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# Update on Chronic Kidney Disease Mineral and Bone Disorder in Cardiovascular Disease

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## Abstract

The Chronic Kidney Disease (CKD) Mineral and Bone Disorder (MBD) encompasses changes in mineral ion and vitamin D metabolism that are widespread in the setting of CKD and end-stage renal disease (ESRD). MBD components associate with cardiovascular disease in many epidemiologic studies. Through impacts on hypertension, activation of the renin-angiotensin-aldosterone system, vascular calcification, endothelial function, and cardiac remodeling and conduction, MBD may be a direct and targetable cause of cardiovascular disease. However, assessment and treatment of MBD is rife with challenges due to biological tensions between its many components, such as: calcium and phosphorus with their regulatory hormones fibroblast growth factor 23 and parathyroid hormone; fibroblast growth factor 23 with its co-receptor klotho; and vitamin D with control of calcium and phosphorus. These complex interactions between MBD components hinder the simple translation to clinical trials, which are ultimately needed to prove the benefits of treating MBD. Deeper investigation using precision medicine tools and principles, including genomics and individualized risk assessment and therapy may help move the field closer towards clinical applications. This review will provide a high level overview of conventional and 'precision' epidemiology in MBD, potential mechanisms of cardiovascular disease pathogenesis, and guiding therapeutic principles for established and emerging treatments.

### Keywords

cardiovascular disease; phosphorus; fibroblast growth factor 23; klotho; vitamin D; mineral metabolism

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## Introduction

Abnormal bone and mineral ion homeostasis frequently complicates chronic kidney disease (CKD) and is a prime suspect in the accelerated development of cardiovascular disease. By definition, the syndrome of CKD mineral and bone disorder (MBD) involves changes in mineral ion homeostasis, bone quality and turnover, and ectopic extraosseous calcification.[1] The current prevailing paradigm roots the pathogenesis of the syndrome in the abnormal handling of phosphorus, calcium and vitamin D, which will be the focus of this review.[2]

Although the full complexity of MBD physiology is beyond our scope, a simplified paradigm is critical to understanding the multiple components in MBD and their inherent collusion in the pathogenesis of cardiovascular disease. Under this simplified paradigm, the ability to filter and excrete a phosphorus load is progressively compromised as kidney disease progresses, requiring higher fractional excretion of phosphorus to maintain balance. The fractional excretion of phosphorus is controlled by fibroblast growth factor 23 (FGF23) and parathyroid hormone (PTH) each of which reduce expression of sodium-phosphate co-transporters in the kidney's proximal tubule. As FGF23 and then PTH rise in CKD,[3] they exert opposing effects on vitamin D metabolism creating a physiologic "tug of war" culminating in CKD-MBD. For instance, whereas PTH stimulates transcription of 1-α hydroxylase that converts 25-hydroxyvitamin D (25-D to 1,25-dihydroxyvitamin D (1,25-D), FGF23 inhibits it. Rising FGF23 creates a state of 1,25-D deficiency that drives down serum calcium and further elevates PTH.[4] In the distal tubule of the kidney, both PTH and FGF23 appear to increase calcium reabsorption (Figure 1).[5,6] In the case of FGF23 this action may compensate for low gastrointestinal calcium absorption induced by 1,25-D deficiency. In the case of PTH this action helps raise serum calcium, the dominant function of PTH. In both cases calcium reabsorption prevents urine calcium phosphorus supersaturation which may otherwise result from enhanced phosphaturia.[5,6]

Exacerbating this physiologic spiral in CKD is a simultaneous loss of expression of α-klotho, the co-receptor for FGF23.[7] Klotho is a membrane-bound protein that interacts with fibroblast growth factor (FGF) receptors to increase their specificity for FGF23 and to drive signaling pathways that are responsible for its effects on mineral ion balance and vitamin D metabolism.[8] In animals, klotho transcription can be suppressed by FGF23, phosphorus loading and vitamin D deficiency, suggesting additional physiologic feedback.[9] Additionally, klotho can be cleaved or alternatively spliced to result in soluble forms of unclear physiologic significance.[10–12] Ultimately, the additional loss of klotho activity creates resistance to FGF23, further driving levels to concentrations up to 100–1000 times normal in end stage renal disease (ESRD).[13,14]

In this review we provide a high-level overview of the current knowledge linking the above described changes in mineral ion and vitamin D homeostasis with cardiovascular disease in CKD. With many high quality and comprehensive reviews in the field, here we focus on integrating across epidemiology, basic biology, precision medicine, and therapeutic trials to derive 'big picture' lessons on the road ahead. We highlight the many promising and biologically intertwined targets in MBD and argue that its inherent complexity and feedback will require a holistic, multifaceted approach aimed at the full mineral and vitamin D axis to

provide the highest likelihood of success in identifying and combating its role in cardiovascular disease.

## Epidemiologic Associations of MBD and Clinical Cardiovascular Disease

The recognition of MBD as a risk factor for premature mortality and cardiovascular disease largely began with observations about risk related to higher levels of serum phosphorus.[15] Reports linked higher serum phosphorus to heightened risk of all-cause and cardiovascular mortality, cardiovascular events, and heart failure in many populations including patients with kidney disease and the general population.[16–21] Meanwhile, as this literature proliferated, FGF23 was discovered as a novel hormone regulating both phosphorus and vitamin D homeostasis.[22,23]

Since its discovery, higher FGF23 has been strongly associated with numerous adverse outcomes including all-cause and cardiovascular mortality, cardiovascular events, atrial fibrillation, and heart failure with a generally larger magnitude of association than observed in studies of phosphorus.[14,24–33] Like phosphorus, increased cardiovascular risk associated with higher FGF23 was reported in a wide variety of groups including those with ESRD, CKD, and the general population with the strongest risks in patients with CKD and ESRD.[34] Although FGF23 has been associated with many non-cardiovascular outcomes as well, [29,33,35–38] some of the most commonly reported and robust associations are with heart failure.[34]

FGF23 has a feedback relationship with its co-receptor, klotho, such that klotho deficiency can raise FGF23 and high FGF23 can exacerbate klotho deficiency via low 1,25-D.[9] Using epidemiology to disentangle the exact role of klotho versus FGF23 in cardiovascular disease is challenging because klotho functions primarily as a membrane-bound receptor in tissues which are not regularly sampled in human studies. Cleaved and alternatively spliced forms of klotho circulate, but their role is not firmly established.[10] Current measurement methods to detect circulating klotho have significant limitations due to assays and sample stability.[7,39] For instance, although animal models show decline in membrane-bound klotho with worsening kidney function, many of the existing studies of circulating klotho in humans show only a modest or no decline in klotho expression with worse CKD.[40–42] In light of these challenges, most epidemiologic studies of klotho are small with limited power and show mixed results.[39,40,43–46] Only a few studies report that reduced circulating klotho is associated with increased mortality or worse cardiovascular outcomes including atrial fibrillation.[39,46]

Vitamin D deficiency is a central link between FGF23, klotho, phosphorus and other MBD components such as PTH and calcium. A large observational literature reports associations between low levels of vitamin D with incidence of several cardiovascular phenotypes, including cardiovascular mortality and major cardiovascular events, with most studies focused on 25-D.[47–50]Despite many studies, relationships between vitamin D and cardiovascular disease have not been robust across different populations,[51,52] in meta-analyses of cohort studies, or in clinical trials primarily of surrogate outcomes.[53,54] However, not all of these studies have targeted CKD populations in which vitamin D metabolism is deranged resulting in low levels of 1,25-D specifically. Observational studies

within the ESRD population in particular demonstrate that treatment with 1,25-D in the form of calcitriol or vitamin D analogs is associated with improved mortality.[55,56] Placebo-controlled clinical trials have not been performed to confirm these benefits in ESRD. In pre-dialysis CKD, trials of 1,25-D with surrogate cardiovascular outcomes have been performed with mixed results.[57–59]

One of the challenges with treating and studying vitamin D in the CKD and ESRD populations is that 1,25-D is often not measured clinically or in cohorts and may not be reliably assessed in the circulation due to its shorter half-life and significant local production and paracrine action. High PTH and lower serum calcium both are common clinical 'read-outs' of 1,25-D deficiency that are associated with mortality in some observational studies in CKD, but not consistently.[17] Magnesium is an additional factor that may interact with vitamin D and calcium homeostasis promoting deficiency of these MBD components.[60] Serum and dietary magnesium have received increasing attention as risk factors for cardiovascular disease in the general population and populations with CKD.[21,61,62] In ESRD patients on hemodialysis, low magnesium dialysate which depletes total body magnesium also associates with higher cardiovascular risk.[63]

## MBD and Mechanisms of Cardiovascular Disease

The well-established epidemiologic links of the MBD components with clinical cardiovascular disease have stimulated a large body of work evaluating pathways that could mediate these effects. Discovery of biologically plausible pathways of cardiovascular disease that can be demonstrated experimentally in animals or observed consistently in studies of patients can help bolster the conclusion that the epidemiologic associations are potentially causal and not merely the result of confounding or other biases. In this section we briefly review some of the candidate mechanisms with support in the literature.

**Vascular and Endothelial Function—**Vascular calcification is common and premature in patients with kidney disease leading to poor vascular compliance and end organ damage.[64–66] Procalcific stimuli in kidney disease include increased serum phosphorus, excess use of vitamin D, calcium loading from calcium-based phosphorus binders, supplements and dialysate, and inflammation. These effects can be exacerbated by insufficient activity of calcification inhibitors, including magnesium, vitamin K, or reduced klotho expression.[67,68] For instance, phosphorus loading and klotho depletion consistently induce calcification and reduce vascular compliance *in vitro* and *in vivo* in animals.[69–71] Similarly, restoration of normal klotho expression in animals with vitamin D agonists, or reduction in phosphorus exposure through diet can reverse or prevent the calcific phenotype.[72,73] In patients, simultaneously reducing procalcific stimuli, such as phosphorus, while bolstering calcification inhibitors through use of vitamin D, magnesium or vitamin K may be a strong rational for combination therapy of MBD, but trials are needed.

Apart from calcification per se, vascular and endothelial dysfunction are common sequelae of CKD, with several studies implicating features of MBD in this altered physiology. High phosphorus impairs endothelial function *in vitro* and in patients,[74–76] whereas soluble klotho appears to have beneficial effects on the vasculature by promoting the survival of vascular

smooth muscle cells and stimulating nitric oxide production.[76,77] Due to their effects on klotho or directly via the vitamin D receptor, vitamin D and vitamin D receptor agonists improve endothelial function and vascular stiffness in multiple pilot studies in CKD.[58,78–81] The role of FGF23 in the vasculature is less clear, however indirect effects are plausible via its interaction with the renin-angiotensin-aldosterone system (RAAS), promotion of inflammation, and antagonism of active vitamin D.[82–84] To better understand the landscape of ongoing, but unpublished, studies in MBD and cardiovascular disease we performed a review of registered ongoing studies in ClinicalTrials.gov using keyword terms for MBD components and focused on interventional studies in active, ongoing or recruiting status. Based on our review, the role of 1,25-D, magnesium, and vitamin K in reducing vascular calcification in CKD and the role of dietary phosphorus in vascular stiffness and endothelial function are the subject of ongoing studies (See Selected Examples in Table 1)[85,88].

**Hypertension and RAAS Activation—**Elevated blood pressure is a major risk factor for clinical cardiovascular disease, including coronary artery disease, stroke and heart failure, with a growing burden globally.[89] Vitamin D deficiency has long been linked to hypertension observationally.[53] High levels of vitamin D inhibit renin thereby downregulating RAAS and potentially blood pressure.[90] Clinical trials have not confirmed benefits of vitamin D on brachial blood pressure,[53] however a recent study suggests a potential impact on central blood pressure which was not measured in many prior studies.[91]

In animal models high dietary phosphorus also raises blood pressure.[92,93] Investigators have suggested potential mechanisms including changes in sympathetic activity,[92] activation of the RAAS,[93] or effects of phosphorus-regulatory hormones on sodium excretion.[94] Observational human studies have largely reported a neutral or favorable association between higher phosphorus intake and lower blood pressure;[95–97] However these studies cannot easily distinguish inorganic phosphorus common in dietary additives from healthy sources of phosphorus such as whole grains, legumes, dairy, and animal-based protein that are believed to have blood pressure lowering effects.[98] Other minerals including calcium and magnesium may also be important in blood pressure regulation and often correlate with dietary phosphorus intake.[99–101] Ongoing interventional studies may help reconcile the effects of phosphorus additives on blood pressure in healthy individuals (Table 1).[88]

The role of FGF23 and klotho in blood pressure is less well studied. Recent reports suggest an association of FGF23 with hypertension, potentially due to increasing expression of the sodium chloride co-transporter in the distal tubule.[94,102] FGF23 may also increase blood pressure indirectly through its inhibition of 1,25-D or by activating RAAS directly.[103] Some support for this hypothesis comes from studies demonstrating an impact of FGF23 to reduce angiotensin converting enzyme 2, an enzyme which degrades angiotensin.[82,103] Although this area of investigation is immature, remarkably high risk of blood pressure dependent outcomes such as heart failure and stroke,[34] and interactions between circulating FGF23, phosphorus and efficacy of RAAS blockade and diuretics suggests that this is a fruitful area for additional investigation.[104–109]

**Abnormal Cardiac Geometry and Function—**In many human studies, abnormalities of MBD components including phosphorus, vitamin D, PTH and FGF23 associate with

adverse changes in cardiac structure or function that are independent of static blood pressure.[16,18,53,110] Relationships of higher FGF23 with left ventricular hypertrophy, concentric and eccentric remodeling and diastolic dysfunction are some of the most widely reported, with independent associations found in adults and children with and without kidney disease. [31,111–117].Experiments in preclinical models suggest that these associations may be the result of direct effects of FGF23 on the myocardium,[113,118,119] due to biased signaling via fibroblast growth factor receptor 4 (FGFR4) without klotho as a co-receptor. [120,121] Perhaps by promoting this klotho-independent signaling pathway, cardiac hypertrophy is present in heterozygous klotho knockout mice who also have higher FGF23.[113,122,123] Additionally, experimental manipulations that increase klotho can partially abrogate hypertrophy related to these and other stimuli.[122,124] Given their inherent feedback in many studies it is difficult to disentangle direct klotho effects from compensatory changes in FGF23. Nonetheless, the current framework in which adverse cardiac effects of FGF23 rely on klotho-independent signaling,[120] suggests a unifying paradigm in which high FGF23 coupled with low klotho expression increasingly directs FGF23 signaling towards its klotho-independent adverse effects.[121] With this in mind interventions to reduce FGF23, raise klotho, or both need to be tested in patients with CKD to improve cardiac remodeling and function. Reduction in dietary or serum phosphorus could be one strategy supported by some observations, as could interventions to increase klotho expression via 1,25-D.[18,110] Initial trials of phosphorus reduction are underway (Table 1).[88,125] Trials of active vitamin D sterols in patients with CKD have not demonstrated the expected benefits on cardiac remodeling to date.[57,59]

**Abnormal Cardiac Rhythm and Sudden Death—**Managing MBD can be particularly difficult because of the critical role of calcium and magnesium in cardiac conduction. Uncontrolled MBD is often characterized by hypocalcemia related to severe 1,25-D deficiency. Furthermore, core treatments for MBD including nutritional and active vitamin D, calcimimetics and phosphorus binders can affect these divalent cations as major adverse effects. Use of low dialysate calcium (<2.5 mEq/L) and magnesium (<1.0 mEq/L) have each been associated with increased risk of sudden death, presumably of an arrhythmic cause. [63,126] Other mineral metabolites including high levels of FGF23 and low klotho have been associated with arrhythmias such as atrial fibrillation in some studies, potentially due to effects on cardiac remodeling.[25,28,46]

**Confounding and Limitations—**Despite compelling and consistent associations of many components of MBD with cardiovascular disease and plausible disease pathways, residual confounding of these relationships is hard to rule out without interventional trials. For example, high levels of FGF23 may be driven by other adverse risk factors including iron deficiency, inflammation, obesity and hyperaldosteronism.[83,127–129] Additionally, inadequate nutrition and chronic disease such as gastrointestinal and liver disease may impact levels of 25-D, calcium, and magnesium resulting in confounding.[60,130] 25-D may be impacted by reduced outdoor activity, obesity or an unhealthful diet without normal dietary sources such as fatty fish and fortified foods,[54,130] and multiple MBD factors including 25-D, phosphorus, FGF23 and PTH are affected by kidney function (Figure 2).[3] Each of these factors and others may confound the associations seen in many observational studies.

In animal models, FGF23 transcription is induced by adverse physiologic events such as myocardial ischemia, myocardial pressure overload and acute kidney injury.[131–133] Expression of FGF23 has also been reported in coronary plaques and cardiac tissue from CKD patients.[134] These studies raise the possibility that strong associations between FGF23, cardiovascular outcomes and mortality could be driven by reverse causality where FGF23 is a result, not a cause, of pathophysiologic changes. In nearly all cases, the complex web of MBD changes induced by interventions in animal models makes it difficult to isolate a single factor as the cause of the phenotype. With this in mind interpreting the full body of evidence including observational studies, animal studies, trials and other robust designs is needed to evaluate the most promising targets.

## "Precision" Epidemiology of MBD and Cardiovascular Disease

In light of the numerous risks reported in human and animal studies, targeting MBD risk factors for cardiovascular disease prevention appears obvious and deceivingly simple at first glance. However, initial biologic agents aimed at reducing FGF23 demonstrated increased mortality in preclinical rat models,[135] and phosphorus lowering therapies paradoxically associated with increased vascular calcification in initial small clinical trials.[136] Small trials of dietary phosphorus reduction and vitamin D supplementation show mixed effectiveness on surrogate outcomes such as MBD risk factors and cardiac geometry.[16,53,125] Fully-powered placebo-controlled trials of phosphorus binders and vitamin D sterols have not been conducted, but an initial large trial of cinacalcet to lower PTH failed to demonstrate a reduction in cardiovascular disease.[137] These observations could suggest that the epidemiologic associations described above are not truly causal, but are instead the result of confounding and other biases. Alternatively, heterogeneous risks and treatment effects across groups, or the substantial biological tensions in MBD physiology (**Box**) may cause discrepant, and sometimes unexpected, results across studies. The precision medicine paradigm provides a deeper lens to bolster causal inference and to explore heterogeneity and interactions among different MBD factors. For instance, if multiple disparate factors that converge to raise 25-D show expected associations with a disease outcome, then the evidence for a central role of 25-D in the disease process is strengthened.

In the next section we review the emerging epidemiologic literature with a precision focus, evaluating known genetic, environmental and other contextual factors that can help strengthen causal inference around MBD and cardiovascular disease and calibrate MBD biomarkers and health interventions to specific populations. Although not exhaustive, the examples described demonstrate the role these studies may play in understanding the potentially causal role of MBD in cardiovascular disease and in resolving across-study heterogeneity.

**Genomics—**A robust body of literature describes differences in MBD physiology by race and ethnicity, suggesting potentially important genetic contributions.[138] A search of the Database of Genotypes and Phenotypes identifies over 50 unique single nucleotide polymorphisms (SNPs) in or near >40 genes that have been linked to circulating MBD factors, including phosphorus, calcium, magnesium, vitamin D, vitamin D binding protein and PTH.[139–149] A selected list of the most relevant genes and their functions related to

MBD are provided in Table 2. Some of these candidate MBD genes have at least suggestive associations with cardiovascular phenotypes including coronary heart disease (GALNT2; and ATP2B1)[150,151] and inflammation (GCKR)[152–155] in genome wide studies, and hypertension in genome wide and confirmatory studies (CASR; and ATP2B1).[9,156–166] Variants in the gene encoding the calcium-sensing receptor (CASR) have been marginally associated with cardiac valve calcification in small studies.[167] These common associations could suggest that mineral metabolites are in fact on the causal pathway between these genes and cardiovascular disease ( Figure 3a); however other possibilities include pleiotropic gene effects that affect both pathways independently (Figure 3b), such as effects of GALNT2 on serum lipids,[168,169] or GCKR on inflammation.[152–155]

However a large number of MBD genes, including some of the candidates that are most likely to directly affect mineral metabolite levels based on our current biological understanding, have not emerged in genome wide screens for cardiovascular disease.[170–174] On the one hand the lack of associations could suggest that the MBD-disease associations are not causal, but these conclusions are challenging because some MBD traits may not be strongly influenced by common genetic variants. In addition, known MBD genes may have small effects on the biological risk factors and disease that are difficult to rule out in large scale genetic studies that employ stringent statistical criteria for significance due to the large number of tests performed. Candidate gene and Mendelian Randomization studies can evaluate the effect of specific genes that are known to be important in MBD and determine purportedly causal associations with cardiovascular risk. Only a few studies to date have evaluated cardiovascular outcomes related to SNPs influencing vitamin D, phosphorus, calcium, magnesium, PTH, klotho and FGF23 as candidates. In some, variants in CASR associate with high PTH as well as coronary artery disease.[175] In others, no clear associations have emerged.[176] Some, but not all,[177–182] candidate gene and Mendelian Randomization studies have linked genetic differences in vitamin D metabolism to cardiovascular disease including hypertension, heart failure, coronary artery calcification, and atherosclerotic coronary artery disease.[183–186] Variants in the klotho gene have been linked to mortality in ESRD, particularly in the absence of active vitamin D sterols which augment endogenous klotho.[187] In some small studies klotho variants associate with vascular disease or risk of kidney disease.[188,189] However, associations of klotho variants with vascular calcification was not observed in a larger, healthy population.[190]

Inconsistent and absent genetic associations may also reflect substantial complexity in the role of MBD factors in cardiovascular disease pathogenesis. For instance, effects of MBD genes on cardiovascular disease could depend upon other factors including environmental and host factors that interact to cause disease. An emerging body of literature supports interaction between vitamin D-related genes and circulating vitamin D for some cardiovascular event types, such as heart failure and possibly stroke, as well as other adverse event composites.[51,191–193] Others demonstrate interactions between the genotype of vitamin D pathway genes and the efficacy of vitamin D supplementation.[194] To continue to deepen our understanding of how MBD may contribute to cardiovascular disease pathogenesis we need additional studies that account for the confluence of multiple biological factors, including genetic factors, and exacerbating factors in our environment and patients (Figure 3c).

**Environmental influences and biologic processing—**Environmental factors can interact with MBD components to alter their pharmacokinetics. These environmental influences need to be considered not only confounders but also as potential biological interactions that may affect the impact of genes, treatments or other exposures related to MBD. For instance, cutaneous synthesis of vitamin D, which is a primary source of circulating 25-D in humans, is increased by environmental factors that expose individuals to greater intensity and duration of sunlight. Factors that have been described in the literature include latitude closer to the equator, outdoor occupations and recreational activities, and seasonal changes, all of which affect intensity and cumulative exposure to sunlight-derived ultraviolet radiation.[130,195,196] Similarly, dietary composition and use of mineral/vitamin supplements influence circulating levels of calcium, phosphorus, magnesium, and 25-D. A recent trial demonstrated increased efficacy of vitamin D supplementation in the setting of common variants in vitamin D pathway genes including the vitamin D receptor, CYP2R1 encoding the 25-hydroxylase, and CYP24A1 encoding the 24-hydroxylase.[194] Additional studies in this area are ongoing (Table 1). Studies of gene-environment interaction in other MBD components may identify additional complex determinants of both circulating levels and, ultimately, treatment efficacy.

Certain medications and comorbid illnesses may also influence pharmacokinetics of MBD components and modify the effectiveness of supplementation or restriction. Examples include intake of prebiotics, such as non-digestible oligosaccharides, that increase intestinal absorption of calcium, magnesium, and other minerals,[197,198] as well as oral contraceptives that may increase 25-D in women by increasing circulating levels of vitamin D binding protein.[199,200] Obesity also may interact with 25-D levels by providing a storage depot for the fat-soluble 25-D.[130] Thus, deeper study of the complex interaction of genomic, dietary and other biologic factors could help resolve inconsistency across studies and personalize therapy. Our review of ClinicalTrials.gov identified several examples of ongoing studies leveraging interaction between MBD components and genes, obesity and other biologic factors (Table 1).

## Treatment of MBD and Cardiovascular Disease

Although few well-powered clinical trials are currently available to guide management of MBD, initial proof-of-concept studies in the general population, CKD and ESRD continue to proliferate to help solidify the role of MBD in cardiovascular disease and refine future approaches. Several key principles that could guide management of MBD include the following:

1. **Reduce exposure to highly absorbable phosphorus.—**High phosphorus exposure can induce adverse biochemical changes including rise in serum phosphorus, FGF23, PTH, and fall in klotho and 1,25-D.[16] Whether phosphorus binders or other pharmacologic agents, such as niacin derivatives and tenapanor that block gastrointestinal phosphorus absorption, can reverse these changes in CKD or ESRD remains controversial and is an area of active investigation.[125,201–206] In observational comparative effectiveness studies, use of phosphorus binders associates with improved survival in ESRD and CKD.[207–209] In ESRD, studies of alternative phosphorus binders have been conducted,[210–213] but

there are not adequately powered studies of phosphorus binders versus placebo or alternative serum phosphorus targets.[214] In CKD, initial studies have provided some warnings including a paradoxically higher risk of vascular calcification with phosphorus binders and higher mortality in trials of niacin.[136,215] Before advocating expanded indications for these treatments adequately powered and rigorous studies are needed.

At a population level, reducing exposure to food additives containing highly absorbable phosphorus salts is an attractive strategy for preventive health. Although only a few observational studies have clearly demonstrated risks of high dietary phosphorus intake, interventional studies have shown that increased intake of highly absorbable phosphorus salts can drive higher FGF23, lower 1,25-D and, to a lesser extent, improve serum phosphorus, with reduced intake mitigating some of these changes.[16,216,217] Ongoing studies continue to evaluate this critical public health question (Table 1).[88]

**2. Pharmacologic replacement of vitamin D.—**Although observational studies suggest benefits of 1,25-D and activated vitamin D analogs in patients with ESRD,[55,56] no clinical trials have demonstrated a reduction in cardiovascular events or mortality with these therapies. Their widespread use in ESRD to control secondary hyperparathyroidism will make placebo controlled trials unlikely. Effects of 1,25-D to increase calcium and phosphorus also need to be weighed. Theoretically, additional effects of 1,25-D to raise FGF23 may be harmful or offset by stimulation of endogenous klotho expression. Studies evaluating dosing and monitoring of vitamin D agents in CKD are needed to provide optimal replacement without adverse MBD-related effects. Trials of 1,25-D or active vitamin D analogs in pre-dialysis CKD are currently sparse, with some studies demonstrating modest benefits on surrogate outcomes,[58,78–81,218] but several studies demonstrating no benefit.[57,59] Currently there are no adequately powered, placebo-controlled trials of hard clinical events.[219]

Treatment of 25-D deficiency with high dose cholecalciferol may lower PTH in CKD,[220] however definitive effects on cardiovascular disease have not been demonstrated.[219] Ongoing trials may shed some light in these areas including a large-scale study in the general population focused on the effects of 25-D supplementation on cardiovascular events. Nested ancillary studies will evaluate mechanisms including hypertension and atrial fibrillation.[88,221,222]

**3. Calcimimetics to lower PTH and FGF23.—**Whereas vitamin D receptor agonists raise FGF23 through a positive feedback loop, treatment with calcimimetics lowers FGF23, perhaps as an indirect effect of PTH reduction.[4,223–225] As expected based on the integrated physiology of MBD (Figure 1), calcimimetics also reduce 1,25-D. Thus, in ESRD when PTH and FGF23 are no longer effective at promoting urinary phosphorus excretion, they have the additional biochemical benefit of lowering phosphorus. On the other hand, lowered 1,25-D and impaired PTH response results in calcium lowering as well, a potentially dangerous side effect.[137] Despite favorable effects of the calcimimetic cinacalcet on phosphorus and FGF23, a reduction in cardiovascular events was not seen among patient with ESRD on dialysis randomized to cinacalcet compared with placebo in the Evaluation of Cinacalcet Hydrochloride Therapy to Lower Cardiovascular Events (EVOLVE) trial.[137] An

observational post-hoc analysis of EVOLVE demonstrated a reduction in cardiovascular events among participants randomized to cinacalcet that achieved a ≥30% reduction in FGF23 compared to those who did not.[223] This nonrandomized result should be viewed cautiously due to null results in the overall trial[137] and because reduction in FGF23 could be more simply a marker of adherence to therapy. More adherent participants regularly experience better outcomes compared to less adherent participants in trials even with placebo or ineffective interventions.[226]

With multiple examples of biological interactions and tensions between MBD components, approaches may need to consider strategies that achieve balance in MBD control (**Box**). For instance therapies that lower FGF23 directly, such as cinacalcet, may be most effective in ESRD on dialysis, but have risks in CKD where FGF23 promotes urinary phosphorus excretion and maintains phosphorus control. Optimal dosing of vitamin D, cinacalcet and phosphorus binders must achieve the potential benefits without excessive effects on calcium and phosphorus that could be harmful. The interaction of many MBD components suggests potential value of multifactorial therapy for MBD. In clinical trials of patients with ESRD on dialysis, combination therapy with vitamin D agonists and calcimimetics yields the most favorable changes across all MBD components due to their opposing effects on phosphorus, calcium and FGF23.[227,228] Studies of clinical outcomes using combination treatment strategies are needed. In the future, our growing understanding of FGF23 and klotho signaling may also suggest novel biologic agents that could interrupt adverse signaling pathways while maintaining function of critical homeostatic functions.

## Challenges and Future Directions in MBD and Cardiovascular Disease

Translating the complex biology of MBD to ultimately benefit patients will require observational and interventional studies to capture and consider a wide variety of influences on MBD, including genes, environment, diet, and disease status, to identify target groups and best approaches (Figure 2). Recent pharmacogenomics studies provide a few examples that may point to the future of MBD-cardiovascular disease studies, including identification of common variants in CASR that predict adverse hypocalcemic side effects of cinacalcet; variants in vitamin D binding protein and the vitamin D receptor that modify associations between 25-D and risk; and variants in vitamin D metabolic pathways that predict the response to vitamin D supplementation.[51,194,229] To understand these important disease and therapeutic modifiers, future studies will need to enroll and study diverse populations with adequate power for subgroup and interaction testing. Expansion of big data through electronic health records and a growing commitment to data sharing should make such studies more feasible and promote advances.

Additionally, widespread improvements in measurement of the MBD will also transform our ability to study and treat its potential effects on cardiovascular disease. Critical measurement challenges include diurnal, seasonal and random variation in many MBD components that limit reproducibility and comparability over time and across individuals.[230,231] Poor assay calibration and standardization continues to hinder studies of novel MBD risk factors, such as soluble klotho and FGF23, and limit the utility of established clinical measurements for

PTH and vitamin D.[7,232,233] Ongoing efforts to improve research assays, and standardize performance and calibration for clinical assays will enable progress in the field.[234,235]

While daunting, 'next generation' epidemiologic studies and targeted trials may help support causal inference and resolve heterogeneity in MBD-cardiovascular disease studies to risk stratify and optimally treat patients for MBD. The tremendous biological insights of the last two decades in MBD broadly have set the stage for rational therapies approaching the complex and intertwined physiology, ultimately leading to real success for future patients.

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**Text Box Key Biological and Therapeutic Tensions in CKD-MBD**

- Balance between FGF23 and klotho
- Potential tradeoff between FGF23 and phosphorus control (CKD)
- Tradeoff between PTH and calcium control
- Therapeutic window of Vitamin D and calcium-based binders

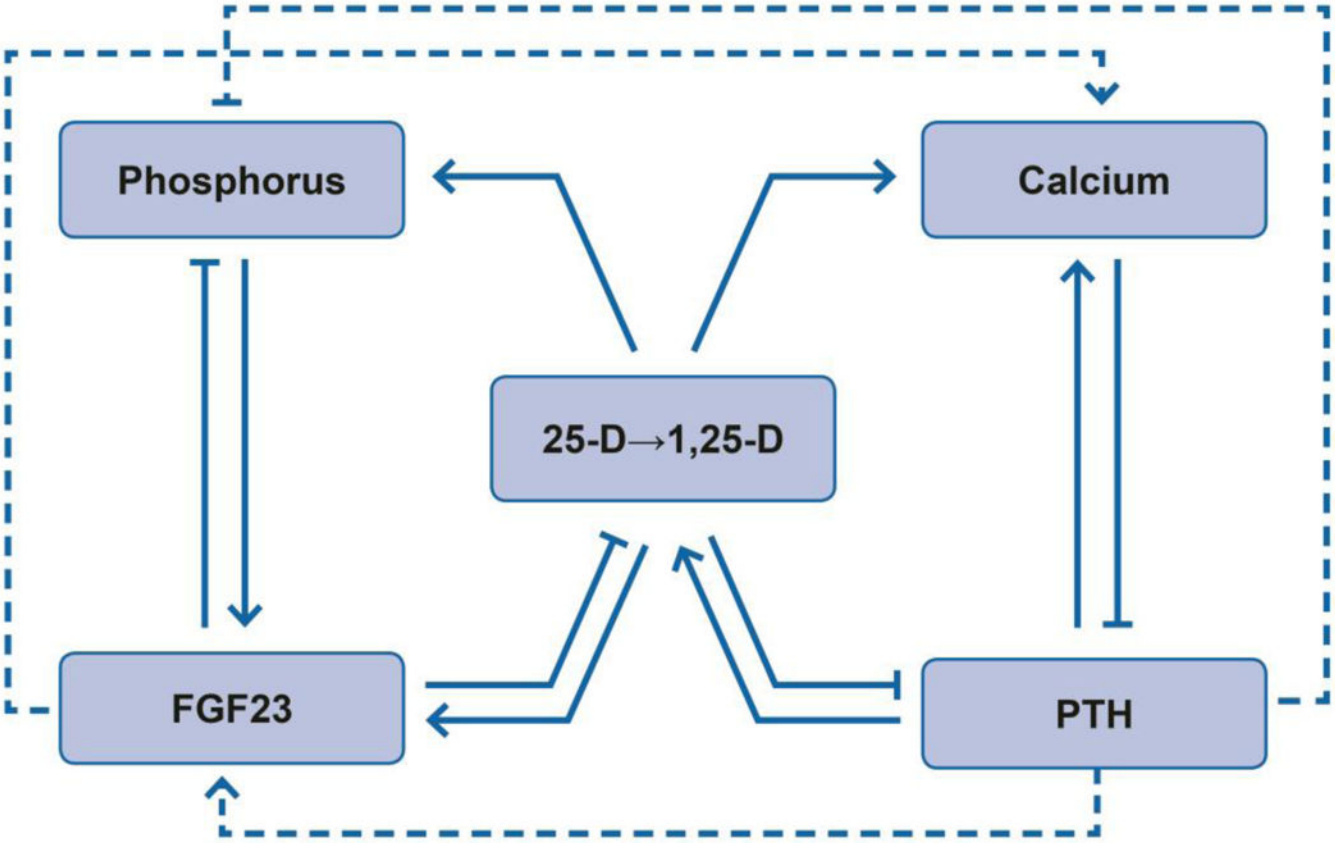


**Figure 1. Simplified Schematic of Mineral and Bone Disorder (MBD) Physiology in Chronic Kidney Disease.**

Solid lines and arrows depict dominant physiologic effects on circulating MBD factors including: (1) effects of fibroblast growth factor 23 (FGF23) to lower serum phosphorus by inhibiting 1α-hydroxylase that converts 25-hydroxyvitamin D (25-D) to 1,25-dihydroxyvitamin D (1,25-D) and stimulating urinary phosphorus excretion; (2) effects of parathyroid hormone (PTH) to raise serum calcium by stimulating 1α-hydroxylase and increasing urinary calcium reabsorption and bone remodeling; (3) effects of vitamin D to promote gastrointestinal absorption of calcium and phosphorus and feedback on FGF23 (stimulation) and PTH (inhibition). Dashed lines and arrows depict additional non-dominant effects of FGF23 to increase urinary calcium reabsorption and PTH to increase urinary phosphorus excretion and FGF23 transcription. In each case, arrows (→) represent actions that raise the associated MBD factor whereas capped lines (⊣) represent actions that lower the associated MBD factor. Altogether, the physiology encompasses major effects of FGF23 to reduce phosphorus and vitamin D and major effects of PTH to increase calcium and vitamin D, along with substantial redundancy, feedback, and crosstalk.

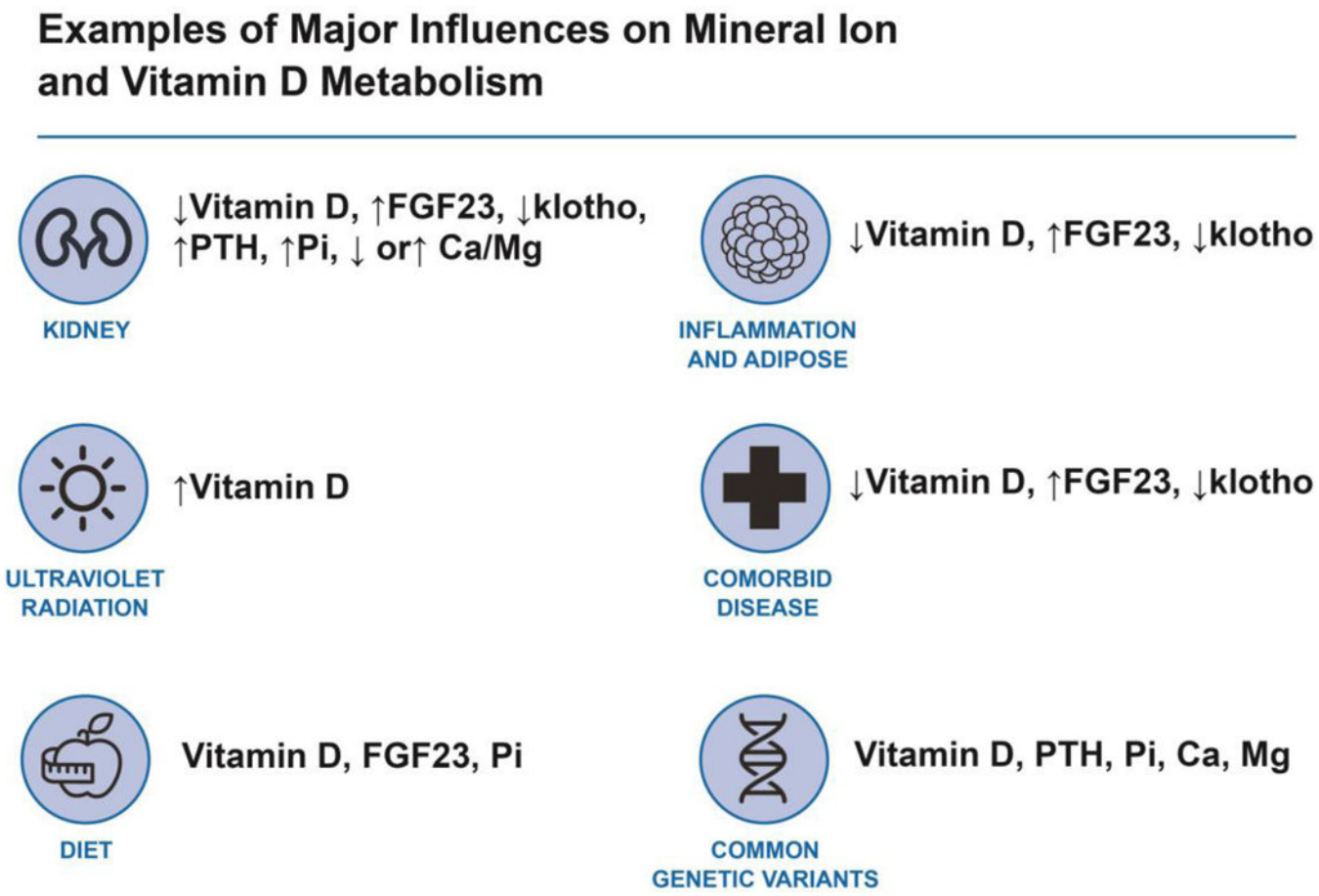


**Figure 2. Examples of Major Factors that Influence Mineral and Bone Disorder (MBD).**
These factors may confound associations or interact to modify associations leading to heterogeneity across studies. FGF23, fibroblast growth factor 23; PTH, parathyroid hormone; Pi, inorganic phosphorus; Ca, calcium; Mg, magnesium.

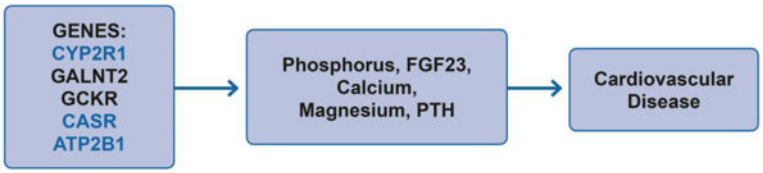


Figure 3b.

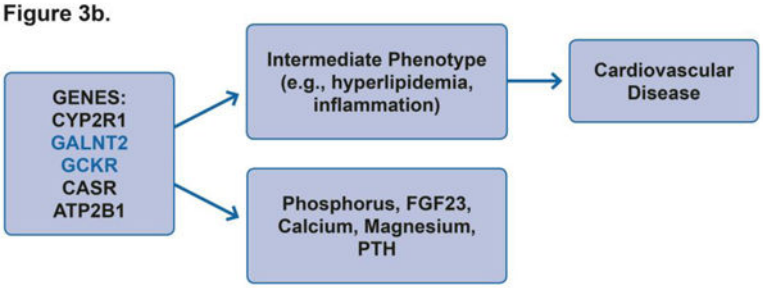


Figure 3c.

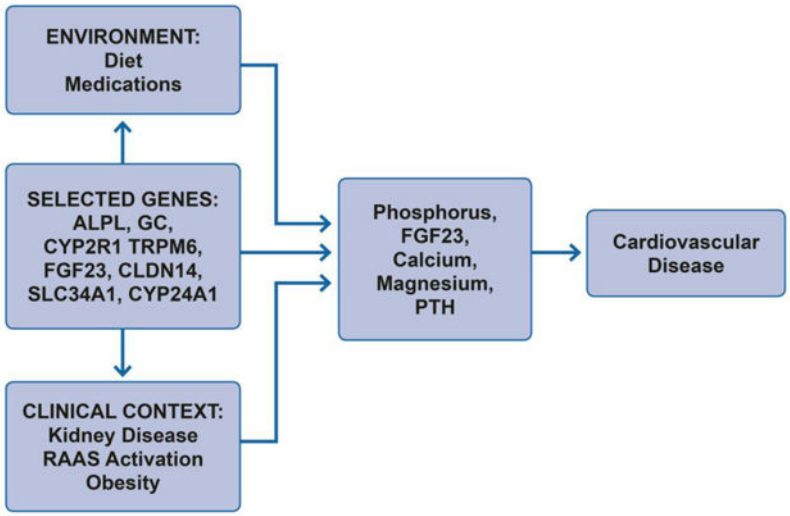


**Figure 3. Theoretical Framework for Incorporating Genetic Data in Studies of Mineral and Bone Disorder (MBD) and Cardiovascular Disease.**

In panel A genetic variants impact cardiovascular disease via effects on MBD intermediates without any other influences on cardiovascular disease pathways supporting causal inference. In panel B genetic variants may influence both MBD and other unrelated intermediate pathways leading to cardiovascular disease, demonstrating pleiotropy. Candidate genes with known primary biological effects on MBD and without other known unrelated biological effects may provide stronger causal inference (blue 3a) compared to genes with known pleiotropic effects (blue 3b). In panel C MBD related variants may interact with other patient and environmental factors to more strongly influence MBD and cardiovascular disease. Studies elucidating these effects may help identify subtle effects on common environmental exposures, explain across study heterogeneity, and allow

personalized therapy. FGF23, fibroblast growth factor 23; PTH, parathyroid hormone; RAAS, renin angiotensin aldosterone system.

**Table 1.**

Selected Registered Clinical Trials* Addressing Mineral and Bone Disorder (MBD) and Cardiovascular Disease (CVD) or Personalized MBD Therapy

| **Example Ongoing Studies of MBD and CVD Registered on Clinicaltrials.gov** | | | | | | |
|---|---|---|---|---|---|---|
| **NCT #** | **MBD/CVD** | **Population** | **ClinicalTrials.gov Status** | **Intervention** | **Duration** | **CVD Outcome** |
| **03234361** | Inorganic phosphorus and BP | Healthy individuals | Ongoing | Sodium phosphate vs. sodium chloride | 4 weeks | 24 hour ABPM |
| **02837328** | Magnesium and arrhythmia | Healthy individuals | Recruitment completed | Magnesium citrate vs. placebo | 4 weeks | Premature atrial contractions |
| **02620449** | Dietary phosphorus and vascular function | Healthy individuals | Ongoing | Diet low in additive-based phosphorus | 10 weeks | Pulse wave velocity; Flow-mediated dilatation- |
| **02545426** | Dialysate calcium and myocardial stunning | Patients with ESRD on hemodialysis | Recruitment completed | Dialysate calcium 2.5 vs. 3.5 mEq/L | 1 week | Echocardiographic strain |
| **02224144** | 1,25-D and vascular calcification | Kidney transplant recipients | Active, not recruiting | Calcitriol vs. placebo added to vitamin D3 | 12 months | Lower extremity vascular calcifications |
| **02542319** | Magnesium supplementation and vascular calcification | Patients with CKD | Recruiting | Oral magnesium supplementation | 12 months | Coronary artery calcification score |
| **02087683** | Vitamin D and cardiac remodeling | Patients with heart failure and vitamin D deficiency | Recruiting | Vitamin D supplementation | 12 months | Change in myocardial function and structure |
| **01528800 02870829 01742273** | Vitamin K and vascular calcification | Patients with ESRD on hemodialysis | Active, not recruiting/ Recruiting | Vitamin K | 12–18months | Coronary artery calcification |
| **02258074** | Phosphorus lowering and cardiac remodeling | Patients with CKD | Active, not recruiting | Factorial: Lanthanum carbonate vs. placebo, nicotinamide vs. placebo | 12 months | Left ventricular mass and geometry |
| **Example Ongoing Studies of Personalized MBD Therapy Registered on Clinicaltrials.gov** | | | | | | |
| **NCT #** | **MBD Theme** | **Population** | **ClinicalTrials.gov Status** | **Intervention/Question** | **Duration** | **Personalized Outcome** |
| **02925195** | Vitamin D response | General population | Ongoing | Cholecalciferol; Effect modification by clinical traits and genes | 16 weeks | Vitamin D concentrations; PTH |
| **02802449** | Vitamin D in African Americans | African Americans | Active, not recruiting | Vitamin D supplementation; Interaction with genetic and biologic factors | 8 weeks | PTH; inflammatory markers |
| **03134417** | Vitamin D and magnesium | Individuals with obesity | Recruiting | Vitamin D vs. Vitamin D plus magnesium vs. placebo; Magnesium as critical co-factor | 12 weeks | PTH; lipids; BP |
| **02572960** | Vitamin D, PTH and RAAS interaction | Vitamin D deficiency and secondary hyperparathyroidism | Recruiting | Factorial: Valsartan vs. placebo, Vitamin $D_3$ vs. placebo; Interaction of Vitamin D and RAAS | 12 weeks | Aldosterone; PTH; vascular measures |

[#] NCT , ClinicTrials.gov identifier; BP, blood pressure; ABPM, ambulatory blood pressure monitoring; ESRD, end-stage renal disease; 1,25-D, 1,25-dihydroxyvitamin D; CKD, chronic kidney disease; PTH, parathyroid hormone; RAAS, renin angiotensin aldosterone system

[*] Studies of MBD were identified by systematically searching ClinicalTrials.gov using keywords including “phosphorus”, “calcium”, “parathyroid”, “vitamin D”, “fibroblast growth factor 23”, “magnesium”, and “mineral and bone disorder”. Subsequently, example interventional studies were selected from among those in active, ongoing or recruiting status.

**Table 2.**

Selected Examples of Proposed Genes Related to Mineral and Bone Disorder (MBD) Identified on Database of Genotypes and Phenotypes (dbGaP)139 and Published Links to Cardiovascular Disease (CVD)

| MBD Phenotype | Example Proposed Gene | MBD-Related Function | Example of Described Relationship to CVD |
|---|---|---|---|
| **Vitamin D** | | | |
| **Circulating DBP**[147] | GC | Encodes DBP | |
| | ST6GALNAC3 | Glycosylates DBP | |
| | GALNT2 | Glycosylates DBP | Lipids[168,169]; Coronary Artery Disease[151] |
| **25-D**[143,145] | DHCR7 | Biosynthesis of vitamin $D_3$ | |
| | CYP2R1 | Biosynthesis of 25-D | Coronary Artery Disease[183] |
| | GC | Encodes DBP | |
| **Calcium (Ca)** [141,142] | | | |
| | CASR | Calcium-sensing receptor | Myocardial Infarction[175], Hypertension[166] |
| | CYP24A1 | Degrades 25-D and 1,25-D | Coronary Artery Calcification[184] |
| | GATA3† | Differentiation of parathyroid gland | |
| | CARS | Linked to Mendelian calcemic disorders | |
| | GCKR | Unknown; May decrease serum albumin | Inflammation[152–155] |
| **Phosphorus**[146] | | | |
| | CASR† | Calcium -sensing receptor | Myocardial Infarction[175], Hypertension[166] |
| | FGF23† | Phosphaturic hormone | |
| | SLC34A1† | Sodium-phosphate co-transporter | |
| | ALPL† | Encodes alkaline phosphatase | |
| **Magnesium (Mg)** [148,149] | | | |
| | TRMP6 | Magnesium transport in kidney and gut | |
| | ATP2B1† | Ca-ATPase; may control Mg cellular efflux | Hypertension[9,156–165]; Coronary Artery Disease[150] |
| **Parathyroid Hormone**[144] | | | |
| | CYP24A1 | Degrades 25-and 1,25-D | |
| | CASR† | Calcium-sensing receptor | Myocardial Infarction[175], Hypertension[166] |
| | CLDN14† | Paracellular transport of calcium and magnesium | |

Note: Single nucleotide polymorphism (SNP) associated with MBD phenotype is within the proposed gene unless noted otherwise.

†Proposed gene is located near or in strong linkage disequilibrium with a SNP that has been associated with the MBD phenotype MBD, mineral and bone disorder; CVD, cardiovascular disease; DBP, vitamin D binding protein; 25-D, 25-hydroxyvitamin D; 1,25-D, 1,25-dihydroxyvitamin D