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The new kidney disease: improving global outcomes (KDIGO) guidelines – expert clinical focus on bone and vascular calcification

G. London[1], **D. Coyne**[2], **K. Hruska**[3], **H.H. Malluche**[4], and **K.J. Martin**[5]

[1]Service de Néphrologie, Centre Hospitalier Manhès, Fleury Mérogis, France

[2]Renal Division, Washington University School of Medicine

[3]Department of Pediatrics, Renal Division, Washington University, Saint Louis, MO

[4]Division of Nephrology, Bone and Mineral Metabolism, University of Kentucky, Lexington, KY

[5]Division of Nephrology, Saint Louis University, Saint Louis, MO, USA

Abstract

Chronic kidney disease-mineral and bone disorder (CKD-MBD) defines a triad of interrelated abnormalities of serum biochemistry, bone and the vasculature associated with chronic kidney disease (CKD). The new kidney disease: improving global outcomes (KDIGO) guidelines define the quality and depth of evidence supporting therapeutic intervention in CKD-MBD. They also highlight where patient management decisions lack a strong evidence base. Expert interpretation of the guidelines, along with informed opinion, where evidence is weak, may help develop effective clinical practice. The body of evidence linking poor bone health and reservoir function (the ability of bone to buffer calcium and phosphorus) with vascular calcification and cardiovascular outcomes is growing. Treating renal bone disease should be one of the primary aims of therapy for CKD. Evaluation of the biochemical parameters of CKD-MBD (primarily phosphorus, calcium, parathyroid hormone and vitamin D levels) as early as CKD Stage 3, and an assessment of bone status (by the best means available), should be used to guide treatment decisions. The adverse effects of high phosphorus intake relative to renal clearance (including stimulation of hyperparathyroidism) precede hyperphosphatemia, which presents late in CKD. Early reduction of phosphorus load may ameliorate these adverse effects. Evidence that calcium load may influence progression of vascular calcification with effects on mortality should also be considered when choosing the type and dose of phosphate binder to be used. The risks, benefits, and strength of evidence for various treatment options for the abnormalities of CKD-MBD are considered.

Keywords

kidney disease: improving global outcomes; chronic kidney disease; mineral and bone disorder; phosphorus; renal bone disease

Correspondence to: Dr. G. London, Service de Néphrologie, Centre Hospitalier Manhès, 8 rue Roger Clavier, 91712 Fleury-Mérogis Cedex, France, glondon@club-internet.fr.

Conflict of interest

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Introduction

The new kidney disease: improving global outcomes (KDIGO) guidelines are intended to define the quality and depth of evidence used to support therapeutic intervention in chronic kidney disease-mineral and bone disorder (CKD-MBD), and offer expert evidence-based opinion on management [1]. According to the KDIGO mission statement, this represents an attempt to improve the care and outcomes of kidney disease patients worldwide.

The new KDIGO guidelines are most rigorous and helpful when recommending management based on strong evidence and highlighting where management decisions cannot be offered due to lack of sufficient evidence. CKD-MBD encompasses a complex triad of interrelated abnormalities, and given the gaps in evidence and inability to create a simple treatment algorithm, we present our interpretation of the guidelines, along with informed opinion where evidence is weak, to help guide effective clinical practice.

Bone disease in CKD-MBD

Improvement of renal bone disease should be one of the primary aims of treatment within CKD-MBD, as an increasing body of evidence links impaired bone health and diminished reservoir function (the ability of bone to buffer calcium and phosphorus)with vascular calcification and ultimately, cardiovascular events [2, 3, 4, 5, 6, 7, 8]. Recent studies have highlighted the involvement of bone morphogenetic proteins and associated signaling components in a sequence of molecular events that result in ossification of the vasculature [9, 10]. This process begins with the loss of expression by the vasculature of constitutive inhibitory proteins, and ends with the expression of chondrocytic, osteoblastic, and osteoclastic-associated proteins that orchestrate the process of calcification [10]. It is unclear if there is a direct causal relationship between bone health and calcification or if this is a common calcification pathway as part of the CKD-MBD disease process. It remains to be proven that normalization of bone parameters slows progression or regresses vascular calcification. Nevertheless, the high mortality associated with fractures in patients with CKD Stage 5D (i.e. on dialysis) demonstrates a clear need to treat bone disease in CKD-MBD [11].

The spectrum of renal bone disease in patients with CKD Stage 5D has changed over the past 20 years, from a predominance of high-turnover bone disease [12, 13, 14] to a greater prevalence of low-turnover bone disease (40 – 70%) today [15, 16, 17] despite the absence of aluminum accumulation in bone. This change is believed to be due to an ageing dialysis population, increased prevalence of diabetes mellitus and the effects of therapy (including dialysate calcium, calcium-based phosphate binders and over-suppression of parathyroid hormone (PTH) with vitamin D receptor activators (VDRAs) or calcimimetics). Left untreated, increasing bone turnover results in hyperparathyroid bone disease, while treatment with calcium, VDRAs and calcimimetics can lead to low-turnover adynamic bone disease. These states can weaken bone thereby increasing fracture risk, and may also be associated with vascular calcification [6, 18]. The goal of treatment of CKD-MBD is to prevent the extremes of bone turnover.

Biochemical assays, such as PTH and alkaline phosphatase (AP) are imperfect predictors of bone turnover, while bone biopsy remains the only accurate method for diagnosis of renal bone disease [19]. The classification system of renal osteodystrophy based on measures of bone turnover, mineralization and volume (endpoint for balance) requires bone histology [20, 21]. KDIGO suggests that it is reasonable to perform a bone biopsy in various settings including, but not limited to, unexplained fractures, persistent bone pain, unexplained hypercalcemia or hypophosphatemia and possible aluminum toxicity, in patients with CKD Stages 3 – 5D. These indications for bone biopsy are observed in relatively few patients and

typically reflect extreme changes in bone pathology. As it is unrealistic to routinely collect bone biopsies from patients with CKD-MBD, we suggest that imaging techniques and interpretation of trends in biochemical parameters, currently under evaluation, be employed for screening and management purposes.

We suggest that observation of the trend in PTH levels (along with AP) is the most appropriate assessment for inferring levels of bone turnover. However, variability and lack of standardization among PTH assays limits the value of PTH as a diagnostic tool [22, 23]. Extremely high or low PTH levels greatly increase the likelihood of high and low bone turnover, respectively, in a particular patient. Ethnicity should also be considered when assessing PTH levels, as Black patients may warrant a somewhat higher PTH to avoid low bone turnover [24]. Unfortunately, intact PTH levels close to or within the range recommended by the 2003 Kidney Disease Outcomes Quality Initiative (KDOQI) guidelines (150 – 300 pg/ml (15.8 – 31.5 pmol/l)) [25] are poorly predictive of bone turnover status.

Levels of several other biochemical markers, including total AP, bone-specific AP (BSAP), osteocalcin, procollagen Type 1 C-terminal peptide (P1CP), procollagen type 1 N-terminal propeptide (P1NP), insulin-like growth factor (IGF)-1 and tartrate-resistant acid phosphatase correlate to some extent with bone turnover [26]. However, correlations alone are not sufficient for diagnosis. AP is routinely measured in clinical practice, usually reflects BSAP and has a similar predictive value for bone turnover as PTH. An elevated AP is associated with increased risk of death in patients with CKD Stage 5D, and may warrant intensifying treatment of secondary hyperparathyroidism. Each of these markers has problems; for example BSAP may be produced during extra-skeletal calcification as well as by bone itself [27]. New biomarker candidates are being investigated using systems biology approaches, including data integration, bioinformatics analyses and functional testing of novel hypotheses [28]. However, at present, analysis of serial PTH levels is the best biochemical tool available for assessment of bone turnover.

Measures of mineralization and volume are also critical to the assessment of bone status, although the only effective way of assessing bone mineralization is by biopsy. Femoral dual energy X-ray absorptiometry (DEXA) is a good non-invasive measure of cortical bone volume, but DEXA of the spine does not give reliable information on cancellous bone volume [29]. Quantitative computed tomography (QCT) is also a viable option to assess bone volume. Unfortunately, we lack large studies demonstrating the relationship between treatments for secondary hyperparathyroidism and changes in these measurements of bone status, or clinical endpoints such as fracture rates. Current evidence does not support a role for imaging in the diagnosis of renal bone disease in patients with CKD [29].

Biochemical abnormalities of CKD-MBD

In patients with an estimated glomerular filtration rate of less than 60 ml/min/1.73 m^2, the KDIGO guidelines recommend monitoring of serum phosphorus, calcium, PTH and AP based on the presence and magnitude of abnormalities, and rate of CKD progression (Table 1).

There is often a tendency to make recommendations based on population data, rather than treating patients as individuals. Unfortunately this reflects an underestimation of the complexity of CKD-MBD, and the importance of patient demographics (e.g. age and race), co-morbidities (including diabetes) and nutritional status is often overlooked. These parameters influence normal ranges for biochemical parameters (phosphorus, calcium and PTH) in different patient populations.

Itis also easyto consider and treatthe different biochemical abnormalities of CKD-MBD (phosphorus, calcium, PTH and vitamin D) in isolation. These abnormalities are interrelated, and intervention to correct one parameter may influence trends in others. As recommended by KDIGO, it is appropriate to guide treatment decisions by examining temporal trends in all CKD-MBD assessments, rather than treating individual numbers.

Phosphorus

As a signaling molecule central to the pathogenesis of CKD-MBD, including vascular calcification [30], it is imperative to treat abnormalities in phosphorus homeostasis. The KDIGO guidelines suggest that in patients with CKD Stages 3 – 5, serum phosphorus levels should be maintained within the normal range (Table 2). In patients with CKD Stage 5D, elevated serum phosphorus levels should be lowered towards the normal range. By comparison, the 2003 KDOQI guidelines recommended treatment of serum phosphorus levels to 3.5 – 5.5 mg/dl (1.13 – 1.78 mmol/l) in patients with CKD Stage 5D [25]. The more ambitious nature of the KDIGO targets reflects recent evidence from observational studies linking serum phosphorus levels, even within the upper reaches of the normal range, with increased mortality risk not only in patients with CKD-MBD, but also in the general population [31, 32, 33, 34].

While hyperphosphatemia is clearly associated with mortality, there is growing belief that total phosphorus burden should instead be the target of therapeutic intervention, although a lack of outcomes evidence currently prevents advocacy of pharmaceutical intervention in normo-phosphatemic patients. As serum phosphorus represents less than 1% of exchangeable phosphorus [3], serum measurements do not accurately reflect total burden. Indeed, serum phosphorus levels do not rise until the later stages of CKD [33, 35, 36]. Alternative markers of phosphorus load (e.g. FGF-23) and their relationship with mortality are currently being investigated [37]. In the meantime, examination of dietary history and assessment of serum and urine samples may allow assessment of phosphorus load, despite acknowledged difficulties associated with 24-h urine collection. While the fractional excretion of phosphorus rises with decreasing glomerular filtration rate, only a careful assessment of phosphate intake and urinary excretion can detect an increase in total body phosphorus load [3, 35].

Nutritional status is also an important factor when considering intervention to treat abnormalities in phosphorus homeostasis. While the KDIGO guidelines note that reduction of phosphorus in the diet of patients with CKD Stages 3 – 5D is effective, this strategy may be associated with the risk of malnutrition, and may contribute to the increased risk of mortality associated with low serum phosphorus levels.

We recommend maintenance of good nutrition and pharmacological intervention to attempt to reduce serum phosphorus levels to within the normal range in patients with CKD Stages 3 – 5D. In dialysis patients, 3.5 – 4.5 mg/dl (1.13 – 1.45 mmol/l) may be ideal, although present interventions prevent attainment of these targets in the large majority of patients. The desired reduction of serum phosphorus should be balanced against the cost of interventions and the burden (including quality of life) on the patient.

Calcium

In patients with CKD Stages 3 – 5D, the KDIGO guidelines suggest maintenance of serum calcium levels within the normal range (approximately 8.5 – 10.0 or 10.5 mg/dl (2.1 – 2.5 or 2.6 mmol/l) [1]; this is consistent with the KDOQI guidelines [25]. KDIGO suggest it is reasonable that phosphate-binder choice for use in a particular patient should be influenced by CKD stage, other components of CKD-MBD, concomitant therapies, and side-effect

profile (Table 3). The available data from randomized, controlled trials is insufficient to allow KDIGO to guide phosphate binder choice for all patients.

The presence of vascular calcification is associated with cardiovascular mortality [38]. While vascular calcification may be present in young patients [39], age is the most consistent risk factor for calcification [2]. The prevalence of vascular calcification is also particularly high among the diabetic population [40]. These factors should be considered when choosing suitable interventions to treat serum phosphorus levels as CKD progresses.

In addition to excess phosphorus burden, excess calcium load from calcium-based phosphate binders has been linked with the progression of vascular calcification [39, 41]. However, in our opinion, it is acceptable to use calcium-based phosphate binders in young non-diabetic patients with the early stages of CKD, who have low serum calcium levels, increasing intact PTH levels, and no evidence of vascular calcification. Here, calcium will bind dietary phosphorus and suppress the rise in PTH levels. However, small doses of VDRAs may be more appropriate than use of calcium-based binders, as vitamin D is required both for efficient absorption of calcium and its incorporation into the skeleton. Use of calcium supplements to maintain normal serum calcium may also be appropriate if non-calcium-based phosphate binders are used.

In patients with CKD Stage 5D, we agree with the opinion of the 2003 KDOQI guidelines [25], that calciumintake should be limited, despite limited direct evidence to support choice of the following values. In general, the total dose of elemental calcium provided by the calcium-based phosphate binders should not exceed 1,500 mg/day, and the total intake of elemental calcium (including dietary calcium) should not exceed 2,000 mg/day. Given average daily phosphate intakes and the binding capacity of calcium, it is extremely difficult in practice to adequately control phosphorus load without exceeding the recommended calcium intake. Therefore, use of non-calcium-based phosphate binders should be considered.

Non-calcium-based phosphate binders should also be used in preference to calciumbased agents in patients with elevated serum calcium levels as the use of calcium-based phosphate binders has been associated with higher serum calcium and more frequent episodes of hypercalcemia when compared with non-calcium-based binders [42, 43].

As the use of calcium based binders has been linked with reduced bone activity and the progression of vascular calcification [5, 41], the use of non-calcium-based phosphate binders may be more appropriate in patients with evidence of vascular calcification, or histological evidence of impaired bone health, although further research is required to support this recommendation.

Compared with calcium-based binders, lanthanum carbonate and sevelamer hydrochloride are less likely to lead to adynamic bone disease caused by over-suppression of PTH levels [16, 44, 45, 46]. This positive effect on bone health and reservoir function may influence the progression of vascular calcification. In a number of studies, including the treat-to-goal [47] and renagel in new dialysis patients (RIND) [42] trials, the noncalcium-based phosphate binder sevelamer hydrochloride was shown to attenuate the progression of arterial calcification in CKD patients when compared with the use of calcium-based binders. However, the calcium acetate renagel evaluation (CARE-2) study [48] failed to find a difference in the progression of vascular calcification in hemodialysis patients between sevelamer hydrochloride and calcium acetate. CARE-2 used statin therapy to lower low-density-lipoprotein cholesterol to a similar degree in both of the treatment groups, and this may account for its result differing from previous studies [42, 47]. The CARE-2 study also had a higher baseline prevalence of diabetic nephropathy and smoking, both calcification

risk factors, which might have overwhelmed any beneficial effects of a non-calcium-based phosphate binder [49].

The dialysis clinical outcomes revisited (DCOR) study [50] showed no difference in survival between patients randomized to the non-calcium-based binder sevelamer hydrochloride versus calcium-based binders over 2 years in a large but underpowered study. However, there was evidence that older patients may have a survival benefit from noncalcium-based binder treatment, as indicated by results from a subgroup of patients aged ≥ 65 years [50]. Similar to sevelamer hydrochloride, lanthanum carbonate treatment was shown, in a post-hoc analysis, to have a positive effect on survival compared with mainly calcium-based binders, in patients aged > 65 years [51].

Despite the conflicting results from the RIND and CARE-2 studies, and the relatively short duration and design problems of the DCOR study, we still advocate use of noncalcium-based phosphate binders when there is evidence of vascular calcification in patients with CKD Stages 3 – 5D.

PTH and vitamin D

Increasing PTH levels is an adaptive response to the progressive effects of CKD and is desirable to limit the detrimental effects on serum calcium, phosphorus and bone until it becomes maladaptive (i.e. parathyroid gland hyperplasia and osteitis fibrosa). It is very difficult to guide reduction of PTH levels to an ideal target range as age, race and diabetes status all influence “normal” PTH levels in different populations. The afore-mentioned assay variability and lack of standardization make this task even more problematic [22]. Therefore, it makes particular sense to evaluate trends in circulating PTH to guide therapy, with a general goal of a stable and lower PTH than prior to treatment.

As noted by KDIGO, the optimal PTH level is not known for patients with CKD Stages 3 – 5 not on dialysis. KDIGO suggests that in patients with levels of intact PTH above the upper limit of normal (ULN) for the assay, modifiable factors (i.e. hyperphosphatemia, hypocalcemia, and vitamin D deficiency) are evaluated and treated. If intact PTH levels progressively rise and persist above the ULN for the assay despite correction of modifiable factors, treatment with VDRAs is suggested. Observational studies report an increased relative risk of death in patients with CKD Stage 5D who have intact PTH values at the extremes (< 2 or > 9 times the ULN for the assay) [1]. KDIGO therefore suggest maintenance of circulating intact PTH levels to within the range of 2 – 9 times the ULN for the assay, with marked changes resulting in treatment decisions aimed at preventing progression to levels outside of this range (Table 4).

Treatment of vitamin D deficiency with VDRAs directly lowers PTH levels, and will increase calcium absorption, which further lowers PTH levels. With adequate 25-hydroxyvitamin D, VDRAs prevent osteomalacia resulting from vitamin D deficiency at all stages of disease. This is a more appropriate course than supplementation with calcium in the absence of hypocalcemia. However, overuse of VDRAs can result in hypercalcemia, with the potential for the adverse cardiovascular effects described previously.

Calcimimetics, such as cinacalcet, may also be used to reduce PTH levels in patients with CKD Stage 5D. Recent data showed a tendency to result in risk for low-turnover bone disease [52]. Therefore, the authors believe that cinacalcet should be used as an adjuvant therapy to lower excessively elevated intact PTH levels in patients with CKD Stage 5D, in whom VDRA therapy is not appropriate (due to risk of hypercalcemia and/or vascular calcification). We do not advocate use of cinacalcet alone, but it is a valuable tool in combination with VDRAs for use in compliant patients.

Conclusion

The evidence-based KDIGO guidelines highlight the gaps in evidence that must be filled to achieve better diagnosis and management of CKD-MBD. This is an extremely complex disorder with interplay between several biochemical parameters, patient demographics and additional comorbidities. As a result, there are no universal treatment algorithms that should be applied to all patients with CKD-MBD. Rather, physicians need to treat patients as individuals and react to changes in the full spectrum of CKD-MBD parameters.

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Table 1

Monitoring recommendations.

Biochemical abnormality	KDIGO (2009) (Chapter 3.1)	KDOQI (2003) (Guideline 1.1)	Author opinion
Phosphorus and calcium	CKD 3: 6–12 months CKD 4: 3 – 6 months CKD 5 – 5D: 1 – 3 months	CKD 3: 12 months CKD 4: 3 months KD 5 – 5D: monthly	Consider demographics, co-morbidities and nutritional status when interpreting results. Do not consider CKD-MBD parameters in isolation. Examine temporal trends to guide treatment decisions.
Parathyroid hormone	CKD 3: Based on baseline level and CKD progression CKD 4: 6 – 12 months CKD 5–5D: 3–6 months	CKD 3: 12 months CKD 4: 3 months CKD5-5D: monthly	
Alkaline phosphatase	CKD 4 – 5D: every 12 months or more frequently in the presence of elevated PTH	No specific recommendation	

KDIGO recommend that the frequency of monitoring of serum phosphorus, calcium and PTH be based on the presence and magnitude of abnormalities, and the rate of progression of CKD. In CKD patients receiving treatments for CKD-MBD, or in whom biochemical abnormalities are identified, it is reasonable to increase the frequency of measurements to monitor for trends and treatment efficacy and side-effects. KDIGO = kidney disease improving global outcomes; KDOQI = kidney disease outcomes quality initiative; CKD = chronic kidney disease; PTH = parathyroid hormone.

Table 2

Targets for serum phosphorus.

CKD Stage	KDIGO (2009) (Chapter 4.1)	KDOQI (2003) (Guideline 3)	Author opinion
5D	Suggest lowering toward the normal range	3.5 – 5.5 mg/dl (0.87– 1.49 mmol/l)	Maintain good nutrition and use pharmacological intervention to attempt to reduce levels to within the normal range. In CKD Stage 5D 3.5 – 4.5 mg/dl (1.13 – 1.45 mmol/l) would be ideal but difficult to achieve with current interventions. Consider cost and burden on the patient.
5	Suggest maintaining in the normal range		
4		2.7–4.6 mg/dl (1.13–1.78 mmol/l)	
3			

Normal homeostasis maintains serum concentrations between 2.5 and 4.5 mg/dl (0.81 – 1.45 mmol/l) [1]. KDIGO = kidney disease improving global outcomes; KDOQI = kidney disease outcomes quality initiative; CKD = chronic kidney disease.

Table 3

Recommended use of calcium-based versus non-calcium-based phosphate binders.

CKD Stage	KDIGO (2009) (Chapter 4.1)	KDOQI (2003) (Guideline 5)	Author opinion
3	Choice of phosphate binder should take into account CKD stage, presence of other components of CKD-MBD, concomitant therapies, and side-effect profile Recommend restricting the dose of calcium-based phosphate binders and/or the dose of VDRAs in the presence of persistent or recurrent hypercalcemia	Calcium-based phosphate binders are effective in lowering serum phosphorus levels and may be used as the initial binder therapy	It is acceptable to use calcium-based phosphate binders in young non-diabetic patients with early stages of CKD, who have low serum calcium levels, increasing intact PTH levels, and no evidence of vascular calcification However, small doses of VDRAs may be more appropriate than use of calcium-based binders
4			
5 5D	Recommend restricting the dose of calcium-based phosphate binders in the presence of arterial calcification and/or adynamic bone disease and/or if serum PTH levels are persistently low	Total elemental calcium provided by calcium-based phosphate binders should not exceed 1,500 mg/day, and total intake of elemental calcium (including dietary calcium) should not exceed 2,000 mg/day Calcium-based phosphate binders should not be used in dialysis patients who are hypercalcemic (corrected serum calcium of > 10.2 mg/dl (2.54 mmol/l)), or whose plasma PTH levels are < 150 pg/ml (16.5 pmol/l) on two consecutive measurements Non-calcium-based phosphate binders are preferred in dialysis patients with severe vascular and/or other soft-tissue calcifications	Agree with KDOQI guidelines that total elemental calcium intake should be limited Given average daily phosphate intakes and the binding capacity of calcium, high calcium intake may be required to adequately control phosphorus load. Therefore, use of non-calcium-based phosphate binders alone or to limit calcium load should be consid-ered

KDIGO = kidney disease improving global outcomes; KDOQI = kidney disease outcomes quality initiative; CKD = chronic kidney disease; PTH = parathyroid hormone; VDRA = vitamin D receptor activator.

Table 4

Targets for parathyroid hormone (PTH).

CKD Stage	KDIGO (2009) (Chapter 4.2)	KDOQI (2003) (Guideline 1)	Author opinion
5D	Suggest maintaining intact PTH levels in the range of approximately 2–9 times the ULN for the assay. Suggest that marked changes in either direction within this range prompt an initiation or change in therapy to avoid progression to levels outside of this range	150–300 pg/ml (16.5–33.0 pmol/l)	Evaluate trends in circulating PTH to guide therapy, with a general goal of a stable and lower PTH than prior to treatment, and normalization of alkaline phosphatase or bone-specific alkaline phosphatase
5	Suggest that patients with levels of intact PTH above the ULN of the assay are first evaluated for hyperphosphatemia hypocalcemia and vitamin D deficiency, and if present these abnormalities should be corrected In patients in whom PTH is progressively rising and remains persistently above the ULN for the assay despite correction of modifiable factors, treatment with calcitriol or vitamin D analogs is suggested		
4		70–110 pg/ml (7.7–12.1 pmol/l)	
3		35 – 70 pg/ml (3.85–7.7 pmol/l)	

KDIGO = kidney disease improving global outcomes; KDOQI = kidney disease outcomes quality initiative; CKD = chronic kidney disease; ULN = upper limit of normal.