

Improving Global Outcomes in Mineral and Bone Disorders

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Disturbances in mineral and bone metabolism are prevalent in chronic kidney disease and an important cause of morbidity, decreased quality of life, and extraskeletal calcification that have been associated with increased cardiovascular mortality. Kidney Disease: Improving Global Outcomes (KDIGO)'s Global Mineral and Bone Initiative has sought to update the definition, evaluation, and classification of this mineral and bone disorder; improve standardization of assessment tools; enhance education about these complications; and stimulate research. In addition, this international organization sponsored a Controversies Conference in 2005 to define these complications better. The recommendations from that conference were that (1) the term "renal osteodystrophy" be used exclusively to define alterations in bone morphology that are associated with chronic kidney disease and (2) the term "chronic kidney disease–mineral and bone disorder" (CKD-MBD) can be used to describe the broader clinical syndrome that develops as a systemic disorder of mineral and bone metabolism as a result of chronic kidney disease. Chronic kidney disease–related mineral and bone disorders is manifested by an abnormality of any one or a combination of the following: Laboratory (abnormalities of calcium, phosphorus, parathyroid hormone, or vitamin D metabolism), bone (changes in bone turnover, mineralization, volume, linear growth, or strength), and calcification (vascular or other soft tissue calcification). The use of a common, internationally accepted terminology should ease the comparison of studies in this field and eventually improve patient care worldwide.

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In the past 10 yr, there has been an explosion of interest in the field of mineral and bone metabolism because of several factors. First, our understanding of the pathogenesis and interrelationships of bone disease; disturbances in the homeostasis of calcium, phosphorus, vitamin D, and parathyroid hormone (PTH); and extraskeletal calcification has evolved. Second, with increased understanding of the pathophysiology, new treatments have emerged. Third, a number of epidemiologic studies and clinical trials have demonstrated that disorders of mineral and bone disease are associated with cardiovascular disease, including vascular calcification and left ventricular hypertrophy; with fractures; and with mortality in dialysis patients. These new findings have led to a paradigm shift in several concepts regarding the treatment of patients with chronic kidney disease (CKD; Table 1).

Clinical Practice Guidelines

Parallel to these changes in our understanding of the pathophysiology of mineral and bone disorders in CKD is increasing awareness of the need for consistency in patient care and a mechanism to bridge the gap between new knowledge and change in clinical practice (1). The National Kidney Foundation and several other organizations around the world have developed clinical practice guidelines (CPG; <http://www.KDIGO.org/>) through a process that entails a rigorous review of the literature by an independent organization to yield evidence-

based recommendations. The first CPG under the name Dialysis Outcomes Quality Initiative (DOQI) were related to dialysis adequacy and anemia. These were followed by an expansion of the CPG to CKD stages before dialysis (Kidney Disease Outcomes Quality Initiative [K/DOQI]), including a CPG on bone and mineral metabolism published in 2003 (2). These guidelines affected clinical practice in nephrology by setting lower target values for phosphorus, calcium, and calcium \times phosphorus; limiting the amount of calcium intake in the form of calcium-containing phosphate binders; and raising awareness of the importance of nutritional vitamin D deficiency and of the potential hazards associated with pharmacologic dosages of calcitriol or its analogs. However, the development of clinical practice guidelines is only the first step in the process. Equally important is the widespread implementation of guidelines and subsequent determination as to the efficacy of the implementation of these guidelines on patient outcomes.

One of the initial implementation projects by the National Kidney Foundation after the release of the K/DOQI guidelines for bone and mineral metabolism was to hold an international conference of basic and clinical researchers to discuss the guidelines and stimulate research to enhance the evidence base for future guideline updates. This conference was held in Washington, DC, in 2003. Three work groups focused on assessment of bone turnover, osteoporosis, and vascular calcification (3). The primary conclusions of these three work groups have been published. The bone turnover work group determined that PTH and other bone biomarker assays and interpretation of bone biopsy by histomorphometry require international standardization (4). The osteoporosis work group determined that

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Table 1. Paradigm shift in mineral and bone metabolism in the past 10 yr^a

| Previous | Present |
|--|--|
| Push PTH as low as possible! | Well, not that low, and assays are not perfect |
| Give as much activated vitamin D as possible | Well, not that much (and change vitamin D type) |
| Give lots of calcium to suppress PTH | Too much calcium can cause calcium overload and vascular calcification |
| A phosphorus of 7 and calcium × phosphorus of 70 is okay | But that can cause vascular calcification and is associated with mortality |
| 25(OH)-vitamin D is not important | Deficiency is common |

^aPTH, parathyroid hormone.

the assessment of bone fragility in patients with CKD is complicated and that dual x-ray absorptiometry assessments must be interpreted simultaneously with bone turnover before initiation of antiresorptive therapies. Because of this, the group recommended that the term “osteoporosis” be avoided in patients with advanced CKD (5). The third work group concluded that arterial calcification was common in CKD, in part because of the increased prevalence of medial calcification in addition to intimal/atherosclerotic calcification. The group recommended that there be increased education to nephrologists and cardiologists about the differences and similarities of these types of vascular calcification and that simple screening methods be developed and validated (6). Importantly, this conference led to the development of the Global Bone and Mineral Initiative (GBMI; Table 2).

GBMI

The GBMI was subsequently made a formal work group of Kidney Disease: Improving Global Outcomes (KDIGO; <http://www.kdigo.org>), an international independent organization with a mission to “improve the care and outcomes of kidney disease patients worldwide through promoting coordination, collaboration, and integration of initiatives to develop and implement clinical practice guidelines.” The BMI is co-chaired by Drs. Sharon Moe and Tilman Drüeke, with additional leadership by Drs. Geoffrey Block, John Cunningham, Bill Goodman, Gerard London, Kevin Martin, Otto Mehls, Klaus Olgaard, Stuart Sprague, and David Wheeler. The BMI has undertaken several projects in the past 3 yr, including publishing *Clinical Guide: Basics of Bone and Mineral Metabolism in CKD* (available

from the KDIGO web site), evaluating questions related to bone and mineral metabolism for prospective data instrument collection tools, and working to standardize bone biopsy readings and correlate histology with serum biomarkers. Many of these projects are under way, and others were stimulated by the Washington conference and have been undertaken by other investigators. Perhaps the most notable work of KDIGO and GBMI was the hosting of a controversies conference “Definition, Evaluation, and Classification of Renal Osteodystrophy” in Madrid, Spain, in September 2005. The meeting was attended by more than 70 physicians/scientists with expertise in bone and mineral metabolism, representing six continents and 21 countries.

CKD Mineral and Bone Disorder

This conference was held because of the absence of a general agreement on the definition and diagnosis of renal osteodystrophy. The goal was to build international consensus to facilitate the best clinical decision-making, identify what we do not know in preparation for future evidenced-based guidelines, and prioritize and make recommendations on how our knowledge can best be expanded through future research. The results of this conference were published as a position statement from KDIGO (7). The principal conclusion from the conference (Table 3) was that the current nomenclature should be changed. It was recommended that the term “renal osteodystrophy” be used exclusively to define the bone pathology that is associated with CKD. The many clinical, biochemical, and imaging abnormalities that have previously been identified as correlates of renal osteodystrophy should be defined more broadly as a clinical entity or syndrome called “CKD-related mineral and bone disorder” (CKD-MBD). Conference participants examined these two issues separately and made recommendations for the definition, evaluation, and classification of each.

It was agreed that the definition of renal osteodystrophy should be specific to bone pathology that is found in patients with CKD (Table 3). Renal osteodystrophy is one component of the bone disorders that occur as a complication of CKD-MBD. The evaluation and definitive diagnosis of renal osteodystrophy requires a bone biopsy. Qualitative assessment of bone biopsies is sufficient for clinical diagnosis, but histomorphometry should be performed in research studies with results reported (both primary and derived measurements) using the

Table 2. Mission statement of the Global Bone and Mineral Initiative^a

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| <p>Improve outcomes in bone and mineral metabolism in patients with CKD worldwide by establishing standards in the evaluation of bone and mineral metabolism facilitating conduct of research and scientific exchange worldwide developing educational materials</p> |
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^aCKD, chronic kidney disease.

Table 3. Definition of CKD-MBD and renal osteodystrophy (7)^a

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|---|
| <p>CKD-MBD</p> <p>a systemic disorder of mineral and bone metabolism due to CKD manifested by either one or a combination of the following:</p> <ul style="list-style-type: none"> abnormalities of calcium, phosphorus, PTH, or vitamin D metabolism abnormalities in bone turnover, mineralization, volume, linear growth, or strength vascular or other soft tissue calcification <p>Renal osteodystrophy</p> <p>an alteration of bone morphology in patients with CKD</p> <p>it is one measure of the skeletal component of the systemic disorder of CKD-MBD that is quantifiable by histomorphometry of bone biopsy</p> |
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^aCKD-MBD, CKD-related mineral and bone disorder.

standard nomenclature recommended by the American Society for Bone and Mineral Research (8). To clarify the interpretation of bone biopsy results in the evaluation of renal osteodystrophy, it was agreed to use three key histologic descriptors—bone turnover, mineralization and volume (TMV system)—with any combination of each of the descriptors possible in a given specimen. The TMV classification scheme provides a clinically relevant description of the underlying bone pathology as assessed by histomorphometry, which in turn helps to define the pathophysiology and thereby guide therapy (Table 4).

The initial evaluation of CKD-MBD should include circulating PTH, calcium (either ionized or total corrected for albumin), phosphorus, alkaline phosphatases (total or bone specific), and bicarbonate and imaging for soft tissue calcification. If there are inconsistencies in the biochemical markers (*e.g.*, high PTH but low alkaline phosphatases), unexplained bone pain, or unexplained fractures, then a bone biopsy would be indicated. In children with CKD, additional tests to assess linear growth rate are also needed. A framework for CKD-MBD has been proposed (7) and divides patients into four types on the basis of the presence or absence of abnormalities in the three primary com-

Table 4. TMV classification system for renal osteodystrophy^a

| Turnover | Mineralization | Volume |
|----------|----------------|--------|
| Low | Normal | Low |
| Normal | Abnormal | Normal |
| High | | High |

^aAdapted from reference (7), with permission. TMV, turnover, mineralization, and volume.

ponents used in the definition of the disorder: Laboratory abnormalities, bone disease, and calcification of extraskeletal tissue. This framework is an initial attempt to improve communication and stimulate research. It is a working model that will likely be refined on the basis of analysis of patient databases or the prospective evaluation of patients with CKD.

Coexistence of CKD-MBD with Other Causes of Bone and Vascular Disease

There was much discussion on the nomenclature of CKD-MBD, with many individuals suggesting that vascular disease be incorporated into the terminology; however, it was believed that the mechanisms by which mineral and bone disorders affect vascular disease were complex and that it was premature to link all cardiovascular disease with these disorders. In addition, it was believed that MBD should be used rather than BMD (bone and mineral disorder) to avoid confusion of the latter with bone mineral density; therefore, KDIGO settled on the term CKD-MBD. To follow the Bone and Mineral Initiative (BMI) was renamed Mineral and Bone Initiative (MBI).

It was agreed that the definition of CKD-MBD (Table 3) should incorporate elements of abnormal mineral metabolism, altered bone structure and composition, and extraskeletal calcification with the following caveats: (1) Bone disease and vascular calcification are discrete entities that are not exclusive to the CKD population; (2) bone disease and vascular calcification are multifactorial pathologic processes, and disturbances in mineral metabolism as a result of CKD may not be their primary underlying cause; and (3) our understanding of a link between mineral disturbances and vascular calcification in CKD requires further study.

It is important to emphasize that the use of CKD-MBD should be as specific as possible and limited to disturbances that are caused by significantly reduced kidney function. In general, adult patients with a GFR of >60 ml/min per 1.73 m² should be excluded, because this is the level of kidney function below which CKD-related abnormalities in calcium, phosphorus, PTH, and vitamin D metabolism become detectable; however, in pediatric patients, the level of GFR at which CKD-MBD abnormalities may become detectable is higher (GFR <90 ml/min per 1.73 m²). Conversely, increased bone fragility that is observed with aging (senile or postmenopausal osteoporosis) and atherosclerotic disease with calcification that develops independent of CKD can be present in patients with stages 1 and 2 CKD and can coexist with CKD-MBD after its onset. The latter point is important, because CKD may alter the diagnosis, treatment, and prognosis of osteoporosis and atherosclerosis. Bone, in particular, is likely to be more severely affected by CKD than might be expected from normal aging, either as a result of the extremes of turnover or remodeling that occur in CKD in adults and children or from abnormalities of modeling that occur in growing children. This in turn might have a major impact on bone strength, perhaps even more so than that of altered bone mass or volume. In addition, several studies have demonstrated that for any age group, the atherosclerotic lesions

are more calcified in patients with CKD than in the general population (9). The presence of increased calcification in these cases may affect the response to common therapies such as angioplasty; therefore, although CKD-MBD should refer to conditions that are caused by CKD, the precise contribution of CKD-related changes to disease states that are commonly found in the general population will require increased understanding of the underlying pathophysiology, more sensitive diagnostic tools, and a different therapeutic approach.

Conclusions

Mineral and bone disorders are complex abnormalities that cause morbidity and decreased quality of life in patients with CKD. The KDIGO Global Mineral and Bone Initiative has helped to increase awareness, facilitate standardization of assessment tools, and stimulate research. In addition, a new term, CKD-MBD, has been established to describe the syndrome of biochemical, bone, and extraskeletal calcification abnormalities that occur in patients with CKD, preserving the term renal osteodystrophy to be used exclusively to define alterations in bone morphology that are associated with CKD. The latter can be further assessed by histomorphometry with results reported on the basis of a the TMV system. It is the hope that these efforts will enhance communication, facilitate clinical decision-making, and promote the evolution of evidence-based clinical practice guidelines worldwide.

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