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CKJ REVIEW

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Pathophysiology of chronic kidney disease–mineral bone disorder (CKD-MBD): from adaptive to maladaptive mineral homeostasis

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ABSTRACT

Chronic kidney disease–mineral bone disorder (CKD-MBD) is a multifaceted condition commonly seen in people with reduced kidney function. It involves a range of interconnected issues in mineral metabolism, bone health and cardiovascular calcification, which are linked to a lower quality of life and shorter life expectancy. Although various epidemiological studies show that the laboratory changes defining CKD-MBD become more common as the glomerular filtration rate declines, the pathophysiology of CKD-MBD is still largely unexplained. We herein review the current understanding of CKD-MBD, provide a conceptual framework to understand this syndrome, and review the genetic and environmental factors that may influence the clinical manifestation of CKD-MBD. However, a deeper understanding of the pathophysiology of CKD-MBD is needed to understand the phenotype variability and the relative contribution to organ damage of factors involved in CKD-MBD to develop more effective interventions to improve outcomes in patients with CKD.

Keywords: CKD, CKD-MBD, dialysis, outcome, pathophysiology

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KEY LEARNING POINTS

- CKD-MBD results from complex mineral homeostasis disruption due to declining kidney function.
- As CKD progresses, mechanisms involving FGF-23, PTH, klotho and CPPs fail to maintain mineral balance, leading to complications like VC and bone disorders.
- Clinical manifestations vary among CKD patients, influenced by genetic factors and comorbidities like diabetes and hypertension.
- Understanding CKD-MBD's pathophysiology and phenotype variability is crucial for developing effective interventions.
- Therapeutic strategies include klotho restoration (enhancing klotho function or expression) and CPP inhibition (preventing CPP formation or promoting clearance) and miRNA manipulation.
- Experimental therapies like klotho supplementation or gene therapy and CPP inhibitors are being explored.
- A multifaceted approach is needed to manage bone mineral metabolism and prevent maladaptive responses.
- Early intervention and individualized treatment plans could improve patient outcomes and slow CKD progression.

INTRODUCTION

Chronic kidney disease–mineral bone disorder (CKD-MBD) is a complex syndrome frequently observed in individuals with impaired renal function [1–4]. It encompasses a spectrum of interrelated abnormalities in mineral metabolism, bone structure and cardiovascular calcification, and is associated with low quality of life, reduced life expectancy and higher healthcare expenditures [1, 2, 5]. Numerous epidemiological studies indicate that laboratory alterations that characterize CKD-MBD become progressively more prevalent as the glomerular filtration rate (GFR) decreases [6–8]. In chronic kidney disease (CKD) stage 3, approximately 40%–50% of patients exhibit abnormalities in calcium, phosphorus and parathormone (PTH) levels. As CKD progresses, the prevalence of these abnormalities increases further to around 60%–70% in stage 4 and even to 80%–90% in stage 5 CKD (including those on dialysis) [1, 2, 5].

Although the mechanisms that link deregulated bone mineral metabolism with an unfavorable outcome are still largely speculative, it is plausible to consider that both skeletal and extra-skeletal complications of altered bone metabolism contribute to the dismal risk to which CKD patients are exposed [9, 10]. The bone complications of CKD-MBD are represented by various forms of renal osteodystrophy (ROD) and skeletal fractures [11]. In contrast, extra-skeletal complications include cardiovascular and soft tissue calcifications and left ventricular hypertrophy. Other clinical complications that have been associated with CKD-MBD are (i) endocrine disorders, (ii) immune system alterations, (iii) neurobehavioral changes and (iv) alterations in erythropoiesis [2].

Although it is still unclear what the *primum movens* is, it has been repeatedly documented that serum levels of vitamin D, PTH, calcium, phosphorus, and fibroblast growth factor-23 (FGF-23) are routinely altered from the earliest stages of CKD [12]. Importantly, laboratory studies document how calcium, phosphorus and vitamin D can promote the formation of calcifications of the middle layer of the arterial wall, thus supporting the idea of a plausible link between serum biomarkers and cardiovascular and soft tissue calcifications and the risk of cardiovascular event associated with CKD-MBD [13].

This review summarizes the main factors and mechanisms linking alterations in bone mineral metabolism with clinical bone and cardiovascular manifestations of CKD-MBD.

PATHOPHYSIOLOGY OF CKD-MBD: THE PHOSPHOROCENTRIC VIEW

A central feature in the pathogenesis of CKD-MBD is the disruption of phosphorus homeostasis due to declining kidney function [7, 14]. Although focusing on one single factor, such as phosphate, does not entirely capture CKD-MBD pathophysiology, it represents a simple conceptual framework to explain how adaptive control of mineral metabolism may turn maladaptive under certain conditions (Fig. 1).

Under normal circumstances, phosphorus balance is tightly regulated through three primary mechanisms: intestinal absorption, renal excretion and exchange with bone stores [15–17] (Fig. 1). Dietary phosphorus is absorbed mainly in the duodenum and jejunum, with approximately 80% of ingested phosphorus being absorbed [17]. The kidneys play a pivotal role in maintaining phosphorus homeostasis by adjusting the GFR and fractional excretion of phosphate (FEp) to match dietary intake [18, 19].

Several hormones and proteins finely regulate phosphorus metabolism, including vitamin D, PTH, FGF-23 and klotho [19–22]. Vitamin D enhances intestinal absorption and renal reabsorption of phosphorus and calcium [20]. PTH increases renal excretion of phosphorus while promoting calcium reabsorption and mobilization of minerals from bone [20]. FGF-23, produced by osteocytes and osteoblasts in response to increased phosphorus or vitamin D levels, decreases renal phosphate reabsorption and suppresses vitamin D activation, thus lowering the body pool of phosphate [23, 24]. Klotho is a co-receptor for FGF-23, facilitating its actions [25, 26].

In CKD, the progressive loss of nephron mass impairs the kidneys' ability to excrete phosphorus, leading to disruptions in mineral metabolism even before hyperphosphatemia becomes apparent [12, 23] (Fig. 1). Elevated levels of FGF-23 and PTH are detectable as early as stages 2–3a CKD, serving as compensatory mechanisms to maintain normal serum phosphorus levels by increasing FEp [18, 27, 28]. However, as GFR declines below approximately 30 mL/min, these compensatory mechanisms become insufficient, and hyperphosphatemia ensues [29].

The kidneys' inability to excrete excess phosphorus leads to a positive phosphate balance, which is central to the pathophysiology of CKD-MBD [12, 30]. The accumulation of phosphorus contributes to vascular calcification (VC) and induces renal tubular damage, promoting further decline in kidney function [31–33]. High phosphate levels can stimulate the formation of calciprotein particles (CPPs) [34, 35]: complexes of calcium, phosphorus and serum proteins like fetuin-A, which solubilize and transfer minerals. Moreover, mineral excess in CKD can induce calcium and phosphate deposition in soft and vascular tissues, driving cardiovascular calcification.

ROLE OF FGF-23 AND PTH IN CKD-MBD

Elevated FGF-23 levels in CKD have been associated with adverse outcomes, including left ventricular hypertrophy, heart

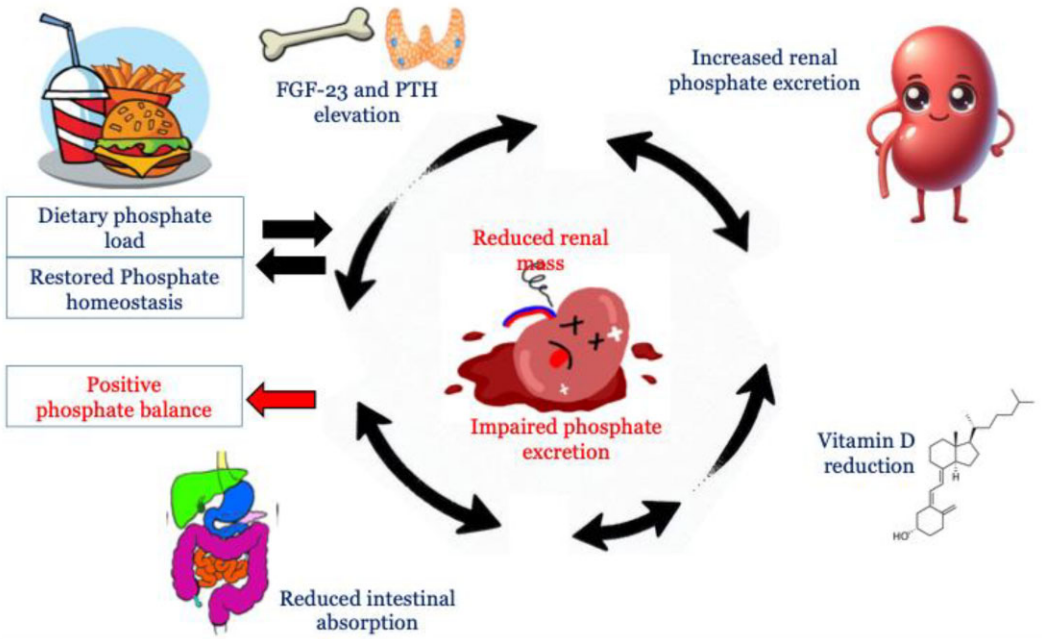

Figure 1: Under normal physiological conditions (blue part), the body pool of phosphorus is neutral, and the amount ingested from the diet is excreted by the kidneys, stimulated by FGF-23 and PTH. In addition, these hormones reduce vitamin D activation, resulting in decreased intestinal absorption of phosphorus. All these actions enable the maintenance of phosphorus homeostasis. However, when renal function is reduced (red part), renal excretion of phosphorus is no longer sufficient, and a vicious cycle is triggered that leads to a progressive expansion of the body's phosphorus pool despite overexpression of FGF-23 and PTH.

failure, inflammation, innate immune cell dysfunction and increased mortality [24, 33, 36–39]. While FGF-23 initially helps to prevent hyperphosphatemia, persistently high levels can have pathological effects on multiple organ systems. Indeed, data suggest that maladaptive increases of FGF-23 are involved in left ventricular hypertrophy development, heart failure, cardiac arrhythmias and abnormalities in the microcirculation, ultimately portending an increased CV risk [24, 40]. In addition, synergistic effects of FGF-23 and inflammation may further complicate the vicious cycle, ultimately leading to end organ damage and risk of adverse effects. As recently observed, FGF-23 cleavage is influenced by inflammatory cytokines that may alter the ratio of intact FGF-23 and its metabolites, possibly aggravating CKD-MBD [41].

Although the exact mechanisms of FGF-23 need to be further elucidated, FGF-23 primarily binds to FGF receptor 1 (FGFR1) in the presence of the co-receptor α-klotho, which is crucial for its biological actions in the kidneys. FGF-23 can also interact with FGFR2 and FGFR3, although with lower affinity. These klotho-dependent actions are thought to play a role in mineral metabolism homeostasis. However, at high levels, FGF-23 can bind to FGFR4 independently of klotho, leading to klotho-independent effects such as cardiac hypertrophy [24, 29, 33].

Elevated levels of FGF-23 are closely associated with the progression of CKD and increased proteinuria, and have been shown to reduce the efficacy of renin–angiotensin–aldosterone system inhibitors, complicating CKD management [42, 43]. High FGF-23 levels in CKD patients indicate a poorer prognosis and more rapid disease progression [42, 43].

Similarly, elevated PTH levels contribute to CKD-MBD by promoting bone resorption, leading to renal osteodystrophy [44]. When CKD-MBD disturbances are not corrected, parathyroid gland hyperplasia occurs, leading to an increase in parathyroid gland volume and abnormal PTH secretion. This enlargement reduces the expression of calcium-sensing receptors and vitamin D receptors, perpetuating the cycle of secondary hyperparathyroidism (SHPT) [45]. By stimulating osteoclast activity, PTH promotes high bone turnover and releases additional phosphorus and calcium into the circulation, further complicating the mineral imbalance. PTH also enhances calcium reabsorption in the kidneys, reducing its excretion. Additionally, it stimulates the conversion of vitamin D to its active form, calcitriol, which increases intestinal calcium absorption. However, while prolonged elevated PTH levels lead to bone loss, intermittent PTH administration can stimulate bone formation by activating osteoblasts, contributing to both bone resorption and deposition [46].

ROLE OF KLOTHO IN CKD-MBD

Klotho is a transmembrane protein that plays a crucial role in mineral homeostasis, particularly in regulating phosphorus and calcium levels. It is a co-receptor for FGF-23, enhancing its binding affinity to FGF receptors and facilitating the phosphaturic actions [22, 25, 26]. Klotho expression is abundant in healthy kidneys, but its levels decline significantly in CKD due to nephron loss and renal fibrosis [22, 26]. The reduction of klotho in CKD patients contributes to FGF-23 resistance, wherein elevated FGF-23 levels fail to exert their phosphaturic effects effectively [22, 26]. This resistance exacerbates hyperphosphatemia and promotes VC. Additionally, klotho has been shown to possess antioxidant and anti-inflammatory properties, and its deficiency may lead to endothelial dysfunction and accelerated aging phenomena observed in CKD patients [22, 26].

Studies suggest that klotho deficiency independently contributes to CKD-MBD progression by enhancing phosphate retention and increasing calcitriol deficiency. The diminished klotho levels also impair calcium reabsorption in the distal renal

tubules, further disrupting mineral balance [22, 26]. Therapeutic strategies to restore klotho expression or function may offer potential benefits in mitigating CKD-MBD complications.

CCPS AND VASCULAR CALCIFICATION

CCPs are nanoscale colloidal complexes formed when supersaturated calcium and phosphate precipitate in the presence of serum proteins like fetuin-A [34]. CPPs act as carriers that prevent the immediate precipitation of calcium-phosphate crystals in soft tissues. However, elevated serum phosphate and calcium levels in CKD promote excessive CPP formation, overwhelming protective mechanisms [34, 35, 47, 48].

There are two types of CPPs: primary CPPs, containing amorphous calcium-phosphate complexes, and secondary CPPs, which have a crystalline structure and are considered more pathogenic [34]. The transition from primary to secondary CPPs is associated with increased pro-inflammatory and procalcific effects. Elevated levels of CPPs in CKD patients have been linked to endothelial dysfunction, arterial stiffness and VC [34, 35, 47, 48].

CPPs can induce vascular smooth muscle cell transformation into osteogenic-like cells, promoting calcium-phosphate deposition in the vascular wall [34, 35, 47, 48]. This process contributes significantly to the high cardiovascular morbidity and mortality observed in CKD patients. Moreover, CPPs may activate inflammatory pathways by engaging with toll-like receptors on immune cells, leading to systemic inflammation and further vascular damage [33].

MICROPARTICLES

Microparticles (MPs) may play a significant role in CKD-MBD by contributing to the pathophysiology of the disease [49, 50]. As important intercellular signaling molecules, these tiny vesicles, shed from various cell types, can carry bioactive molecules such as proteins, lipids and nucleic acids. In particular, the small non-coding microRNAs (miRNAs) represent a promising group of molecules that are virtually involved in all pathophysiological processes and potentially serve as a therapeutic target for CKD-MBD [49, 50]. In CKD-MBD, MPs are involved in promoting inflammation, VC and bone remodeling. They can also serve as biomarkers for disease progression and therapeutic targets, offering the potential for new diagnostic and treatment strategies [49, 50].

GENETIC AND ENVIRONMENTAL FACTORS

Genetic factors

Several lines of evidence point towards a genetic basis for variability in serum PTH, vitamin D and FGF-23 concentrations. First, various rare Mendelian disorders cause abnormalities in mineral metabolism [51–55]. Second, a classical twin study indicated heritability for PTH of 60%, for 25-hydroxyvitamin D 43% and for 1,25-hydroxyvitamin D 65% [56]. Subsequently, genome-wide association studies (GWAS) identified single nucleotide polymorphisms (SNPs) that displayed independent associations with serum concentrations of PTH, 25-hydroxyvitamin D and FGF-23 (Table 1). While heritability of mineral metabolism factors seems considerable, so far only small percentages of their variances have been explained by GWAS. The top loci associated with serum PTH levels explained only 4.5% of the variance in serum PTH [57]. Similarly, the top five loci associated with FGF-23 together explained 3% of the variance in circulating FGF-23 [58]. The total variance in plasma 25-hydroxyvitamin D levels explained by 138 conditionally independent genome-wide significant vitamin D SNPs was 4.9% [59]. Of note, there seems to be some overlap between the genetic drivers of the three major hormones involved in bone and mineral homeostasis (Table 1). The *RGS14* gene encodes Regulator of G protein signaling 14, a protein that was recently identified to regulate PTH- and FGF-23-sensitive renal phosphate uptake mediated by the sodium phosphate cotransporter 2A (NPT2A) [60]. In addition, genetic variants in *CYP24A1*, encoding vitamin D 24-hydroxylase, are strongly related to serum vitamin D, PTH and FGF-23 levels. This is not surprising, given the well-established regulation of FGF-23 and PTH (through an increase in plasma calcium levels) by active vitamin D (1,25-dihydroxyvitamin D), which is degraded by the enzyme 24-hydroxylase. Together, this comparison of their genetic drives underlines the interrelationships between individual components of bone mineral homeostasis.

Of interest, genetically predicted plasma levels can be used as instruments to analyze potentially causal relationships with outcomes. A genetically predicted higher plasma FGF-23 level was associated with an increased risk of heart failure with preserved ejection fraction in individuals with low genetically predicted eGFR in one cohort [61]. At variance with this result, a more recent Mendelian randomization study showed that a higher FGF-23 level is linked with a lower heart failure risk, although this study did not include sub-analyses focusing on impaired kidney function [62]. Mendelian randomization studies also suggested that higher vitamin D levels might reduce the risk of hypertension [63] and the risk of heart failure in type 2 diabetes [64]. In contrast, a phenome-wide Mendelian randomization study in the UK Biobank did not support a causal effect of vitamin D on multiple health outcomes including blood pressure, ischemic heart disease and all-cause mortality [65]. A GWAS of coronary artery calcification revealed significant enrichment of factors related to regulation of phosphate homeostasis (ENPP1/ENPP3 and FGF-23) [66]. Together, these findings seem to suggest that abnormalities in mineral metabolism are linked with adverse cardiovascular outcomes particularly in high-risk populations such as patients with diabetes or CKD.

Environmental factors

As approximately half of the variability in hormones regulating mineral metabolism is explained by genetic variation, the other half is under the control of environmental factors. Following the same reasoning, it has been postulated that 38%–54% of the variance in areal bone mineral density may be explained by environmental factors [67]. Major environmental factors that influence bone homeostasis and strength include exercise, vitamin D status, dietary intake of calcium and phosphate, smoking and alcohol consumption (Fig. 2). The identification of these factors is important since they are modifiable non-pharmacologic approaches that can be implemented as first-step measures and should be considered to prevent and treat CKD-associated osteoporosis in all CKD patients. At the same time, there have been (and still are) extensive discussions about the recommended intake of vitamin D, calcium and phosphate in CKD patients. Because vitamin D deficiency is a well-known driver of secondary hyperparathyroidism, current guidelines recommend correcting vitamin D deficiency in patients with hyperparathyroidism. Indeed, a recent meta-analysis confirmed a reduction in PTH following vitamin D supplementation in CKD stages G3–4; at

Table 1: Genetics of serum PTH, 25-hydroxyvitamin D and FGF-23 levels: top five SNPs.

SNP	Nearest gene	Gene name	Beta[a] (SE)	P-value
Trait: serum PTH ($N_{discovery+validation} = 29\,165$)				
rs6127099	*CYP24A1*	Cytochrome P450, family 24, subfamily A, polypeptide 1 (24-hydroxylase)	0.07 (0.003)	2.4×10^{-72}
rs4074995	*RGS14*	Regulator of G-protein signaling 14	0.03 (0.003)	3.3×10^{-23}
rs219779	*CLDN14*	Claudin 14	0.04 (0.003)	8.9×10^{-22}
rs4443100	*RTDR1*	Radial spoke head 14 homolog	0.02 (0.003)	4.1×10^{-11}
rs73186030	*CASR*	Calcium-sensing receptor	0.03 (0.004)	1.2×10^{-9}
Trait: serum FGF-23 ($N = 16\,224$)				
rs17216707	*CYP24A1*	Cytochrome P450, family 24, subfamily A, polypeptide 1 (24-hydroxylase)	0.054 (0.005)	3.0×10^{-24}
rs2769071	*ABO*	ABO blood group transferase	0.037 (0.005)	6.1×10^{-17}
rs11741640	*RGS14*	Regulator of G-protein signaling 14	0.039 (0.005)	1.6×10^{-16}
rs17479566	*LINC01506*	Long intergenic non–protein coding RNA 1506	0.031 (0.005)	2.0×10^{-9}
rs9925837	*LINC01229*	Long intergenic non–protein coding RNA 1229	0.035 (0.006)	5.1×10^{-9}
Trait: serum 25-hydroxyvitamin D ($N = 443\,734$)				
rs11723621	*GC*	Vitamin D binding protein	–0.187 (0.002)	2.9×10^{-1689}
rs117913124	*CYP2R1*	Cytochrome P450 2R1, vitamin D 25-hydroxylase	–0.354 (0.006)	1.7×10^{-775}
rs200454003	*DHCR7/NADSYN1*	7-dehydrocholesterol reductase/nicotinamide adenine dinucleotide synthetase 1	–0.087 (0.003)	2.2×10^{-253}
rs112285002	*SULT2A1*	Sulfotransferase 2A1	0.060 (0.003)	1.8×10^{-110}
rs6127099	*CYP24A1*	Cytochrome P450, family 24, subfamily A, polypeptide 1 (24-hydroxylase)	–0.037 (0.002)	9.3×10^{-62}

[a]Beta estimates are interpreted as the relative difference in FGF-23 concentration per minor allele; e.g. 0.07 is a 7% higher FGF-23 concentration per additional allele. SE, standard error.

the same time, this analysis also identified small study sizes and heterogeneity across supplements (cholecalciferol, ergocalciferol or calcifediol), dosages and duration of follow-up as important limitations [68]. Whether correction of vitamin D deficiency using nutritional vitamin D improves bone or cardiovascular outcomes in CKD remains a subject of debate. At present, there is no evidence for a benefit of vitamin D supplementation on the risk of bone loss, fractures or cardiovascular events in adults with CKD. A recently published European consensus statement advised on calcium intake in CKD. The main conclusions included a suggested total calcium intake from diet and medications together of 800–1000 mg per day, but without exceeding 1500 mg per day, to maintain a neutral calcium balance in adults with CKD [69]. Finally, dietary phosphate intake influences parameters of mineral metabolism [70]. As CKD stage 4–5D is considered a state of positive phosphate balance, therapeutic strategies aim at correcting this among others by limiting dietary phosphate intake and the use of phosphate binders. At the same time, too aggressive dietary phosphate restriction has the potential to compromise adequate intake of other nutrients, especially proteins. Avoiding dietary supplements, medications and ultra-processed foods that contain large amounts of inorganic phosphate [71] could be a feasible strategy. Moreover, plant phosphate is less absorbable in the gastro-intestinal tract than animal phosphate, and a vegetarian diet had a favorable effect on phosphate homeostasis in CKD patients, compared with a meat diet [72].

INFLUENCE OF COMORBIDITIES

Diabetes

Diabetes is considered a risk factor for osteoporosis, but whether diabetes is also an independent predictor of adverse bone outcomes in CKD remains controversial. Several cohort studies could not demonstrate that co-existing diabetes independently predicts fracture risk in dialysis patients [73, 74], whereas other studies in either prevalent hemodialysis patients [75] or wait-listed hemodialysis patients and transplant recipients [76] did identify diabetes as a risk factor for fractures.

Interestingly, similar mechanisms seem to drive VC in patients with CKD as in those with diabetes. Phosphate induces a phenotypic change in vascular smooth muscle cells (VSMCs) towards a bone phenotype, a phenomenon also known as osteochondrogenic differentiation, through phosphate transporter-1 (PiT-1) [77, 78]. Interestingly, exposure of VSMCs to high glucose concentrations led to upregulation of PiT-1 expression [79, 80]. Moreover, combined high doses of phosphate and glucose led to more pronounced calcification of VSMCs, compared with normoglycemic conditions [79, 80]. Together, these findings seem to suggest that high-glucose conditions render VSMCs more susceptible to phosphate-induced VC. In line with these *in vitro* observations, a recent cohort study demonstrated interaction by the presence of type 2 diabetes for the association between plasma phosphate and all-cause mortality. In individuals with type 2 diabetes, individuals within the highest plasma

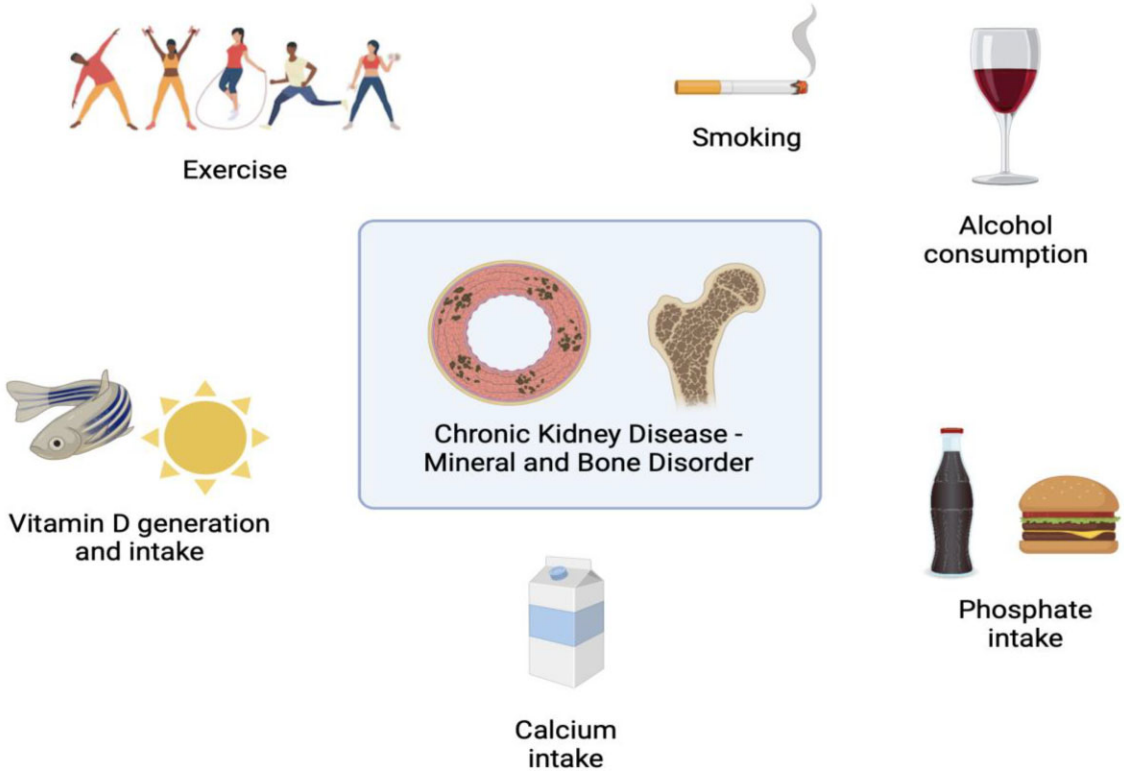

Figure 2: Environmental/lifestyle factors that influence CKD-MBD. Overview of environmental/lifestyle factors that are considered to influence bone mineral density, fracture risk, VC or a combination of these in patients with CKD. Figure created with Biorender.com.

phosphate tertile had a higher mortality risk than those in the intermediate tertile, while no such association was observed in individuals without type 2 diabetes.

Serum T_{50}, reflecting an individual's propensity to develop VC based upon the conversion of primary to secondary CPPs, has been associated with an increased risk of (cardiovascular) morbidity and mortality across stages of CKD [81–83]. Interestingly, T_{50} has also been (weakly) associated with cardiovascular mortality in the general population, but this risk was stronger in individuals with co-existing CKD, diabetes or both [84]. A subsequent study in a cohort of patients with type 2 diabetes confirmed that T_{50} is associated with cardiovascular mortality in this population and improved risk prediction, compared with a model containing only traditional cardiovascular risk factors [85]. Taken together, while diabetes and CKD seem to have shared pathophysiological pathways that promote cardiovascular risk, the co-existence of both amplifies the risk of cardiovascular disease and premature mortality.

Hypertension

Hypertension is among the traditional cardiovascular risk factors and abundantly prevalent in the CKD population. While deregulated mineral metabolism is considered to play a major role in vascular stiffening, leading to an increased blood pressure, little is known about the interaction between CKD-MBD and hypertension in relation to cardiovascular outcomes. Mineral parameters such as PTH, FGF-23 and osteoprotegerin have been associated with both hypertension and cardiovascular outcomes in CKD patients [86–89]. Interestingly, FGF-23 seems to have off-target effects on the sodium-chloride co-transporter NCC, promoting sodium retention, which could provide an additional mechanistic explanation for the link between FGF-23 and hypertension [90]. CKD patients with a higher plasma FGF-23 level showed a less pronounced antiproteinuric response to dietary sodium restriction than those with a lower FGF-23 level [91]. Though plausible, it has not been clearly established whether elevated blood pressure is on the causal pathway between mineral abnormalities and cardiovascular outcomes. Both hypertension and mineral metabolism are considered independent modifiable risk factors for cardiovascular disease in CKD.

CLINICAL MANIFESTATIONS OF CKD-MBD

Although other clinical manifestations may be described, the main clinical manifestations associated with CKD-MBD include bone disease and VC. Prevalence and severity of clinical manifestations may vary depending on the degree of renal function and the time since CKD inception, and they may persist even after a successful kidney transplantation (RTx). In a recent observational study, as much as 75%–80% of the observed subjects exhibited elevated PTH 1 year after RTx. Notably, high PTH levels during the first year of RTx seem to be associated with long-term graft loss [92].

Bone manifestations

ROD refers to specific morphological bone abnormalities directly linked to CKD. The term "renal osteodystrophy" should be reserved to describe the bone pathology directly associated with CKD [1, 2, 93, 94]. Accurate evaluation typically requires a bone

biopsy, which allows for a detailed assessment using the expanded Turnover, Mineralization and Volume (TMV) classification system established during the 2006 Kidney Disease: Improving Global Outcomes (KDIGO) consensus conference [1]. According to the TMV classification system, several types of bone abnormalities are identified through bone biopsy:

- Osteitis fibrosa (high bone turnover) is characterized by high bone turnover and is typically caused by increased PTH, as seen in SHPT in CKD patients. Histologically, it is marked by excessive osteoclastic and osteoblastic activity, leading to woven bone and marrow fibrosis formation [1, 95, 96].
- Adynamic bone disease (low bone turnover) is characterized by markedly reduced bone turnover, often due to over-suppression of PTH, either from excessive use of calcium-based phosphate binders, vitamin D analogs or calcimimetics. Histologically, it is characterized by minimal osteoblastic activity and reduced osteoid and bone formation rates, leading to a fragile bone structure [1, 97].
- Osteomalacia (defective mineralization) is primarily a defect in bone mineralization, often due to low vitamin D levels, aluminum toxicity or certain medications. Histologically, this results in an accumulation of unmineralized bone matrix (osteoid) with insufficient deposition of calcium and phosphate, leading to the softening of the bone [1, 98].
- Mixed uremic osteodystrophy is a condition that combines features of both high bone turnover (osteitis fibrosa) and defective mineralization (osteomalacia). Histologically, this results in a complex bone pathology where both excessive bone resorption and impaired mineralization are present simultaneously [1].

Clinically, ROD manifests as bone pain, skeletal deformities and an increased risk of fractures. In particular, high turnover diseases are characterized by bone pain, especially in long bones, and deformities due to excessive bone resorption, mainly occurring in the cortical bone. Prolonged exposure to increased levels of PTH may also lead to brown tumors, a bone lesion that arises in settings of excess osteoclast activity [26]. In contrast, low turnover diseases such as adynamic bone disease (ABD) present with subtler pain but a higher risk of fractures, especially in the hip and spine, due to reduced bone remodeling [95, 97]. Osteomalacia, characterized by poor bone mineralization, leads to diffuse pain, muscle weakness and fractures, particularly in weight-bearing bones [98]. Finally, mixed uremic osteodystrophy combines these features, complicating diagnosis and management [98].

The gold standard for diagnosing ROD remains bone biopsy with histomorphometric analysis. This allows direct assessment of bone turnover, mineralization and volume [1, 2, 93, 99, 100]. Despite its accuracy, the invasive nature of bone biopsy limits its routine use in clinical practice. In this regard, in the KDIGO clinical guidelines on CKD-MBD management, bone biopsy is not routinely recommended but should be considered in patients with CKD stages G3a through G5D, if the specific type of renal osteodystrophy is likely to influence treatment decisions [2].

Surrogate markers and imaging studies to assess bone health in CKD have been extensively studied. Noninvasive imaging techniques like dual-energy X-ray absorptiometry (DXA) and high-resolution peripheral quantitative computed tomography (HR-pQCT) offer valuable insights into bone mineral density and microarchitecture, respectively [101].

Biomarkers such as (intact) PTH, bone-specific alkaline phosphatase (bALP) and the amino-terminal propeptide of type 1 procollagen (P1NP) can be used to evaluate bone turnover [97, 102]. However, while these markers are commonly used in the general population, their use in CKD patients to assess bone turnover as a single or combination of biomarkers warrants further validation. Consistently, current KDIGO guidelines do not advocate their introduction in clinical practice and recommend using trends in PTH levels, rather than absolute values, to guide treatment decisions for bone disease [2].

Vascular calcification

VC is a common and severe complication of CKD, significantly contributing to high cardiovascular morbidity and mortality. The prevalence and severity of VC increase progressively as renal function declines. It is estimated that about 40% of patients with stage 4 CKD, 60% of incident dialysis patients and 80% of prevalent dialysis patients have VC [103, 104].

VC is a degenerative process characterized by the deposition of calcium and phosphate in the context of the intimal or medial layer of the arterial wall (Fig. 3). Intimal calcification typically occurs because of atherosclerosis and is caused by lipid and cholesterol accumulation underneath the injured endothelium. It is usually linked to traditional cardiovascular risk factors [105, 106] and leads to ischemic events such as coronary, cerebrovascular and limb events [106]. In contrast, medial calcification involves mineral deposition within the medial layer of the arterial wall where vascular smooth muscle cells (VSMCs) are located. This type of calcification is more specific to CKD patients [107] and results in arterial stiffness, reduced compliance, and increased pulse pressure, all of which contribute to left ventricular hypertrophy, heart failure and increased cardiovascular mortality.

VCs are often detected incidentally on imaging [9, 108–110]. Non-invasive techniques like plain X-rays, two-dimensional ultrasound or computed tomography (CT) can assess VC but cannot distinguish intimal from medial calcification [9, 108–110]. Plain radiography is an easy and widely available tool for determining the presence and, in a semi-quantitative way, the extension of vessel calcification [9, 108–110]. The commonly used Kauppila index scores abdominal aortic calcification (AAC) using lateral lumbar spine radiographs, while the Adragao score evaluates calcification in the pelvis and hands. Ultrasound detects calcifications in superficial arteries and measures pulse wave velocity, an arterial stiffness index [9, 108–110]. Finally, multi-detector CT (MDCT) is highly sensitive for assessing and quantitatively estimating VC in districts, such as coronary arteries inaccessible by plain X-ray or ultrasound [9, 108–110]. Higher coronary artery calcification (CAC) correlates with atherosclerotic plaque burden and CV outcomes and, as suggested by the Chronic Renal Insufficiency Cohort (CRIC) study results, is a valid tool for the risk of myocardial infarction or heart failure stratification in CKD subjects [111]. However, CT CAC scoring is limited by high radiation exposure and cost, and low accessibility. Consistently, the current KDIGO guidelines do not advocate VC screening in all CKD subjects but suggest the use of the information of VC derived by imaging studies to guide the management of patients [9, 108–110].

CONCLUSIONS

CKD-MBD results from a complex disruption of mineral homeostasis due to declining kidney function. As CKD progresses, the compensatory mechanisms involving FGF-23, PTH, klotho, CPPs, MPs and other factors become insufficient to maintain mineral

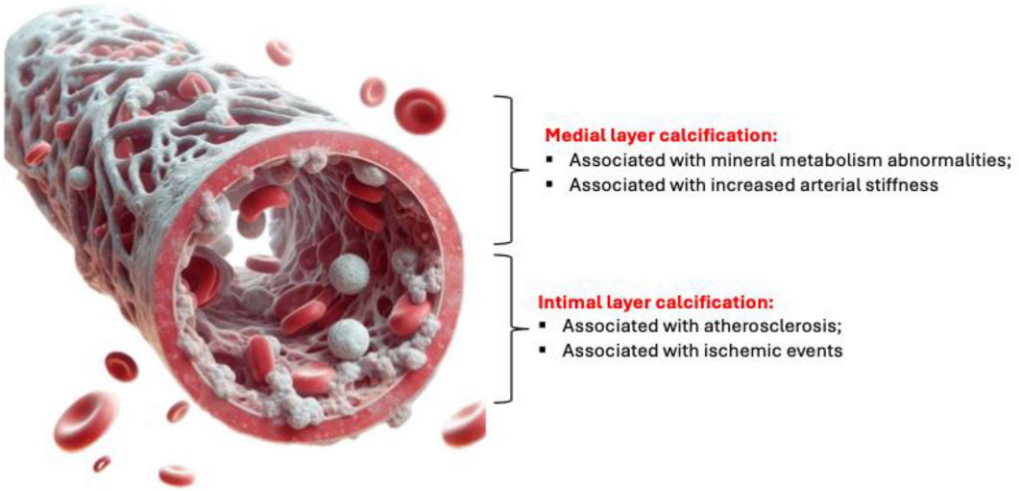

Figure 3: At least two types of VCs have been identified in renal insufficiency. One is located in the intima layer of the arterial wall and is likely associated with atherosclerosis; the other is located in the media layer of the arterial wall and is associated with CKD-MBD.

homeostasis, leading to CKD-MBD complications such as VC and bone disorders. Although clinical CKD-MBD manifestations are more prevalent as renal function declines, there is a significant variability in clinical manifestations among CKD patients. Genetic studies suggest that these abnormalities only explain part of the clinical variability, and numerous questions regarding the interaction with different medical conditions, such as diabetes or hypertension, are still unresolved. A deeper understanding of the pathophysiology of CKD-MBD is needed to understand the phenotype variability and the relative contribution to organ damage of factors involved in CKD-MBD to develop more effective interventions to improve outcomes in patients with CKD.

FUTURE PERSPECTIVES

Therapeutic strategies targeting CKD-MBD factors hold promise for improving patient outcomes. One potential approach is klotho restoration; enhancing klotho expression or function may improve FGF-23 sensitivity and restore mineral homeostasis. Experimental therapies using klotho supplementation or gene therapy are being explored [25]. Another strategy focuses on CPP inhibition—developing agents that prevent CPP formation (or transition to secondary forms) or promote their clearance could reduce the risk of VC [34]. All these approaches could complement available therapeutic strategies to retard CKD progression and organ damage. Similarly, a better understanding of miRNA could provide potential therapeutic targets to manipulate bone metabolism and perhaps VC deposition [49].

Indeed, a multifaceted approach is likely required to tune bone mineral metabolism and avoid adaptive mechanisms turning into maladaptive ones. Addressing the interconnected disturbances of CKD-MBD in different medical conditions might lead to early intervention and individualized treatment plans to prevent the progression of CKD-MBD and improve patient outcomes.

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DATA AVAILABILITY STATEMENT

No new data were generated or analysed in support of this research.

CONFLICT OF INTEREST STATEMENT

A.B. attended advisory boards and received speaking honoraria from Amgen, Sanofi and Sanifit. Other authors do not have any conflict to disclose concerning this publication.

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