

 CHRONIC KIDNEY DISEASE

KDIGO CKD–MBD guideline update: evolution in the face of uncertainty

Wei Chen and David A. Bushinsky

Management of mineral and bone disorders in patients with chronic kidney disease (CKD–MBD) requires an understanding of the complex interactions among ions, hormones and their target organs. Since publication of the KDIGO CKD–MBD guideline in 2009, our understanding of disease pathophysiology has improved; however, a paucity of high-quality clinical evidence to support specific interventions remains. Using available data, KDIGO has now updated diagnostic and therapeutic recommendations for patients with CKD–MBD.

*Refers to Kidney Disease: Improving Global Outcomes (KDIGO) CKD–MBD Update Work Group. KDIGO 2017 Clinical Practice Guideline update for the diagnosis, evaluation, prevention, and treatment of Chronic Kidney Disease–Mineral and Bone Disorder (CKD–MBD). *Kidney Int. Suppl.* 7, 1–59 (2017)*

The development of mineral and bone disorders in patients with chronic kidney disease (CKD–MBD) contributes to the cardiovascular disease, bone fractures and mortality of this population. The new Kidney Disease: Improving Global Outcomes (KDIGO) CKD–MBD guideline¹ is an update of the 2009 guideline². Despite the availability of new studies published in the past 8 years, the guideline committee emphasizes the lack of strong clinical evidence in several areas, highlighting the need to base recommendations on our understanding of the underlying disease mechanisms and stressing the need for rigorous clinical trials in this field.

“ The evolution of the ... guidelines reflects our current understanding of the pathophysiology of CKD–MBD ”

CKD–MBD results from alterations in calcium (Ca) and phosphorus (P) homeostasis, increases in the levels of parathyroid hormone (PTH) and fibroblast growth factor 23 (FGF23), and a reduction in 1,25-dihydroxyvitamin D (1,25 D) levels. These changes result in dysregulated bone

remodelling and extra-skeletal calcification, contributing to mortality in affected patients. As kidney function declines, Ca excretion progressively falls due to a decrease in its filtered load and an increase in PTH level; urine P excretion also falls, despite increased levels of the phosphaturic hormones PTH and FGF23. Levels of 1,25D, which enhances Ca and P absorption, fall in parallel with renal divalent ion excretion, helping to prevent a positive total body balance of these ions³. This coordinated adaptive hormonal response is remarkably efficient at maintaining the ionic levels of Ca and P within a reasonable physiologic range, although total body Ca, and perhaps P, accumulates^{4,5}. Neither total body Ca nor P is directly sensed or regulated.

With progressive deterioration of renal function, however, this adaptive hormonal response can become maladaptive³. Elevated PTH induces net bone resorption, leading to the release of Ca and P into the extracellular fluid, whereas elevated FGF23 levels can induce cardiac hypertrophy. Patients with minimal renal function are often acidaemic, which also promotes bone resorption. Use of 1,25D or its analogues in an effort to lower PTH levels — especially in conjunction with Ca-containing P binders — leads to the increased gastrointestinal absorption of Ca. Supplemental 1,25D also increases P absorption and, with

high doses, bone resorption. Use of a high Ca concentration dialysate results in an influx of Ca into the patient. This influx of Ca and P from the bone and intestine, and Ca from the dialysate, into the extracellular fluid cannot be excreted and promotes the transformation of vascular smooth muscle cells into osteoblasts, which lay down a collagen matrix. The added Ca and P calcifies this matrix, leading to arterial stiffness and contributing to mortality.

The evolution of the KDIGO CKD–MBD guidelines reflects our current understanding of the pathophysiology of CKD–MBD. The guidelines emphasize the need to prevent the increase in total body Ca and P and avoid elevated serum Ca and P levels, to minimize calcification of the newly deposited collagen matrix in the vasculature and soft tissues (FIG. 1). KDIGO suggests lowering elevated P levels toward the normal range and avoiding hypercalcaemia by limiting Ca and P intake, restricting the use of Ca-based P binders and by avoiding high Ca concentrations in dialysate fluid¹. In predialysis patients with CKD, the optimal PTH level is not known and the guidelines recognize that modest increases in PTH might represent an appropriate adaptive response to declining kidney function. In these patients, new trials have demonstrated a risk of hypercalcaemia with supplementation of 1,25D or its analogues without beneficial effects on cardiac end points^{6,7}, leading KDIGO to advise against their routine use in this group of patients.

“ The quality of supporting evidence is, at best, moderate ”

Patients with CKD develop bone disease due, in part, to insufficient or excessive bone turnover. Fracture rates in these patients are high relative to those of age-matched controls in the general population, and contribute to increased morbidity and mortality in those with CKD. In the general population, bone mineral density (BMD), as measured by dual-energy X-ray absorptiometry, is useful in predicting fracture risk, and recent prospective cohort studies support the hypothesis that low BMD predicts incident fractures in patients with CKD^{8,9}. In recognition of this

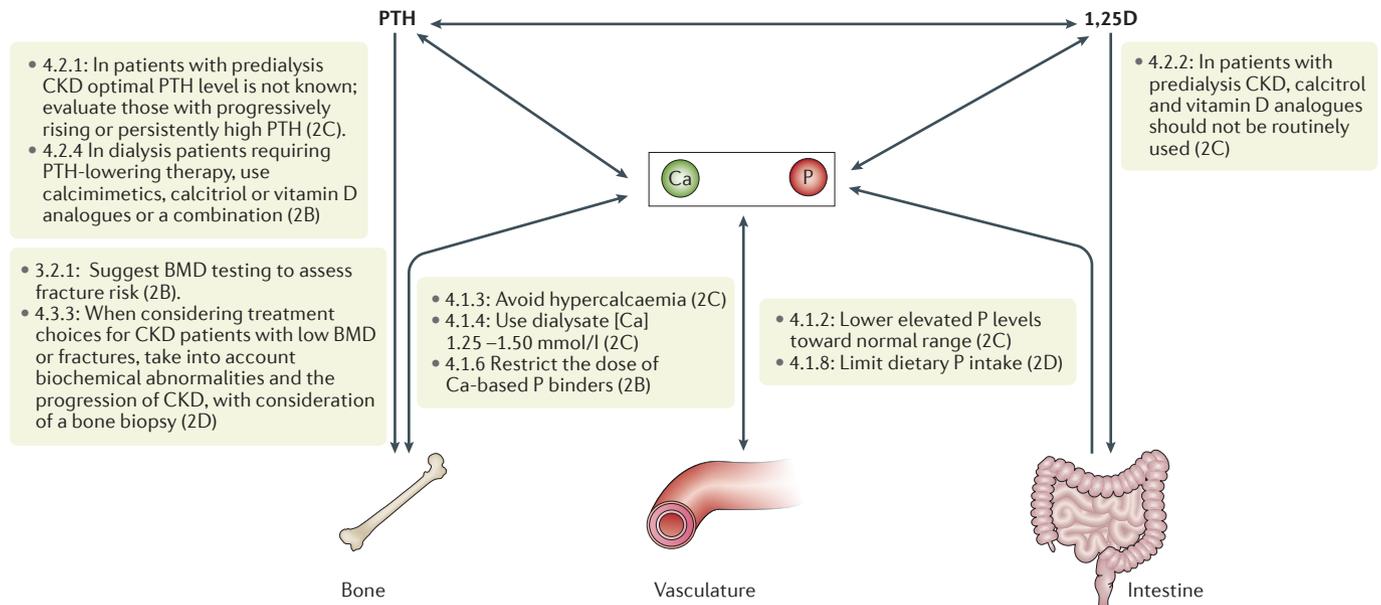


Figure 1 | Revised recommendations from the 2017 KDIGO CKD-MBD guideline. Only recommendations that are graded and apply to patients with chronic kidney disease and no history of kidney transplantation are shown, alongside the chapter from which the recommendation appears. Nomenclature for grading recommendations is as follows: level 2 (2, “we suggest”) indicates

that different choices will be appropriate for different patients; grade B (B) indicates moderate quality evidence; C, low-quality evidence; D, very low-quality evidence. 1,25D, 1,25-dihydroxyvitamin D; BMD, bone mineral density; Ca, calcium; [Ca], calcium concentration; CKD, chronic kidney disease; P, phosphorus; PTH, parathyroid hormone; MBD, mineral and bone disorder.

new information, the revised KDIGO guidelines suggest BMD assessment to determine fracture risk if the results will affect treatment decisions¹. Several studies have demonstrated the beneficial effect of anti-resorptive agents on improving BMD in patients with moderately reduced kidney function¹⁰. However, these data are based on *post hoc* analyses of trial data, and although valuable, the associations revealed by these analyses are associated with a high probability of false positives, which limits their interpretation. A bone biopsy is necessary to definitively determine the presence of high turnover disease, for which an anti-resorptive agent would be of benefit, or low turnover disease, for which an anabolic agent would be beneficial. Although bone biopsies are not routinely performed in management of CKD-MBD, they have an important role in directing therapy, especially as new anabolic agents designed to treat postmenopausal osteoporosis become available. The KDIGO suggestion for BMD testing precedes that for performing a bone biopsy¹. Thus, the inability to do a bone biopsy should not preclude the use of anti-resorptive therapy in patients with moderate CKD and low BMD or fractures.

The revised KDIGO CKD-MBD guidelines provide a critical analysis of the most recent literature and will be valuable to practicing nephrologists in providing the best possible care to patients with this disorder. Unfortunately, the recommendations are

only graded as suggestions (level 2) or are not graded at all. Moreover, the quality of supporting evidence is, at best, moderate (grade B). The rationale for the suggested interventions in patients with CKD-MBD are based, with few exceptions, on our understanding of the pathophysiology of disease, the assumed biological plausibility for a treatment effect, epidemiological studies, or of achieving a desired level of an ion or hormone. We as a nephrology community should focus our investigative efforts on testing hypotheses in randomized controlled trials with clinically important end points such as CKD progression, cardiovascular events, fractures or mortality, which will enable stronger recommendations to be made in the next revision of the KDIGO CKD-MBD guidelines.

Wei Chen is at the Department of Medicine, University of Rochester School of Medicine and Dentistry.

David A. Bushinsky is at the Department of Medicine and Department of Pharmacology and Physiology, University of Rochester School of Medicine and Dentistry, 601 Elmwood Avenue, BOX 675, Rochester, New York 14642, USA.

Correspondence to D.A.B. david_bushinsky@urmc.rochester.edu

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Competing interests statement

D.A.B. is a consultant for Relyspa, Amgen, Sanofi/Genzyme, Vifor, and Tricida and has an equity interest in Amgen and Tricida. W.C. declares no competing interests.