**CHRONIC KIDNEY DISEASE**

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

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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.

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 guideline1. 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 ions1. 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, accumulates2. 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 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 points4, leading KDIGO to advise against their routine use in this group of patients.

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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 CKD5,6. In recognition of this...
new information, the revised KDIGO guidelines suggest BMD assessment to determine fracture risk if the results will affect treatment decisions. Several studies have demonstrated the beneficial effect of anti-resorptive agents on improving BMD in patients with moderately reduced kidney function. 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 interpretations. 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 biopsy. 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.

**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, phosphorous; PTH, parathyroid hormone; MBD, mineral and bone disorder.

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**References**


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**Competing interests statement**

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