidelines for the time being. Specifically, the nephrology community must be a willing partner in conducting randomized trials and create a culture that stimulates and values the production and implementation of such research.

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APPENDIX

Conflict of Interest Information for Work Group Members

CSN Member	Type of Potential Conflict of Interest	Role	Period	Sponsor[a]
Chan	None			
Hodsman	Advisory Board	Advisory Board	2006-2009	Shire
Jindal	Speaker	Speaker	2006-2009	Novartis, Boehringer-Ingelheim Canada, Pfizer
	Industry clinical trial	Site Investigator	2006-2009	Amgen
Klarenbach	Consultant	Consultant	2006-2009	Canadian Agency for Drugs and Technology in Health
	Unrestricted research grant; investigator initiated	Coinvestigator (Alberta Kidney Disease Network)	2006-2008	Amgen
Manns	Unrestricted research grant; investigator initiated	Coinvestigator (Alberta Kidney Disease Network)	2006-2008	Amgen
Mendelssohn	Speaker	Speaker	2006-2009	Amgen, Ortho Biotech, Genzyme, Shire, Roche, Baxter, Bayer
	Advisory Board	Advisory Board	2006-2009	Amgen, Ortho Biotech, Genzyme, Shire, Roche, Baxter, Astra Zeneca
	Research grant, multicenter studies	Principal Investigator	2006-2009	Ortho Biotech
	Research grant	Site Investigator	2006-2009	Amgen
Soroka	Speaker	Speaker	2006-2009	Amgen Canada, Genzyme, Shire
Zimmerman	Advisory Board/Speaker	Speaker, Advisory Board	2006-2009	Amgen
	Speaker	Speaker	2006-2009	Ortho Biotech, Aventis

Note: Information provided concerns the past 3 years.

Abbreviation: CSN, Canadian Society of Nephrology.

[a]List restricted to companies that make products for the management of mineral metabolism and companies that make dialysis technology.