Published in final edited form as:

Semin Nephrol. 2018 July ; 38(4): 397–409. doi:10.1016/j.semnephrol.2018.05.009.

Personalized Management of Bone and Mineral Disorders and Precision Medicine in End-Stage Kidney Disease

Anna Jovanovich, MD^{*,†} and Jessica Kendrick, MD, MPH^{*}

^{*}Division of Renal Diseases and Hypertension, University of Colorado Denver, Aurora, CO.

[†]VA Eastern Colorado Healthcare System, Denver, CO.

Summary:

Chronic kidney disease mineral bone disorder (CKD-MBD) is common in end-stage renal disease and is associated with an increased risk of cardiovascular morbidity and mortality. Mainstays of treatment include decreasing serum phosphorus level toward the normal range with dietary interventions and phosphate binders and treating increased parathyroid hormone levels with activated vitamin D and/or calcimimetics. There is significant variation in serum levels of mineral metabolism markers, intestinal absorption of phosphorus, and therapeutic response among individual patients and subgroups of patients with end-stage renal disease. This variation may be partly explained by polymorphisms in genes associated with calcium and phosphorus homeostasis such as the calcium-sensing receptor gene, the vitamin D-binding receptor gene, and genes associated with vascular calcification. In this review, we discuss how personalized medicine may be used for the management of CKD-MBD and how it ultimately may lead to improved clinical outcomes. Although genetic variants may seem attractive targets to tailor CKD-MBD therapy, complete understanding of how these polymorphisms function and their clinical utility and applicability to personalized medicine need to be determined.

Keywords

Personalized medicine; CKD-MBD; secondary hyperparathyroidism; precision medicine

End-stage renal disease (ESRD) is associated with an increased risk of cardiovascular disease and death.¹ Disorders of bone mineral metabolism characteristic of ESRD are thought to play a key role in this excess morbidity and mortality. The kidneys are critical for the regulation of serum calcium and phosphorus concentrations. Altered mineral metabolism occurs early in chronic kidney disease and includes progressive increases in fibroblast growth factor-23 (FGF23), decreasing calcitriol levels, increasing parathyroid hormone (PTH) levels, and an increase in phosphorus levels. Collectively, these abnormalities are termed *chronic kidney disease-mineral bone disorder* (CKD-MBD).² CKD-MBD is associated with bone disease, vascular calcification, left ventricular hypertrophy, cardiovascular disease, and death.^{3–6} Thus, significant emphasis is placed on the

Address reprint requests to Jessica Kendrick, MD, MPH, Division of Renal Diseases and Hypertension, University of Colorado Anschutz Medical Campus, 12700 E 19th Ave, C281, Aurora, CO 80045. Jessica.Kendrick@ucdenver.edu.

Conflict of interest statement: none.

management of CKD-MBD as outlined in the Kidney Disease: Improving Global Outcomes (KDIGO) guidelines. However, the evidence to support many of these recommendations is lacking and no large randomized trials modifying CKD-MBD have shown clinical benefit in reducing cardiovascular events or mortality.² Part of the issue is the great interdependency of the parameters of CKD-MBD. Therapies aimed at only one parameter often have unintentional effects on another. In addition, despite evidence that calcium and phosphorus homeostasis differs among distinct populations, treatment for CKD-MBD is not individualized.

Recent evidence has suggested that there is significant variability in markers of mineral metabolism across subgroups of patients with CKD. Race has been identified as an important factor that may influence serum PTH, vitamin D, and phosphorus levels. Compared with individuals of European ancestry, individuals with African ancestry have lower 25-hydroxyvitamin D levels.^{7,8} Despite lower 25-vitamin D levels, individuals with African ancestry have higher levels of calcitriol.^{7,8} In addition, compared with whites, blacks have higher serum phosphorus and lower urinary phosphorus excretion despite higher levels of PTH and FGF23.^{8–10} The increase in PTH levels observed with increasing CKD stage is more pronounced in blacks than in non-blacks.¹¹ Furthermore, white patients on dialysis are more likely to present with low bone turnover than black patients.¹² The reasons for these differences are unknown. It has been hypothesized that responsiveness and sensitivity to both PTH and FGF23 differs. Thus, underlying genetic variations may account for these racial differences.

Sex differences in mineral metabolism also exist. Women with ESRD have a higher risk of developing nodular hyperplasia of the parathyroid glands and have more severe secondary hyperparathyroidism compared with men.^{13–16} Studies also have reported greater failure of medical treatment and a higher parathyroidectomy rate in women with CKD compared with men.^{15–17} In addition, compared with men with ESRD, women with ESRD have lower bone mineral density despite similar PTH and alkaline phosphatase levels.¹⁸ In animal models, female sex favors proliferation of parathyroid cells.¹⁹ The mechanisms behind these differences are unclear but estrogen may play a role. Estrogen results in increased phosphorus excretion in the kidney.²⁰ Thus, decreased estrogen levels in postmenopausal women may account for the higher serum phosphorus burden observed in women with CKD.^{13,14} Women in the general population have higher FGF23 levels than men. Treatment with estrogen increases FGF23 levels in women and in animal models.^{21,22} In addition, in animal models estrogen results in decreased PTH levels.²²

Despite these racial and sex-specific differences, the current general recommendations for the treatment of CKD-MBD apply uniformly to all patients with CKD. In addition, genetic factors may impact CKD-MBD and its management regardless of race and sex. Indeed, genetic studies could transform the approach to the diagnosis and management of CKD-MBD, resulting in personalized therapy (Fig. 1). Personalized medicine focuses on a personalized approach aimed at preventing disease and tailoring therapy to improve patient care—the goal is to determine the right drug, for the right patient, at the right time. The ability to accurately diagnose and predict progression of CKD-MBD and to choose therapies that are targeted to an individual patient may revolutionize the management of CKD-MBD.

Although there currently are a lack of data regarding personalized medicine in CKD-MBD, promising findings and ongoing studies suggest that personalized management of CKD-MBD may not be too far off. In this review, we discuss how personalized medicine may be used for the management of CKD-MBD in patients with ESRD and how it ultimately may lead to improved clinical outcomes.

PHOSPHORUS

Phosphorus plays a pivotal role in the development of CKD-MBD and control of serum phosphate levels is a key treatment of CKD-MBD. High serum phosphate levels are associated with vascular calcification, cardiovascular disease, and death in dialysis patients.^{3–5} Management of hyperphosphatemia in dialysis patients includes low dietary intake and removal of phosphate by dialysis and oral phosphate binders. Because dietary modifications are difficult to follow and conventional dialysis does not completely correct serum phosphorus, phosphate binders are the mainstay of therapy in ESRD. Nearly all dialysis patients are prescribed phosphate binders. Despite the widespread use of binders, phosphorus control remains challenging. Adherence to an adequate phosphate-binder regimen is problematic for many patients because binders must be taken several times per day and cause significant side effects. An optimal phosphate binder would be effective with a low pill burden and a favorable side-effect profile. Unfortunately, the optimal binder does not exist (Table 1). Furthermore, there are little data to suggest that one class is superior in efficacy over another. In current practice, agent selection is guided by cost, serum calcium concentrations, side effects, and comorbid conditions. With poor overall phosphorus control in ESRD patients, it is clear that a different approach is necessary and personalized medicine may meet that need.

Individualized management of phosphorus may lead to significant improvements in phosphorus control. Not all patients respond to phosphate binders or to dialytic phosphorus removal similarly, and genetic differences may, in part, explain this phenomenon. The classic teaching is that approximately 800 to 1,000 mg of phosphorus is removed during a standard hemodialysis session.²³ However, individual variability in dialytic phosphate removal is large. For example, in a study of dialysis patients with similar body weight and equivalent predialysis serum phosphorus, phosphorus removal ranged from 597 to 1,082 mg depending on the individual.²⁴ Another study of phosphorus kinetics in 21 patients during hemodialysis found a wide range of phosphorus mobilization from 51 to 208 mL/min.²⁵ Hence, understanding the amount of phosphorus removed during dialysis on an individual patient level may assist with the dialysis prescription and phosphate binder requirements. For example, a patient who mobilizes phosphorus rapidly from intracellular stores during dialytic removal may benefit significantly from increasing dialysis time.

Variability in dietary phosphorus absorption frequently goes unnoticed. Approximately 60% of dietary phosphorus is absorbed.²⁶ However, the variability in absorption among 5 patients that were included in this pivotal study is remarkable (26%, 40%, 69%, 84%, and 85%).²⁶ In another phosphorus balance study, the mean and SD of fecal phosphate excretion was 371 $\pm$ 129 mg among normal subjects on a fixed 1,200 mg/d phosphate diet.²⁷ The SD of 129 mg indicates that more than 30% of the patients were outside of the 60% phosphorus

absorption range. From a clinical perspective, these data imply that an individual whose fecal excretion is at the lower end needs a larger amount of phosphate binders to increase fecal excretion. In addition, phosphorus absorption induced by activated vitamin D (calcitriol) is variable. In a study of five dialysis patients receiving 2 μ g of calcitriol daily for 2 weeks, phosphorus absorption doubled in two patients but only increased by a mean of 21% in the other three patients.²⁶ Hence, it is clear that variations in phosphorus absorption may explain, in part, hyperphosphatemia even among patients who are adherent to a low phosphorus diet and phosphate-binder regimen.

Genetic differences may partly explain these wide interindividual variations in dialytic phosphorus removal and dietary phosphorus absorption/excretion (Table 2). An analysis of more than 16,000 individuals of European ancestry and a replication cohort of more than 5,000 individuals found seven common genetic variants that were associated significantly with serum phosphorus concentrations.²⁸ Many of these single-nucleotide polymorphisms (SNPs) were located near or were in strong linkage disequilibrium with genes or other SNPs involved in phosphorus homeostasis including *SLC34A1*, the gene encoding the kidney-specific type IIa sodium phosphate co-transporter, a SNP in the calcium-sensing receptor gene, and the *FGF23* gene. Although the seven significant genetic variants identified in this study only accounted for approximately 0.4 mg/dL variation in serum phosphorus, other common genetic polymorphisms have been associated with circulating parathyroid hormone levels²⁹ and vitamin D levels,³⁰ hormones that control serum phosphorus levels. Thus, it is plausible that certain combinations of these polymorphisms and how they interact with each other could account for this large variation in phosphorus handling.

The efficacy of binders in removing phosphorus also varies among individual patients. In a study of 10 patients given 4.3 g of calcium acetate, the phosphorus-binding efficacy ranged from 15.0 to 36.1 mg per dose.³¹ Thus, in a patient with low binding efficacy increasing the dosage of binders may not result in a large improvement in serum phosphorus. In clinical practice, we often notice variation in the effectiveness of different binders among patients, but this observation has not been studied.

Taken together, all of these data support an individualized approach as critical for the management of hyperphosphatemia. Currently, the only way to determine the absorption of phosphorus and the efficacy of dialysis and binders is to perform carefully designed balance studies. These are cumbersome for patients and not practical for routine clinical care. Other techniques to identify these traits would be ideal. There are no studies to date that evaluate a personalized approach to selecting an optimal phosphate binder. Numerous phosphate binders are available (Table 1). The choice of phosphate binder currently is individualized based on laboratory test results, cost, and side effects, whereas it should be individualized based on other patient-specific factors such as sex, race, absorption/excretion dynamics, and genetic background.

SECONDARY HYPERPARATHYROIDISM

Secondary hyperparathyroidism is a serious and costly manifestation of ESRD. Parathyroid hormone is a key factor in the pathogenesis of CKD-MBD. Serum PTH levels increase early

in the course of CKD such that at least 50% of patients have secondary hyperparathyroidism by the time they need dialysis.⁵ Current treatment consists of serum phosphate reduction, control of PTH with vitamin D/vitamin D metabolites, and/or the use of calcimimetics. Parathyroidectomy remains a viable treatment strategy, especially in patients in whom pharmacotherapy has failed. The clinical management of secondary hyperparathyroidism currently relies on serum PTH levels. However, the optimal PTH level in dialysis patients is unknown and may differ across individual patients. Moreover, response to pharmacotherapy varies among patients. Several genetic variants located in or near genes involved in vitamin D metabolism and calcium and phosphorus transport have been identified (Table 2). Understanding and using this genetic information may lead to better therapies to treat secondary hyperparathyroidism.

Calcium-Sensing Receptor and Serum Calcium

The calcium-sensing receptor (CaSR) is a ubiquitous G-protein–coupled receptor protein whose function in the parathyroid gland and renal tubules is to respond to extracellular calcium concentrations to maintain calcium homeostasis. Calcium-sensing receptor polymorphisms have been well described and are associated with urinary³² and serum^{33–40} calcium concentrations in various healthy populations but not others.⁴¹ Fewer studies have investigated CaSR genetic variants in patients with kidney disease; however, the existing studies have suggested that certain CaSR polymorphisms may predict the severity of secondary hyperparathyroidism and response to interventions and medications. These common polymorphisms are located in exon 7 (A986S, R990G, and Q1011E) and the promoter regions of the CaSR gene.

Among hemodialysis patients, genetic variants in codons 990 and 1011 have been associated with changes in CaSR sensitivity. As early as 2000, polymorphisms in the CaSR codon 990 were observed to be associated with serum PTH levels among 122 Japanese hemodialysis patients. In particular, those with the AA genotype showed significantly higher PTH levels compared with the GG genotype.⁴² Similar results were found among 192 Turkish dialysis patients—the presence of both 990-AA and 1011-CC CaSR genotypes was significantly higher among patients who required parathyroidectomy; likewise, patients with genotypes 990-AA and 1011-CC showed higher calcium and PTH levels, respectively, compared with 990-AG and 1011-CG, respectively.⁴³ Among patients with nephrolithiasis-related ESRD, the AA genotype for the CaSR SNP, rs7652589, was associated with more severe secondary hyperparathyroidism, defined as higher calcium and PTH concentrations. Furthermore, the AA genotype was associated with reduced CaSR transcript levels in peripheral blood mononuclear cells, indicating lower expression of the CaSR among patients with the AA genotype. Thus, rs7652589 AA carriers may have more severe secondary hyperparathyroidism owing to down-regulation of the CaSR.⁴⁴ However, another study investigating 284 renal transplant patients found no significant relationship between polymorphisms in codons 990 or 1011 or the rs7652589 SNP and serum calcium or PTH concentrations. Only those who were heterozygous (Cytosine/Thymine) for the CaSR promoter region SNP, rs115759455, had significantly higher serum phosphorus compared with those who were homozygous for the major allele. As opposed to healthy populations, there were no significant associations between CaSR gene variants and serum calcium in this

cohort of transplant patients.⁴⁵ Further investigation in larger cohorts is required to confirm these observations.

Despite the fact that CaSR genetic variants have been linked to more severe secondary hyperparathyroidism and other mineral abnormalities, they have never been linked to hard clinical outcomes such as cardiovascular disease events or mortality among patients with kidney disease.^{44–46} Nonetheless, CaSR genetic variants may be useful for selecting optimal therapies to treat secondary hyperparathyroidism. In 77 Japanese dialysis patients, those without the R allele of CaSR R990G polymorphism showed a significant reduction of intact PTH levels in response to increased dialysate calcium concentration, although no effect was observed among those patients with GR or RR genotypes.⁴⁷ A large study evaluated CaSR polymorphisms among 1,067 subjects of European ancestry and 405 subjects of African ancestry with ESRD who participated in the Evaluation of Cinacalcet Hydrochloride Therapy to Lower Cardiovascular Events (EVOLVE) study.⁴⁸ At baseline the missense variant rs1042636 (R990G) was associated with PTH whereas rs1801725 (A986S) was associated with phosphate and PTH among subjects of European ancestry. Among subjects of African ancestry, different SNPs were associated with baseline values: rs1393199 was associated with phosphorus and rs4300957 was associated with calcium. These results may explain differences in PTH levels observed among Caucasian and black dialysis patients for similar levels of bone turnover in the US dialysis population. One SNP, rs 9740, was associated with change in serum calcium in response to cinacalcet treatment among subjects of European and African ancestry, a finding that supports the notion that CaSR genetic variants may be useful in selecting optimal therapies for secondary hyperparathyroidism. As for all observations of CaSR genetic variants, these results need to be replicated.

Although the CaSR is the best-characterized gene that governs calcium homeostasis, several other genetic loci have been identified and are associated significantly with serum calcium concentrations and expressed in the gut, kidney, and bone—important organs in calcium homeostasis. Moreover, in an animal model, dietary calcium intake modified gene expression at these loci.⁴⁹ Further research is needed to determine the role of these genes and the environment in the treatment of CKD-MBD.

Vitamin D and the Vitamin D Receptor

The major circulating form of vitamin D, 25-hydroxyvitamin D (25[OH]D), and its active form, 1,25-dihydroxyvitamin D (1,25[OH]₂D), originally were recognized as important endocrine hormones in calcium homeostasis and bone health. However, it now is well established that vitamin D plays a broader physiologic role in endothelial function, cell proliferation, and immunity via the ubiquitous vitamin D receptor (VDR). As kidney disease progresses, circulating 1,25(OH)₂D levels decrease because of the inability of the kidney to produce sufficient 1- α -hydroxylase, the enzyme that converts nutritional 25 (OH)D to the active form. Increased circulating FGF23 levels also inhibit 1- α -hydroxylase, which further exacerbates 1,25(OH)₂D deficiency. Active vitamin D (1,25 (OH)₂D), or calcitriol, is important for the regulation of parathyroid hormone. Indeed, the mainstay of treatment for secondary hyperparathyroidism is exogenous calcitriol or synthetic VDR agonists.

Calcitriol affects the parathyroid gland and other cells via the VDR. Numerous VDR polymorphisms have been characterized and two, Bsm1 and Fok1, seem to be particularly important in kidney disease. In 1997, the Bsm1 was first observed to influence parathyroid levels among hemodialysis patients. In a small cohort of 66 Spanish chronic dialysis patients, the presence of the BB genotype was more common among those with very low serum intact PTH of less than 12 pg/mL compared with those with intact PTH greater than 60 pg/mL.⁵⁰ Similar observations have been made in other dialysis populations.^{51,52} However, other factors such as diabetes status and dialysis vintage also were found to be strong predictors of PTH, suggesting that these polymorphisms may be among a number of factors influencing PTH.⁵¹ The VDR Bsm1 polymorphism also may influence response to calcitriol. Among a small group of dialysis patients with similar PTH levels, patients with the *Bsm1* BB genotype showed a more robust PTH-lowering response to a single dose of calcitriol compared with patients with the bb genotype.⁵³ Similarly, the presence of the Bsm1 BB genotype in a predialysis kidney disease cohort was associated with less severe secondary hyperparathyroidism and greater circulating calcitriol levels at all stages of CKD compared with those with the b allele.⁵⁴ Parathyroidectomy was delayed among dialysis patients with the BB Bsm1 genotype compared with those with the b allele.⁵⁵ These data support the notion that the BB Bsm1 genotype attenuates secondary hyperparathyroidism and may improve response to treatment with calcitriol. Nonetheless, these hypotheses need to be tested in larger and more diverse cohorts.

The Fok1 VDR polymorphism also may affect vitamin D homeostasis. An analysis of patients with CKD who also possessed the Fok1 C allele compared with those who were homozygous for the TT allele suggested that those with the C allele had greater circulating calcitriol at every level of estimated glomerular filtration rate compared with those with the TT allele.⁵⁶ The relationship between the Fok1 VDR polymorphism requires further testing and to date there are no data supporting how it may change current management of CKD-MBD. Nonetheless, these findings may have the potential to guide treatment decisions.

Although the Bsm1 BB genotype is associated with less severe secondary hyperparathyroidism^{54,55} and higher levels of calcitriol,⁵⁵ newer data suggest that the Bsm1 B allele may be an important risk factor for left ventricular hypertrophy among both CKD and dialysis patients.^{57–59} Despite the fact that hemodialysis patients with the Bsm1 BB genotype showed a more robust PTH-lowering response to a single bolus of calcitriol,⁵³ vitamin D therapy and cardiac structure and function in patients with chronic kidney disease (PRIMO)⁶⁰ and the Effect of Paricalcitol on Left Ventricular Mass and Function in CKD (OPERA)⁶¹ trials found no difference between paricalcitol, a VDR agonist, and placebo in change in left ventricular mass among hemodialysis and predialysis CKD patients. Although the possibility of tailoring therapy based on genetic variants is intriguing, these somewhat conflicting results show the complexity of VDR signaling and potential knowledge gaps regarding the current understanding of VDR genetic variants. Further research is needed to determine if and how approaches to CKD-MBD treatment should be varied according to VDR polymorphism.

RENAL OSTEODYSTROPHY

Renal osteodystrophy is a key consequence of CKD-MBD. The abnormalities in CKD-MBD parameters result in an increased fracture risk by reducing bone mass and bone quality. Patients with CKD have a significantly higher risk of fracture compared with the general population.^{62,63} Fractures in ESRD patients are associated with significant morbidity and mortality.⁶⁴ Optimization of CKD-MBD may improve bone quality. Better identification and management of fracture risk in CKD patients could significantly reduce health care costs and morbidity.

Treatment of renal osteodystrophy is based on bone turnover and osteomalacia. Bone turnover may be low (adynamic bone disease) or high (osteitis fibrosa cystica). Antiresorptive agents may be beneficial in patients with high turnover but should not be used in patients with low turnover. Thus, determining bone turnover is essential in the management of renal osteodystrophy. Noninvasive assessment of bone turnover is measured by PTH levels and bone turnover markers: bone-specific alkaline phosphatase (BSAP) is used most commonly. Although extremely high or extremely low levels of PTH predict bone turnover in dialysis patients,^{65,66} the prediction of turnover when PTH levels are in the middle range is poor. BSAP is linked to histologic bone parameters and may be slightly better than PTH at predicting low turnover.⁶⁷ However, the best biomarker for bone turnover may differ across race. In African American patients on dialysis, BSAP was a better predictor of bone histology than PTH because no patient with a BSAP level greater than 22 ng/mL had adynamic bone disease.⁶⁸ The combination of BSAP and PTH was useful in further classifying subjects, specifically those at risk for high turnover bone disease. However, in a recent study of 492 dialysis patients, neither PTH nor BSAP was able to diagnose turnover in an individual patient.⁶⁶ In the future, genetic polymorphisms may be used to identify bone turnover, fracture risk, and response to therapy. Three CaSR SNPs (rs4678044, rs4300957, and rs767446) have been associated with greater fracture risk among dialysis subjects of European ancestry and treatment with cinacalcet reduced the fracture risk in patients with these SNPs.⁴⁸ Although various genetic polymorphisms have been associated with renal osteodystrophy (Table 2) in dialysis patients, no uniform trend has been identified and analysis of genetic variants is not used in clinical practice. Therefore, the currently available biomarkers are not able to adequately assess turnover and guide therapy in individual patients.

Dual-energy x-ray absorptiometry (DXA) is used to measure bone mass and fracture risk noninvasively in the general population. The ability of DXA to predict fractures in patients with CKD has been questioned. However, recent studies have shown that in patients with CKD stages 3 to 5D, DXA does predict fractures.^{69–71} In a study of 485 hemodialysis patients, lower baseline femoral neck and total hip BMD predicted a greater risk of fracture.⁶⁹ The 2016 updated KDIGO Guidelines now recommend using DXA to assess fracture risk in patients with CKD.⁷² However, DXA does not assess bone quality or determine the type of renal osteodystrophy present, hence bone biopsy remains the gold standard for diagnosis and classification of renal osteodystrophy. A bone biopsy should be considered in patients with unexplained fractures, or when PTH trends are inconsistent or response to treatment is atypical. Bone biopsy results should be used to guide therapy for an individual patient and to

monitor treatment response. Unfortunately, bone biopsies are invasive, expensive, and may not be readily available. Furthermore, bone biopsies only provide information regarding one skeletal site at a single point in time. Even with bone biopsy data guiding therapy, patients may not respond predictably to treatments. Thus, repeated biopsies may be needed to determine the response to treatment in many patients. Development of noninvasive assessments that can predict bone disease, fracture risk, and response to treatment are desperately needed. A new minimally invasive device, the Osteoprobe (Active Life Scientific, Santa Barbara, CA), was developed to assess bone mechanical characteristics at the tissue level. It involves a microindentation technique in which only one skin insertion is needed and successive measurements with small sharp probes are taken.⁷³ By using microindentation, patients with fragility fractures showed worse bone material strength than patients who did not have a fracture.⁷³ In addition, Osteoprobe is sensitive enough to reflect changes in cortical bone indentation after treatment with osteoporosis therapies in patients on glucocorticoid therapy.⁷⁴ Whether or not this technique can be used in CKD patients to determine fracture risk, bone strength, or response to treatment is unknown.

VASCULAR CALCIFICATION

Disordered mineral metabolism is a critical risk factor for vascular calcification in the CKD population.³ Vascular calcification is associated with significant morbidity and mortality in dialysis patients. It is a dynamic process and distinct genetic polymorphisms in regulatory proteins involved in vascular calcification may be associated with different degrees of disease severity and outcomes.⁷⁵ However, only a few have been investigated in patients with CKD^{76–80} (Table 2). Nonetheless, understanding how genetic polymorphisms affect vascular calcification in CKD may improve risk stratification and eventually could be integral in tailoring therapy.

Fetuin-A (also known as α_2 -Heremans-Schmid glycoprotein [AHSG]) prevents vascular ectopic calcification and is a negative acute-phase reactant. Lower circulating levels of fetuin-A are associated with vascular calcification and all-cause and cardiovascular mortality among patients with ESRD.^{81,82} More than 30 years ago, two of the most common AHSG alleles (AHSG1 and AHSG2) were reported to be associated with different levels of serum fetuin-A. The most common AHSG1 allele was associated with higher fetuin-A serum concentrations among North American Caucasian and Caribbean black populations.⁸³ A group of mostly Caucasian hemodialysis patients with the AHSG 265Ser allele had lower fetuin-A levels compared with carriers of other alleles and mortality was increased among those who were inflamed in this group.⁷⁶ Likewise, in a group of Korean peritoneal dialysis patients, distinct AHSG SNPs were found to affect fetuin-A levels and lower fetuin-A levels were associated independently with a greater simple vascular calcification score and higher aortic pulse-wave velocity, a measure of vascular stiffness.⁷⁷ Thus, it is plausible that patients with ESRD who have certain AHSG polymorphisms that predispose to lower fetuin-A levels have a higher risk of vascular calcification and cardiovascular mortality. However, among a smaller group of Italian hemodialysis patients, AHSG alleles were not associated with different levels of fetuin-A,⁸² suggesting the presence of other genetic or environmental factors that may affect this relationship.

Matrix GLA protein (MGP), another inhibitor of vascular calcification, prevents calcium phosphate deposition in the arterial wall. Two MGP polymorphisms have been studied: –7 and –138. The MGP –7A (as opposed to MGP –7G) polymorphism is associated with vascular calcification and atherosclerotic disease, particularly among Caucasians.⁸⁴ MGP promoter polymorphisms –138C and –138T also have been studied in relationship to vascular calcification. MGP-138T showed significantly greater promoter activity compared with –138C, but there was no significant correlation between –138C and greater clinical markers of calcification. There was a trend for increased clinical markers of calcification among the C genotype (TC and CC), but this relationship was not statistically significant.⁸⁵ In a small cohort of dialysis patients who died during 1 year of follow-up evaluation, 94% (16 of 17) carried the MGP-138TT and the MGP-7A (either GA or AA) polymorphisms,⁷⁸ even though 138TT was associated with greater MGP promoter activity and less calcification than 138A in another study.⁸⁵ In yet other cohorts of dialysis patients, MGP-7A was associated with more severe left ventricular hypertrophy and a greater change in the calculated carotid intima media area, a marker of calcification and atherosclerosis.^{79,80} These findings suggest that MGP-7A polymorphism is associated with vascular calcification and poor outcomes among dialysis patients.

The ability to diagnose vascular calcification early may be essential for treatment. In current practice, treatment decisions regarding medications should be guided by the presence or absence of vascular calcification. Calcium-based binders and calcium-containing medications are not recommended for patients with vascular calcification. However, the current issue is how best to diagnose vascular calcification in patients. Although identifying genetic variants that predispose to calcification may be a critical step, there are not enough data to support routine genetic testing in the ESRD population. Currently, vascular calcification is diagnosed by radiologic imaging such as computed tomography. Recently, T₅₀, a novel blood test that measures the overall calcification propensity of serum, was developed. T₅₀ measures the transformation time from calcium phosphate-containing primary calciprotein particles to crystalline hydroxyapatite-containing secondary calciprotein particles.⁸⁶ A higher T₅₀ score represents lower calcification propensity. The T₅₀ test is associated with cardiovascular disease and death in patients with CKD^{87–89} and predicts aortic stiffness, which is linked strongly to vascular calcification.^{87–89} Because the transformation time point is specific for an individual patient's serum, the T₅₀ can determine an individual patient's propensity to calcify. Hence, the T₅₀ test may be a useful marker for the diagnosis and management of calcification. Pilot studies of hemodialysis patients showed that decreasing serum phosphate levels, increasing serum bicarbonate and magnesium levels, and hemodialysis improve the T₅₀ value.^{86,90–92} Thus, T₅₀ offers a potential way to individualize treatments for CKD-MBD as related to vascular calcification. Further studies are needed to determine if the link between T₅₀ and outcomes is causal.

CURRENT PERSONALIZED MANAGEMENT OF CKD-MBD

Although more research certainly is needed to fully implement the personalized management of CKD-MBD using precision parameters such as genetic background, the T₅₀ assay, and the Osteoprobe (Fig. 1), there currently are ways to individualize treatment. It is important to recognize that although treatment algorithms may be helpful, using a

multidisciplinary approach, the treatment of CKD-MBD should and can be individualized for each patient with special consideration given to the age, sex, race, and comorbidities (Fig. 2). Serial assessment of the patient's serum calcium, phosphorus, and PTH levels need to be considered together. Choice of medication must take into account current calcium and phosphorus levels and concomitant medical therapies. For example, in a patient with hypercalcemia and hyperphosphatemia, a calcimimetic is preferred over calcitriol or vitamin D analogues for the treatment of increased PTH levels. The choice of phosphate binder also must be individualized. The updated 2016 KDIGO Guidelines recommend restricting the dose of calcium-based binders regardless of the serum calcium levels. The recommendation is based on data from randomized clinical trials showing a signal toward increased morbidity and mortality in patients treated with calcium-based binders.^{93–95} We believe the evidence supports limiting calcium-based binders when possible. However, for many patients, avoiding calcium-based binders is challenging because of higher costs and more gastrointestinal side effects, which are associated with non-calcium-based binders. Calcium-based binders may be the only option for dialysis patients with little or no prescription coverage because of their low cost. Thus, it is critical to review the cost of medications and side effects with the patient before prescribing them. Calcium-based binders also frequently are used to treat calcimimetic-induced hypocalcemia. Until data are available describing whether or not calcimimetic-induced hypocalcemia is harmful, it may be difficult to restrict calcium-based binders in dialysis patients.

Limiting dietary phosphorus intake remains a mainstay of treatment for CKD-MBD. It is important to recognize that diet varies dramatically between patients. Thus, the role of individualized nutrition education must be emphasized. Each patient should meet with a dietician on a regular basis for nutritional counseling. The phosphorus source (eg, animal, vegetable, additives) must be considered when making dietary recommendations. Medications are also a source of phosphorus load in dialysis patients. Nearly 12% of the 200 most prescribed medications used in US dialysis centers list phosphorus-containing ingredients on the label.⁹⁶ For example, a 10-mg lisinopril tablet contains 32.6 mg of phosphorus. One Renavite tablet (Cypress Pharmaceuticals, Madison, MS) contains 37.7 mg of phosphorus.⁹⁶ Further complicating phosphorus accounting is that different manufacturers of the same drug may use different amounts of phosphorus in their formulation. A careful review of the patient's medication list must be performed. A patient taking lisinopril, Renavite, and amlodipine would require 4 extra doses of sevelamer per day to bind the phosphorus contained in the medications. Patients, providers, and dieticians would benefit from more information on phosphorus content of medications. Unfortunately, there is not an easy way to identify this. The information often can be found in the package label, which usually is available online, and there are publications that have examined the phosphorus content of the most frequently prescribed medications.⁹⁶ The fact that medications contain phosphorus highlights the role of knowing the concomitant medications in an individual patient for the treatment of CKD-MBD.

Identifying dialysis patients at high risk of fracture is of utmost importance. DXA scans are predictive of fracture risk in dialysis patients. If a patient is at a higher risk of fracture based on DXA, nonpharmacologic therapy such as weight-bearing exercise can be implemented. Although pharmacologic therapy may be beneficial, there currently are no studies evaluating

whether medications prevent fractures in dialysis patients. Furthermore, in dialysis patients, it is important to rule out adynamic bone disease before starting antiresorptive agents. As discussed earlier, it is difficult to identify the etiology of renal osteodystrophy and bone turnover noninvasively. Bone biopsies are the gold standard to identify bone turnover. Clinicians who are not trained in bone biopsy should refer patients to providers with the expertise and capability of performing bone biopsies to help guide management.

We will use the following case to illustrate how the management of CKD-MBD can be individualized: Ms. Jones is a 59-year-old patient with ESRD secondary to diabetes who has been on dialysis for 6 years. She has a history of hypertension and was hospitalized 6 months ago for a myocardial infarction. She has no history of bone pain or fractures. She is currently receiving 1,334 mg calcium acetate three times a day with meals. She is not receiving calcitriol, vitamin D analogues, or cinacalcet. Routine quarterly laboratory tests show the following: intact PTH, 580 pg/mL; total calcium, 10.1 mg/dL; and phosphorus, 5.8 mg/dL.

Figure 2 provides an overview of a multidisciplinary approach to the personalized management of Ms. Jones' CKD-MBD. The first step in management is to use serial assessments of the patient's serum calcium, phosphorus, and PTH levels. In review of Ms. Jones trends in calcium, phosphorus and PTH levels, it was found that over the past year her iPTH had increased from 200 to 350 to 580 pg/mL. Her calcium level had been trending at approximately 9.9 to 10.2 mg/dL, and her phosphorus level at 5.5 to 6.0 mg/dL. Although her PTH level is not currently higher than 600 pg/mL, the trend of the PTH level suggests that it will continue to increase. Thus, PTH-decreasing therapies need to be initiated now. The choice of medication (calcitriol/vitamin D analogue versus calcimimetic) should be determined based on her calcium, phosphorus, and PTH levels. Because her calcium and phosphorus levels have remained in the high to high-normal range, a calcimimetic would be an appropriate first-line PTH-decreasing therapy. Her serum phosphorus level remains increased despite the use of calcium acetate. Given her increased calcium level, an appropriate strategy would be to stop the calcium acetate and start a noncalcium-based binder. The noncalcium-based binder selection should be based on cost, side-effect profile, and on the ability of the patient to swallow or chew pills—consultation with the patient, social worker, and dietician will help determine the optimal phosphate binder. In addition, targeted nutrition counseling by a dietician should be introduced. The patient's laboratory values should be repeated in 1 month to assess her response to treatment. The optimal PTH level for Ms. Jones is unknown, but the PTH level should be decreasing and remain greater than 150 pg/mL. A bone-specific alkaline phosphatase level should be drawn at least quarterly as a means to assess bone turnover noninvasively. The goal should be to reduce her serum phosphorus and calcium levels back toward the normal range.

CONCLUSIONS

Optimal management of CKD-MBD is critical for dialysis patients. However, it is often a challenging task for clinicians because therapies aimed at one CKD-MBD parameter may have unintended consequences for another. Studies investigating the role of genetic polymorphisms in the severity of CKD-MBD and potential differences in therapeutic effects

are intriguing and further elucidate the complexity of this disorder. In the future, evaluation of genetic variants potentially may serve to guide CKD-MBD treatment for the individual patient more precisely; however, this strategy still requires extensive investigation and is not yet ready for prime time. Serial laboratory measurements of calcium, phosphorus, and PTH interpreted together (and not in isolation), and increased use of bone biopsy and other radiographic studies along with carefully considered patient factors are tools that already exist to personalize CKD-MBD management.

Acknowledgments

Financial support: Support was provided by National Institutes of Health/National Heart, Lung and Blood Institute grant R01HL132868 (J.K.) and Veterans Administration grant CDA 5IK2CX001030-03 (A.J.).

REFERENCES

1. United States Renal Data System. USRDS annual data report: epidemiology of kidney disease in the United States, 2017 Bethesda, MD: National Institutes of Health, National Institute of Diabetes and Digestive and Kidney Diseases; 2017.
2. Moe S, Drueke T, Cunningham J, et al. Definition, evaluation, and classification of renal osteodystrophy: a position statement from Kidney Disease: Improving Global Outcomes (KDIGO). *Kidney Int* 2006;69:1945–53. [PubMed: 16641930]
3. Palit S, Kendrick J. Vascular calcification in chronic kidney disease: role of disordered mineral metabolism. *Curr Pharm Des* 2014;20:5829–33. [PubMed: 24533939]
4. Kestenbaum B, Sampson JN, Rudser KD, Patterson DJ, Seliger SL, Young B, et al. Serum phosphate levels and mortality risk among people with chronic kidney disease. *J Am Soc Nephrol* 2005;16:520–8. [PubMed: 15615819]
5. Tentori F, Blayney MJ, Albert JM, Gillespie BW, Kerr PG, Bommer J, et al. Mortality risk for dialysis patients with different levels of serum calcium, phosphorus, and PTH: the Dialysis Outcomes and Practice Patterns Study (DOPPS). *Am J Kidney Dis* 2008;52:519–30. [PubMed: 18514987]
6. Gutierrez OM, Mannstadt M, Isakova T, Rauh-Hain JA, Tamez H, Shah A, et al. Fibroblast growth factor 23 and mortality among patients undergoing hemodialysis. *N Engl J Med* 2008;359:584–92. [PubMed: 18687639]
7. Bell NH, Greene A, Epstein S, Oexmann MJ, Shaw S, Shary J. Evidence for alteration of the vitamin D-endocrine system in blacks. *J Clin Invest* 1985;76:470–3. [PubMed: 3839801]
8. Gutierrez OM, Isakova T, Andress DL, Levin A, Wolf M. Prevalence and severity of disordered mineral metabolism in blacks with chronic kidney disease. *Kidney Int* 2008;73:956–62. [PubMed: 18256597]
9. de Boer IH, Rue TC, Kestenbaum B. Serum phosphorus concentrations in the third National Health and Nutrition Examination Survey (NHANES III). *Am J Kidney Dis* 2009;53:399–407. [PubMed: 18992979]
10. Gutierrez OM, Isakova T, Smith K, Epstein M, Patel N, Wolf M. Racial differences in postprandial mineral ion handling in health and in chronic kidney disease. *Nephrol Dial Transplant* 2010;25:3970–7. [PubMed: 20530498]
11. Ennis J, Worcester E, Coe F. Contribution of calcium, phosphorus and 25-hydroxyvitamin D to the excessive severity of secondary hyperparathyroidism in African-Americans with CKD. *Nephrol Dial Transplant* 2012;27:2847–53. [PubMed: 22505656]
12. Jorgetti V, dos Res LM, Ott SM. Ethnic differences in bone and mineral metabolism in healthy people and patients with CKD. *Kidney Int* 2014;85:1283–9. [PubMed: 24352156]
13. Lomonte C, Cazzato F, Casucci F, Chimienti D, Bruno A, Cocola S, et al. Female hemodialysis patients have an increased risk of nodular hyperplasia of parathyroid glands. *J Nephrol* 2005;18:92–5. [PubMed: 15772929]

14. Basile C, Lomonte C, Vernaglione L, Casucci F, Chimienti D, Bruno A, et al. A high body mass index and female gender are associated with an increased risk of nodular hyperplasia of parathyroid glands in chronic uraemia. *Nephrol Dial Transplant* 2006;21:968–74. [PubMed: 16326747]
15. Indridason OS, Pieper CF, Quarles LD. Predictors of short-term changes in serum intact parathyroid hormone levels in hemodialysis patients: role of phosphorus, calcium and gender. *J Clin Endocrinol Metab* 1998;83:3860–6. [PubMed: 9814459]
16. Fan SL, Chan A, Raftery MJ, Yagoob MM. Race and sex: predictors of the severity of hyperparathyroidism in peritoneal dialysis patients. *Nephrology (Carlton)* 2006;11:15–20. [PubMed: 16509926]
17. Foley RN, Li S, Liu J, Gilbertson DT, Chen SC, Collins AJ. The fall and rise of parathyroidectomy in US hemodialysis patients, 1992 to 2002. *J Am Soc Nephrol* 2005;16:210–8. [PubMed: 15563573]
18. Cheng SP, Yang TI, Lee JJ, Chen HH, Wu CJ, Liu TP, et al. Gender differences among patients with secondary hyperparathyroidism undergoing parathyroidectomy. *J Surg Res* 2011;168:82–7. [PubMed: 19932904]
19. Almaden Y, Felsenfeld AJ, Rodriguez M, Canadillas S, Lague F, Bas A, et al. Proliferation in hyperplastic human and normal rat parathyroid glands: role of phosphate, calcitriol, and gender. *Kidney Int* 2003;64:2311–7. [PubMed: 14633156]
20. Farouqi S, Levi M, Soleimani M, Amlal H. Estrogen downregulates the proximal tubule type IIa sodium phosphate cotransporter causing phosphate wasting and hypophosphatemia. *Kidney Int* 2008;73:1141–50. [PubMed: 18305465]
21. Ix JH, Chonchol M, Laughlin GA, Shlipak MG, Whooley MA. Relation of sex and estrogen therapy to serum fibroblast growth factor 23, serum phosphorus and urine phosphorus: the Heart and Soul Study. *Am J Kidney Dis* 2011;58:737–45. [PubMed: 21855188]
22. Carrillo-Lopez N, Roman-Garcia P, Rodriguez-Rebollar A, Fernandez-Martin JL, Naves-Diaz M, Cannata-Andia JB. Indirect regulation of PTH by estrogens may require FGF23. *J Am Soc Nephrol* 2009;20:2009–17. [PubMed: 19628670]
23. Daugirdas JT. Removal of phosphorus by hemodialysis. *Semin Dial* 2015;28:620–3. [PubMed: 26358370]
24. Lornoy W, de Meester J, Because I, Billiow JM, Van Malderen PA, Van Pottelberge M. Impact of convective flow on phosphorus removal in maintenance hemodialysis patients. *J Ren Nutr* 2006;16:47–53. [PubMed: 16414441]
25. Agar BU, Akonar A, Lo YC, Cheung AK, Leypoldt JK. Kinetic model of phosphorus mobilization during and after short and conventional hemodialysis. *Clin J Am Soc Nephrol* 2011;6:2854–60. [PubMed: 22034502]
26. Ramirez JA, Emmett M, White MG, Fathi N, Santa Ana CA, Morawski SG, et al. The absorption of dietary phosphorus and calcium in hemodialysis patients. *Kidney Int* 1986;30:753–9. [PubMed: 3784305]
27. Burke SK, Slatopolsky EA, Goldberg DI. RenaGel, a novel calcium-and aluminum-free phosphate binder, inhibits phosphate absorption in normal volunteers. *Nephrol Dial Transplant* 1997;12:1640–4. [PubMed: 9269642]
28. Kestenbaum B, Glazer NL, Kottgen A, Felix JF, Hwang SJ, Liu Y, et al. Common genetic variants associate with serum phosphorus concentration. *J Am Soc Nephrol* 2010;21:1223–32. [PubMed: 20558539]
29. Robinson-Cohen C, Lutsey PL, Kleber ME, Nielson CM, Mitchell BD, Bis JC, et al. Genetic variants associated with circulating parathyroid hormone. *J Am Soc Nephrol* 2017;28:1553–65. [PubMed: 27927781]
30. Hong J, Hatchel KE, Bradfield JP, Andrew B, Alessandra C, Chao-Qiang L, et al. Trans-ethnic evaluation identifies novel low frequency loci associated with 25-hydroxyvitamin D concentrations. *J Clin Endocrinol Metab* 2018;103(4):1380–92. [PubMed: 29325163]
31. Sheikh MS, Maguire JA, Emmett M, Santa Ana CA, Nicar MJ, Schiller LR, et al. Reduction of dietary phosphorus absorption by phosphorus binders. A theoretical, in vitro, and in vivo study. *J Clin Invest* 1989;83:66–73. [PubMed: 2910921]

32. Jung J, Foroud TM, Eckert GH, Flury-Wetherill L, Edenberg HJ, Xuei X, et al. Association of the calcium-sensing receptor gene with blood pressure and urinary calcium in African-Americans. *J Clin Endocrinol Metab* 2009;94:1042–8. [PubMed: 19066294]
33. O'Seaghdha CM, Yang Q, Glazer NL, Leak TS, Dehghan A, Smith AV, et al. Common variants in the calcium-sensing receptor gene are associated with total serum calcium levels. *Hum Mol Genet* 2010;19:4296–303. [PubMed: 20705733]
34. Kapur K, Johnson T, Beckmann ND, Sehmi J, Tanaka T, Kutalik Z, et al. Genome-side meta-analysis for serum calcium identifies significantly associated SNPs near the calcium-sensing receptor (CASR) gene. *PLoS Genet* 2010;6:e1001035. [PubMed: 20661308]
35. Vinayagamoorthy N, Yim SH, Jung SH, Park SW, Kim YJ, Kim BJ, et al. Association of common variants in the calcium-sensing receptor gene with serum calcium levels in East Asians. *J Hum Genet* 2015;60:407–12. [PubMed: 25972035]
36. Laaksonen MM, Outila TA, Karkkainen MU, Kemi VE, Rita HJ, Perola M, et al. Associations of vitamin D receptor, calcium-sensing receptor and parathyroid hormone gene polymorphisms with calcium homeostasis and peripheral bone density in adult Finns. *J Nutrigenet Nutrigenomics* 2009;2:55–63. [PubMed: 19690432]
37. He Y, Han L, Li W, Shu X, Zhao C, He Y, et al. Effects of the calcium-sensing receptor A986S polymorphism on serum calcium and parathyroid hormone levels in health individuals: a meta-analysis. *Gene* 2012;491:110–5. [PubMed: 22024717]
38. Cole DE, Peltekova VD, Rubin LA, Hawker GA, Vieth R, Liew CC, et al. A986S polymorphism of the calcium-sensing receptor and circulating calcium concentrations. *Lancet* 1999;353:112–5. [PubMed: 10023897]
39. Scillitani A, Guarnieri V, De Geronimo S, Muscarella LA, Battista C, D'Agruma L, et al. Blood ionized calcium is associated with clustered polymorphisms in the carboxyl-terminal tail of the calcium-sensing receptor. *J Clin Endocrinol Metab* 2004;89:5634–8. [PubMed: 15531522]
40. Lorentzon M, Lorentzon R, Lerner UH, Nordstrom P. Calcium sensing receptor gene polymorphism, circulating calcium concentrations and bone mineral density in healthy adolescent girls. *Eur J Endocrinol* 2001;144:257–61. [PubMed: 11248745]
41. Harding B, Curley AJ, Hannan FM, Christie PT, Bowl MR, Turner JJ, et al. Functional characterization of calcium sensing receptor polymorphisms and absence of association with indices of calcium homeostasis and bone mineral density. *Clin Endocrinol (Oxf)* 2006;65:598–605. [PubMed: 17054460]
42. Yano S, Sugimoto T, Kanzawa M, Tsukamoto T, Hattori T, Hattori S, et al. Association of polymorphic alleles of the calcium-sensing receptor gene with parathyroid hormone secretion in hemodialysis patients. *Nephron* 2000;85:317–23. [PubMed: 10940742]
43. Eren PA, Turan K, Berber I, Canbakan M, Kara M, Tellioglu G, et al. The clinical significance of parathyroid tissue calcium sensing receptor gene polymorphisms and expression levels in end-stage renal disease patients. *Clin Nephrol* 2009;72:114–21. [PubMed: 19640368]
44. Grzegorzewska AE, Paciorkowski M, Mostowska A, Frycz B, Warchol W, Stolarek I, et al. Associations of the calcium-sensing receptor gene CASR rs7652589 SNP with nephrolithiasis and secondary hyperparathyroidism in haemodialysis patients. *Sci Rep* 2016;6:35188. [PubMed: 27739473]
45. Babinsky VN, Hannan FM, Youhanna SC, Marechal C, Jadoul M, Devuyst O, et al. Association studies of calcium-sensing receptor (CaSR) polymorphisms with serum concentrations of glucose and phosphate and vascular calcification in renal transplant recipients. *PLoS One* 2015;10:e0119459. [PubMed: 25786244]
46. Grzegorzewska AE, Swideska Mk, Mostowska A, Warchol W, Jagodzinski PP. Polymorphisms of vitamin d signaling pathway genes and calcium-sensing receptor gene in respect to survival of hemodialysis patients: a prospective observational study. *Int J Endocrinol* 2016;2016:2383216. [PubMed: 27642296]
47. Yokoyama K, Shigematsu T, Tsukada T, Hara S, Yamada A, Kawaguchi Y, et al. Calcium-sensing receptor gene polymorphism affects the parathyroid response to moderate hypercalcemic suppression in patients with end-stage renal disease. *Clin Nephrol* 2002;57:131–5. [PubMed: 11863123]

48. Moe SM, Wetherill L, Decker BS, Lai D, Abdalla S, Long J, et al. Calcium-sensing receptor genotype and response to cinacalcet in patients undergoing hemodialysis. *Clin J Am Soc Nephrol* 2017;12:1128–38. [PubMed: 28630081]
49. O'Seaghdha CM, Wu H, Yang Q, Kapur K, Guessous I, Zuber AM, et al. Meta-analysis of genome-wide association studies identifies six new Loci for serum calcium concentrations. *PLoS Genet* 2013;9:e1003796. [PubMed: 24068962]
50. Fernandez E, Fibla J, Betriu A, Piulats JM, Almirall J, Montoliu J. Association between vitamin D receptor gene polymorphism and relative hypoparathyroidism in patients with chronic renal failure. *J Am Soc Nephrol* 1997;8:1546–52. [PubMed: 9335382]
51. Nagaba Y, Heishi M, Tazawa H, Tsukamoto Y, Kobayashi Y. Vitamin D receptor gene polymorphisms affect secondary hyperparathyroidism in hemodialyzed patients. *Am J Kidney Dis* 1998;32:464–9. [PubMed: 9740163]
52. Tagliabue J, Farina M, Imbasciati E, Vergani C, Annoni G. Bsm1 polymorphism of the vitamin D receptor gene in hyperparathyroid or hypoparathyroid dialysis patients. *Am J Clin Pathol* 1999;112:366–70. [PubMed: 10478142]
53. Marco MP, Martinez I, Betriu A, Craver Fibla MJ, Fernandez E. Influence of Bsm1 vitamin D receptor gene polymorphism on the response to a single bolus of calcitriol in hemodialysis patients. *Clin Nephrol* 2001;56:111–6. [PubMed: 11522087]
54. Marco MP, Martinez I, Amoedo ML, Borrás M, Saracho R, Almirall J, et al. Vitamin D receptor genotype influences parathyroid hormone and calcitriol levels in predialysis patients. *Kidney Int* 1999;56:1349–53. [PubMed: 10504487]
55. Borrás M, Torregrossa V, Oliveras A, Almirall J, Ma Paz M, Betriu A. BB genotype of the vitamin D receptor gene polymorphism postpones parathyroidectomy in hemodialysis patients. *J Nephrol* 2003;16:116–20. [PubMed: 12649542]
56. Yokoyama K, Nakashima A, Urashima M, Suga H, Mimura T, Kimura Y, et al. Interactions between serum vitamin D levels and vitamin D receptor gene FokI polymorphisms for renal function in patients with type 2 diabetes. *PLoS One* 2012;7:e51171. [PubMed: 23226566]
57. Testa A, Mallamaci F, Benedetto FA, Pisano A, Tripepi G, Malatino L, et al. Vitamin D receptor (VDR) gene polymorphism is associated with left ventricular (LV) mass and predicts left ventricular hypertrophy (LVH) progression in end-stage renal disease (ESRD) patients. *J Bone Miner Res* 2010;25:313–9. [PubMed: 20422622]
58. El-Shehaby AM, El-Khatib MM, Marzouk S, Battah AA. Relationship of Bsm1 polymorphism of vitamin D receptor gene with left ventricular hypertrophy and atherosclerosis in hemodialysis patients. *Scand J Clin Lab Invest* 2013;73:75–81. [PubMed: 23198772]
59. Santoro D, Gagliostro G, Alibrandi A, Ientile R, Bellinghieri G, Savica V, et al. Vitamin D receptor gene polymorphism and left ventricular hypertrophy in chronic kidney disease. *Nutrients* 2014;6:1029–37. [PubMed: 24618509]
60. Thadani R, Appelbaum E, Pritchett Y, Chang Y, Wenger J, Tamez H, et al. Vitamin D therapy and cardiac structure and function in patient with chronic kidney disease: the PRIMO randomized controlled trial. *JAMA* 2012;307:674–84. [PubMed: 22337679]
61. Wang AY, Fang G, Chan J, Wen YY, Qing S, Chan IH, et al. Effect of paricalcitol on left ventricular mass and function in CKD—the OPERA trial. *J Am Soc Nephrol* 2013;25:175–86. [PubMed: 24052631]
62. Nickolas TL, McMahon DJ, Shane E. Relationship between moderate to severe kidney disease and hip fracture in the United States. *J Am Soc Nephrol* 2006;17:3223–32. [PubMed: 17005938]
63. Alem AM, Sherrard DJ, Gillen DL, Weiss NS, Beresford SA, Heckbert SR, et al. Increased risk of hip fracture among patients with end-stage renal disease. *Kidney Int* 2000;58:396–9. [PubMed: 10886587]
64. Mittalhenkle A, Gillen DL, Stehman-Breen CO. Increased risk of mortality associated with hip fracture in the dialysis population. *Am J Kidney Dis* 2004;44:672–9. [PubMed: 15384018]
65. Herberth J, Branscum AJ, Mawad H, Cantor R, Monier-Faugere MC, Malluche HH. Intact PTH combined with the PTH ratio for diagnosis of bone turnover in dialysis patients: a diagnostic test study. *Am J Kidney Dis* 2010;55:897–906. [PubMed: 20347512]

66. Sprague SM, Bellorin-Font E, Jorgetti V, Carvalho AB, Malluche HH, Ferreira A, et al. Diagnostic accuracy of bone turnover markers and bone histology in patients with CKD treated by dialysis. *Am J Kidney Dis* 2016;67:559–66. [PubMed: 26321176]
67. Couttenye MM, D’Haese PC, Van Hoof VO, Lemoniatou E, Goodman W, Verpooten GA, et al. Low serum levels of alkaline phosphatase of bone origin: a good marker of adynamic bone disease in haemodialysis patients. *Nephrol Dial Transplant* 1996;11:1065–72. [PubMed: 8671970]
68. Yessayan L, Moore C, Lu M, Yee J. Bone-specific alkaline phosphatase and bone turnover in African American hemodialysis patients. *Hemodial Int* 2017;21:90–6. [PubMed: 27350216]
69. Iimori S, Mori Y, Akita W, Kuyama T, Takada S, Asai T, et al. Diagnostic usefulness of bone mineral density and biochemical markers of bone turnover in predicting fracture in CKD stage 5D patients-a single-center cohort study. *Nephrol Dial Transplant* 2012;27:345–51. [PubMed: 21652550]
70. West SL, Lok CE, Langsetmo L, Cheung AM, Szabo E, Pearce D, et al. Bone mineral density predicts fractures in chronic kidney disease. *J Bone Miner Res* 2015;30:913–9. [PubMed: 25400209]
71. Naylor KL, Garg AX, Zou G, Langsetmo L, Leslie WE, Fraser LA, et al. Comparison of fracture risk prediction among individuals with reduced and normal kidney function. *Clin J Am Soc Nephrol* 2015;10:646–53. [PubMed: 25655423]
72. Kidney Disease: Improving Global Outcomes (KDIGO) CKD-MBD Update Work Group. KDIGO 2017 clinical practice guideline update for the diagnosis, evaluation, prevention and treatment of chronic kidney disease-mineral bone disorder (CKD-MBD). *Kidney Int Suppl.* 2017;7:1–59.
73. Malgo F, Hamdy NA, Papapoulos SE, Appelman-Dijkstra NM. Bone material strength as measured by microindentation in vivo is decreased in patients with fragility fractures independently of bone mineral density. *J Clin Endocrinol Metab* 2015;100:2039–45. [PubMed: 25768670]
74. Mellibovsky L, Prieto-Alhambra D, Mellibovsky F, Gueri-Fernandez R, Nogues X, Randall C, et al. Bone tissue properties measurement by reference point indentation in glucocorticoid-induced osteoporosis. *J Bone Miner Res* 2015;30:1651–6. [PubMed: 25736591]
75. Rutsch F, Nitschke Y, Terkeltuab R, Towler DA. Genetics in arterial calcification. *Circ Res* 2011;109:578–92. [PubMed: 21852556]
76. Stenvinkel P, Wang K, Qureshi AR, Axelsson J, Pecoits-Filho R, Gao P, et al. Low fetuin-A levels are associated with cardiovascular death: impact of variations in the gene encoding fetuin. *Kidney Int* 2005;67:2383–92. [PubMed: 15882283]
77. Jwang JY, Hwang YH, Lee H, Ro H, Lee H, Chung W, et al. Association of AHSG gene polymorphisms and aortic stiffness in peritoneal dialysis patients. *Am J Nephrol* 2010;31:510–7. [PubMed: 20453496]
78. Brancaccio D, Biondi ML, Gallieni M, Turri O, Galassi A, Cecchini F, et al. Matrix GLA protein gene polymorphisms: clinical correlates and cardiovascular mortality in chronic kidney disease patients. *Am J Nephrol* 2005;25:548–52. [PubMed: 16210837]
79. Cozzolino M, Biondi ML, Galassi A, Cusi D, Brancaccio D, Gallieni M. Vascular calcification and cardiovascular outcome in dialysis patients: the role of gene polymorphisms. *Blood Purif* 2010;29:347–51. [PubMed: 20357434]
80. Wang K, Honda H, Qureshi AR, Pecoits-Filho R, Axelsson J, Nordfors L, et al. Association between the matrix GLA protein-7 polymorphism and carotid intima-media area and left ventricular hypertrophy in end-stage renal disease patients [abstract]. In: ERA-EDTA XLI Congress; 2004.
81. Ketteler M, Bongartz P, Westenfeld R, Wildberger JE, Mahnken AH, Bohm R, et al. Association of low fetuin-A (AHSG) concentrations in serum with cardiovascular mortality in patients on dialysis: a cross-sectional study. *Lancet* 2003;361:827–33. [PubMed: 12642050]
82. Cozzolini M, Galassi A, Biondi ML, Turri O, Papagni S, Mongelli N, et al. Serum fetuin-A levels link inflammation and cardiovascular calcification in hemodialysis patients. *Am J Nephrol* 2006;26:423–9. [PubMed: 16968979]
83. Cox DW, Andrews BJ, Willis DE. Genetic polymorphism of alpha 2HS-glycoprotein. *Am J Hum Genet* 1986;38:699–706. [PubMed: 3717159]

84. Sheng K, Zhang P, Lin W, Cheng J, Li J, Chen J. Association of Matrix Gla protein gene (rs1800801, rs 1800802, rs4236) polymorphism with vascular calcification and atherosclerotic disease: a meta-analysis. *Sci Rep* 2017;18:8713.
85. Kobayashi N, Kltazawa R, Maeda S, Schurgers L, Kitazawa S. T-138c polymorphism of matric gla promoter alters its expression but is not directly associated with atherosclerotic vascular calcification. *Kobe J Med Sci* 2004;50:69–81. [PubMed: 15864013]
86. Pasch A, Farese S, Graber S, Wald J, Richtering W, Floege J, et al. Nanoparticle-based test measures overall propensity for calcification in serum. *J Am Soc Nephrol* 2012;23:1744–52. [PubMed: 22956818]
87. Raggi P, Bellasi A, Ferramosca E, Islan T, Muntner P, Block GA. Association of pulse wave velocity with vascular and valvular calcification in hemodialysis patients. *Kidney Int* 2007;71:802–7. [PubMed: 17311068]
88. Sigrist MK, Taal MW, Bungay P, McIntyre CW. Progressive vascular calcification over 2 years is associated with arterial stiffening and increased mortality in patients with stages 4 and 5 chronic kidney disease. *Clin J Am Soc Nephrol* 2007;2:1241–8. [PubMed: 17928470]
89. Smith ER, Ford ML, Tomlinson LA, Bodenham E, McMahon LP, Farese S, et al. Serum calcification propensity predicts all-cause mortality in predialysis CKD. *J Am Soc Nephrol* 2014;25:339–48. [PubMed: 24179171]
90. Dekker M, Pasch A, van der Sande F, Konings C, Bachtler M, Dionisi M, et al. High-flux hemodialysis and high-volume hemodiafiltration improve serum calcification propensity. *PLoS One* 2016;11:e0151508. [PubMed: 27064679]
91. Bressendorff I, Hansen D, Schou M, Silver B, Pasch A, Bouchelouche P, et al. Oral magnesium supplementation in chronic kidney disease stages 3 and 4: efficacy, safety and effect on serum calcification propensity-a prospective randomized double-blinded placebo-controlled clinical trial. *Kidney Int Rep* 2016;30:380–9.
92. Berchtold L, Ponte B, Moll S, Haday K, Seyde O, Bachtler M, et al. Phosphocalcic markers and calcification propensity for assessment of interstitial fibrosis and vascular lesions in kidney allograft recipients. *PLoS One* 2016;11:e0167929. [PubMed: 28036331]
93. Block GA, Wheeler DC, Persky MS, Kestenbaum B, Ketteler M, Spiegel DM, et al. Effects of phosphate binders in moderate CKD. *J Am Soc Nephrol* 2012;23:1407–15. [PubMed: 22822075]
94. Di Iorio B, Bellasi A, Russo D. Independent Study Investigators. Mortality in kidney disease patients treated with phosphate binders: a randomized study. *Clin J Am Soc Nephrol* 2012;7:487–93. [PubMed: 22241819]
95. Di Iorio B, Molony D, Bell C, Cucciniello E, Bellizzi V, Russo D, et al. Sevelamer versus calcium carbonate in incident hemodialysis patients: results of an open-label 24-month randomized clinical trial. *Am J Kidney Dis* 2013;62:771–8. [PubMed: 23684755]
96. Sherman RA, Ravella S, Kopolan T. A dearth of data: the problem of phosphorus in prescription medications. *Kidney Int* 2015;87:1097–9. [PubMed: 25760324]
97. Ertuk S. Gene polymorphism association studies in dialysis: bone and mineral metabolism. *Semin Dial* 2006;19:232–7. [PubMed: 16689975]

Figure 1.

Current and evolving personalized treatment of CKD-MBD. Current precision parameters such as considering serum levels of PTH and BSAP together, along with the use of DXA and bone biopsy, are ways to personalize management of CKD-MBD using existing tools. Evolving precision parameters such as examining genetic variants and using the T₅₀ assay to evaluate calcification severity and the Osteoprobe to determine bone strength are methods that may one day enhance the personalized management of CKD-MBD. IV, intravenous.

Figure 2.
A multidisciplinary approach is key to personalized management of CKD-MBD.

Table 1.

Comparison of the Currently Available Phosphate Binders

Binder	Advantages	Disadvantages	Forms	Dosage, mg
Calcium carbonate	Effective Inexpensive Readily available (over the counter) Long-term experience	Potential hypercalcemia Potential for progression of vascular calcification GI side effects Low-turnover bone disease	Tablet, chewable Capsule Liquid Gum	Contains 40% elemental calcium (200 mg elemental calcium per 500 mg) Total dose of elemental calcium should not exceed 2,000–2,500 mg/d
Calcium acetate	Effective Inexpensive Readily available Long-term experience Potentially less calcium absorption than calcium carbonate	Potential hypercalcemia Potential for progression of vascular calcification GI side effects Low-turnover bone disease	Tablet Capsule	Contains 25% elemental calcium (160 mg elemental calcium per 667-mg capsule) Total dose of elemental calcium should not exceed 2,000–2,500 mg/d
Magnesium carbonate/calcium acetate	Effective Inexpensive Decreased calcium load compared with calcium-based binders	Potential hypermagnesemia Potential hypercalcemia GI side effects No long-term experience	Tablet	235 mg/435 mg Maximum dose is 3–6 pills/d
Aluminum hydroxide	Very effective Inexpensive	Potential for aluminum toxicity GI side effects Altered bone mineralization Anemia	Tablet Capsule Liquid	300–600 mg 3 times/d Aluminum content varies from 100 to >200 mg per tablet Limit use to no more than 4 weeks
Lanthanum carbonate	Effective Calcium free	Expensive Potential for lanthanum accumulation in bone and tissue GI side effects No long-term data	Tablet, chewable Powder	500–1,000 mg (3–6 chewable tablets) 3 times/d
Sevelamer hydrochloride	Effective Calcium free Pleiotropic effects Potentially decreased vascular calcification	Expensive GI side effects Metabolic acidosis Potentially interferes with vitamin D and vitamin K absorption	Tablet	800–1,600 mg 3 times/d Maximum dose studied was 13 g/d
Sevelamer carbonate	Effective Calcium free Pleiotropic effects No metabolic acidosis Potentially decreased vascular calcification	Expensive GI side effects Potentially interferes with vitamin D and vitamin K absorption	Tablet Powder	800–1,600 mg 3 times/d Maximum dose studied was 14 g/d
Sucroferric oxyhydroxide	Effective Calcium free Less pill burden than sevelamer Potential to increase transferrin, iron, and hemoglobin levels	Expensive GI side effects Cannot be prescribed with oral levothyroxine Long-term side effects unknown Unknown if iron accumulation long term	Tablets, chewable	500 mg (1 tablet) 3 times/d Maximum dose studied was 3,000 mg/d
Ferric citrate	Effective Calcium free Less pill burden than sevelamer	Expensive GI side effects Long-term side effects unknown Unknown if iron accumulation long term	Tablets	Each tablet contains 210 mg ferric iron Starting dose: 2 tablets 3 times/d Maximum dose is 12 tablets/d

Author Manuscript

Author Manuscript

Author Manuscript

Author Manuscript

Binder	Advantages	Disadvantages	Forms	Dosage, mg
	Potential to increase transferrin, iron, and hemoglobin levels Potential to decrease iron and ESA use			

ESA, erythropoietin-stimulation agents; GI, gastrointestinal.

Table 2.

Gene Polymorphisms Associated With CKD-MBD

Clinical Association	Genetic Variant	Reference
Phosphorus homeostasis		
Serum phosphorus levels in non-CKD populations	rs1697421	28
	rs17265703	
	rs9469578	
	rs947583	
	rs2970818	
SHPT		
CaSR gene		
More severe SHPT and increased Ca	G990R AA genotype in dialysis patients	42,43
	Q1011E CC genotype in dialysis patients	43
	rs7652589 AA genotype in patients with ESRD from nephrolithiasis	44
Increased PTH	rs1042636 (R990G) G allele in dialysis patients with European ancestry	48
	rs1801725 (A986S) G genotype in dialysis patients with European ancestry	
Increased phosphorus	rs115759455 CT genotype in renal transplant	45
	rs1801725 (A986S) T allele in dialysis patients with European ancestry	48
	rs1393199 C allele in dialysis patients with African ancestry	48
Increased calcium	R4300957 T allele in dialysis patients with African ancestry	48
Reduction in PTH with increased dialysate Ca	G990R–R allele	47
Serum Ca response to cinacalcet	rs 9740	48
VDR gene		
Low PTH	Bsm1 BB genotype in dialysis patients	50–52
Better PTH-lowering response to calcitriol		53
Delayed time to parathyroidectomy		55
Less severe SHPT	Bsm1 BB genotype in predialysis CKD patients	54
Greater circulating calcitriol levels	Bsm1 BB genotype in predialysis CKD patients	54
	Fok1 C genotype in predialysis CKD patients	56
Increased risk of LVH	B Bsm1 in predialysis CKD and dialysis-dependent ESRD patients	57–59
Renal osteodystrophy		

Clinical Association	Genetic Variant	Reference
Increased fracture risk	VDR gene SNPs rs4678044, rs4300957, and rs767446 in dialysis patients with European ancestry	48
Bone mineral density	HhaI gene ApoE 4 allele	97
Bone mineral density response to raloxifene	ACE and IL6 gene polymorphisms	
Vascular calcification	ER- α gene polymorphisms	
AHSG gene (Fetuin A)		
Lower fetuin A levels and increased risk of mortality	AHSG 265Ser in dialysis patients	79
Lower fetuin A levels and greater vascular calcification score		80
MGP gene		
Greater mortality during 1 year of follow-up evaluation	MGP-138TT and MGP-7A in dialysis patients	83
Greater severity of LVH, vascular calcification, and atherosclerosis	MGP-7A in dialysis patients	84,85

ACE, angiotensin-converting enzyme; ER- α , estrogen receptor alpha gene polymorphisms; IL, interleukin; LVH, left ventricular hypertrophy; SHPT, secondary hyperparathyroidism.