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

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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.

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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 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

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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

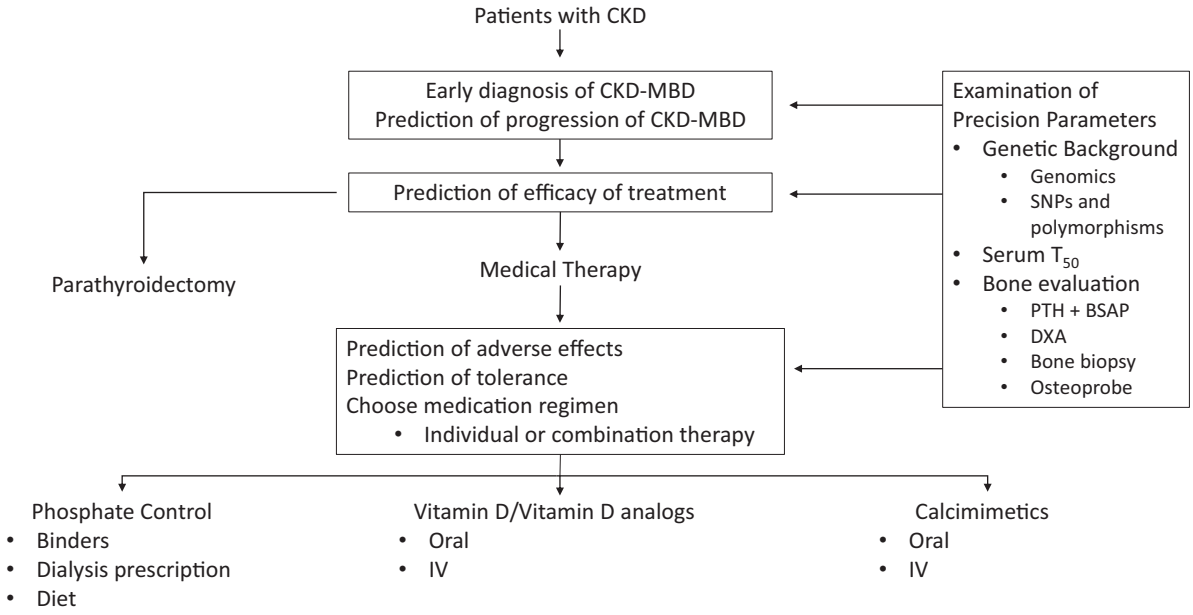

Figure 1. Current and evolving personalized treatment of CKD-MBD. Current precision parameters such as considering serum levels of PTH and BSAP together, along with the use of DXA and bone biopsy, are ways to personalize management of CKD-MBD using existing tools. Evolving precision parameters such as examining genetic variants and using the T_{50} 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.