

Chronic Kidney Disease-Mineral Bone Disorder (CKD-MBD): Overview

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Background

Disorders of mineral and bone metabolism are common in chronic kidney disease (CKD) patients. Traditionally, these disorders have collectively been called renal osteodystrophy. In 2006, an international work group convened by Kidney Disease: Improving Global Outcomes (KDIGO) recommended that the term “renal osteodystrophy” be exclusively used to define bone pathology associated with CKD. Given that mineral and bone disorders contribute to CKD-associated cardiovascular disease and high mortality rates, the new term chronic kidney disease and mineral bone disorder (CKD-MBD) can be used to describe the broader systemic disorder that can occur as a result of CKD¹.

Definition of CKD- MBD and renal osteodystrophy¹

A systemic disorder of mineral and bone metabolism due to chronic kidney disease expressed by one or combination of following:

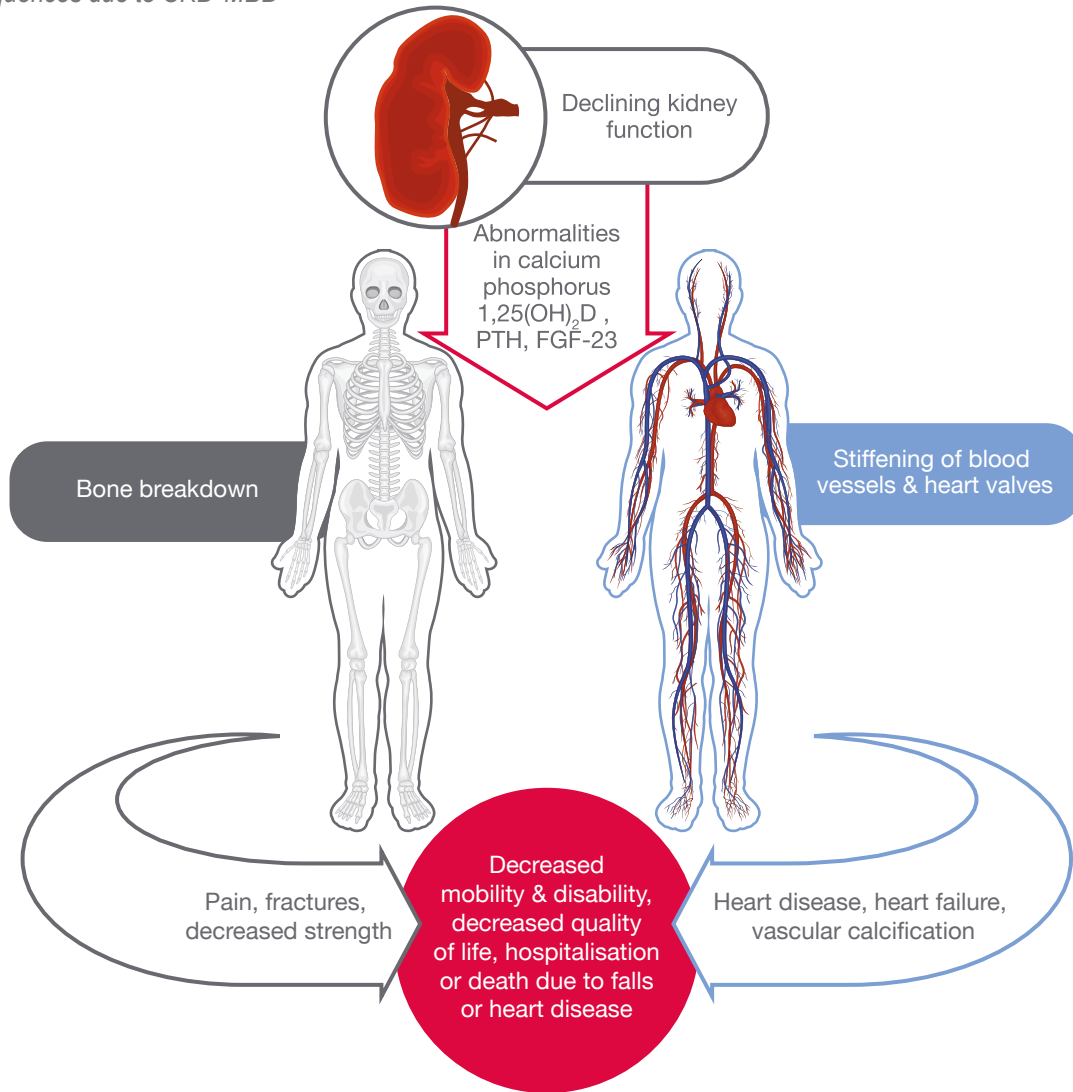
CKD-MBD

- Abnormalities of calcium, phosphate, PTH or vitamin D metabolism
- Abnormalities in bone turnover, mineralisation, volume, linear growth or strength
- Vascular or other soft tissue calcification

Renal osteodystrophy

- Is an alteration of bone morphology in CKD patients
- Is one measure of the skeletal component of CKD-MBD that is quantifiable by histomorphometry of bone biopsy

Fig. 1: Consequences due to CKD-MBD



Introduction

Chronic kidney disease is a global public health problem affecting 8-16% of the population worldwide². As kidney function declines a progressive deterioration in mineral homeostasis occurs, leading to a disruption of normal concentrations of phosphorus and calcium and changes in circulating levels of hormones.

Beginning in CKD stage 3, glomerular filtration rate (GFR) < 60 mL/min/1.73m², the kidney's ability to appropriately filter the phosphate load declines, leading to hyperphosphatemia, elevated parathyroid hormone (PTH) and decreased 1,25-dihydroxyvitamin D (1,25(OH)₂D) with associated elevations in the levels of fibroblast growth factor 23 (FGF-23). The renal hydroxylation of 25-hydroxyvitamin D (25(OH)D) to 1,25(OH)₂D is reduced, lowering intestinal calcium absorption and increasing PTH production. The kidney's inability to adequately respond to either PTH (normally promotes phosphaturia and calcium reabsorption) or FGF-23 (enhances phosphate excretion) further

exacerbates both hypocalcemia and hyperphosphatemia within the patient. The mineral and endocrine functions disturbed in CKD are critically essential in the regulation of both initial bone formation during growth and bone structure and function during adulthood. Consequently, bone abnormalities are found almost in all CKD patients on dialysis treatment (CKD stage 5D) and in the majority of patients at CKD stages 3-5. All these abnormalities are associated with the development of vascular calcifications, and these VC are associated with higher mortality (VC), especially cardiovascular mortality. It is generally well documented that the prevalence of calcification (vascular/other soft tissue) increases with gradually declining kidney functions.

Consequently, CKD-MBD increases hospitalisations or death due to falls or cardiovascular events and death (Fig.1).

Diagnosis of CKD-MBD: abnormalities of calcium, phosphate, PTH or vitamin D metabolism

Biochemical abnormalities are the primary indicators by which the diagnosis and management of CKD-MBD is made. Changes in the laboratory parameters as a result of CKD-MBD could begin in CKD stage 3B, but the manifestation of abnormal values, the rate of changes and the severity of abnormalities are highly variable among patients. The laboratory diagnosis of CKD-MBD includes the use of laboratory testing of PTH, calcium and phosphorus. In some situations, measuring alkaline phosphatase (total or bone specific) and bicarbonate may be needed. To make the diagnosis of CKD-MBD, one or more of the above laboratory abnormalities must be present per KDIGO recommendation.

Table 1 summarises the KDIGO Clinical Practice Guideline for the Diagnosis, Evaluation, Prevention and Treatment of Chronic Kidney Disease-Mineral Bone Disorder (CKD-MBD) frequencies of laboratory parameter measurements according to CKD stage recommendations³.

The guidelines further suggest that these biochemical parameters should be monitored with a frequency based on stage, rate of progression and whether specific therapies have been initiated. Further testing and shorter time intervals would be dependent on the manifestation and severity of biochemical abnormalities. Furthermore, the guidelines suggest that therapeutic decisions are based on trends, rather than a single laboratory value and that they take into account the entire available data set, rather than isolated variables. Assessment of 25(OH)D levels established at baseline may be monitored throughout therapeutic interventions to ensure that Vitamin D deficiency and insufficiency should be corrected according the treatment strategies recommended for the general population.

CKD Stage	Calcium	Phosphorus	PTH	Alkaline Phosphatase (total or bone specific)	25(OH)D
Progressive CKD stage 3	Every 6-12 months	Every 6-12 months	Baseline	Every 6-12 months	Baseline
4	Every 3-6 months	Every 3-6 months	Every 6-12 months	Every 3-6 months	Baseline*
5	Every 1-3 months	Every 1-3 months	Every 3-6 months	Every 1-3 months	Baseline*
5D	Every 1-3 months	Every 1-3 months	Every 3-6 months	Every 1-3 months	Baseline*

Table 1: Suggested frequency of biochemical testing in CKD-MBD.

Adapted from KDIGO Clinical Practice Guideline for the Diagnosis, Evaluation, Prevention and Treatment of Chronic Kidney Disease-Mineral Bone Disorder (CKD-MBD).

**If not receiving vitamin D therapeutic treatments.*

Diagnosis of CKD-MBD: abnormalities in bone turnover, mineralisation, volume, linear growth or strength

The CKD-MBD bone–disease component may result in fractures, bone pain, deformities in growing children, reduced growth velocity and abnormal height³. Complications of hip fractures include bleeding, infection, loss of independence and increased mortality. Vertebral fractures lead to height loss, reduced pulmonary function, gastrointestinal reflux and chronic disability. In children, growth retardation and skeletal deformities reduce quality of life.

It is important to be aware of that most postmenopausal or age-related osteoporosis patients also have early stages of CKD, stages 1 through to early stage 3. In more advanced stages of CKD (stages 3 to 5D) patients, in whom the mineral metabolism biochemical abnormalities that define CKD-MBD are present, have renal osteodystrophy. Although both osteoporosis and renal osteodystrophy lead to increased bone fragility and fractures, these diseases have different pathophysiological backgrounds. Varying combinations of low bone mineral content and bone quality contribute to bone fragility. CKD-MBD can lead to abnormal bone quality even when having normal or high bone mineral content. The gold standard diagnosis for the CKD-MBD's bone component is bone biopsy histomorphometry. On the other hand, bone mineral density (BMD) assessment is the reference diagnostic method for osteoporosis. Owing to the above pathophysiological and diagnostic differences, the 'osteoporosis' definition should be used for adults with CKD stages 1-3; 'CKD-MBD with low BMD' should be designated to those in later stages of CKD with low BMD³.

Clinical use of bone biopsies is now unusual in most parts of the world because the patients will be subjected to a potentially unpleasant, invasive procedure and with limited access to specialised diagnostic and histopathological support services⁴. Bone turnover biochemical markers such as osteocalcin, bone-specific alkaline phosphatase and tartrate-resistance acid phosphatase show correlations with findings on bone biopsies⁵. Recent researchers documented the potential use of novel biomarkers that are not influenced by kidney function such as intact propeptide type 1 collagen (Intact P1NP) and type 5b tartrate-resistance acid phosphatase (TRAcP 5b) for the CKD-MBD bone-disease component^{6,7}. The KDIGO Clinical Practice Guideline for the Diagnosis, Evaluation, Prevention and Treatment of CKD-MBD suggests that measurements of PTH or bone-specific alkaline phosphatase (BAP) can be used to evaluate bone disease in patients with CKD stages 3-5D³.

Diagnosis of CKD-MBD: vascular or other soft tissue calcification

Patients with CKD experience up to 30-fold higher cardiovascular disease mortality than the general population⁸. It is also well acknowledged that the prevalence of calcification increases with progressively decreasing kidney functions. Vascular calcification (VC) in CKD is caused by imbalanced mineral metabolism and the therapies used to control it⁹, but also due to a complex, active process of osteogenesis in vascular smooth muscle cells (VSMCs)¹⁰. VC is highly prevalent in dialysis populations; studies have estimated that nearly 70% have significant coronary and/or aortic calcification¹⁰.

Vascular calcification can occur at two sites: the intima and the media. Both types of calcification are present in CKD patients, but the complications of these two types of VC are different: intima calcification is mainly associated with occlusion of the vessels, and the media calcification is associated with vascular stiffness and sudden death^{11, 12}.

According to the KDIGO guidelines, a lateral abdominal radiograph can be used to detect the presence or absence of VC and an echodiagram can be used to detect valvular calcification³. Multiple new biomarkers of vascular calcification have emerged due to a better understanding of pathogenesis of VC.

In addition to well-known risk markers such as calcium, phosphorus, parathyroid hormone and vitamin D deficiency, it has been suggested that fetuin-A (α₂-Heremans-Schmidt's glycoprotein), matrix- gla protein (MGP), osteopontin, osteoprotegerin (OPG) and fibroblast growth factor-23 (FGF-23) could be considered as novel markers of vascular calcification.

Novel CKD-MBD biomarkers

Emerging CKD-MBD biomarkers show various associations with regard to CKD-progression, cardiovascular events and death in patients with CKD (Table 2)¹³.

Promoter of Calcification in CKD	Inhibitors of Calcification in CKD	Other/Risk Factor of CKD progression
Osteoprotegerin	Matrix-Gla protein	FGF-23
	Fetuin-A	Klotho
	Osteopontin	

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