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Narrow the Gap, Build a Bridge: An Inspirational Approach to CKD-MBD

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Chronic Kidney Disease (CKD) is a major public health problem with substantial economic burden that currently impacts ~13% of the global population. CKD is accompanied by CKD-Mineral and Bone Disorder (CKD-MBD) that is characterized by altered mineral and bone metabolism.[1, 2] As kidney function declines, progressive changes in phosphate and calcium metabolism lead to development of bone fragility, left ventricular hypertrophy (LVH), and vascular calcifications. These intermediate phenotypes are associated with increased risks of adverse clinical events, including hospitalizations and early mortality. Despite efforts to address CKD-MBD, available therapies and interventions have yielded limited progress. A better understanding of the mechanisms involved in the pathogenesis of CKD-MBD is desperately needed to overcome the complexity of this multi-factorial disease and to improve outcomes. In this issue, authors present interesting and important insights into the intricate regulatory mechanisms of bone and mineral metabolism, and their contribution to CKD progression and CKD-associated outcomes. The collection synergistically reflects recent advances towards narrowing a deep knowledge gap and towards building a bridge to success.

The progressive rise in phosphate and phosphate-regulating hormone fibroblast growth factor 23 (FGF23) are two major hallmarks of CKD-MBD.[3] Increased FGF23 production begins early and reaches supraphysiological levels as kidney function declines. While this initially contributes to maintaining circulating phosphate levels within acceptable range, it becomes ultimately maladaptive and is associated with cardiovascular toxicity and increased mortality.[4] To date, much attention has been directed to the cardiovascular implications of elevated FGF23 in CKD. However, as explained by Jansson et al., studies also support an association between increased FGF23 and adverse kidney outcomes. Currently, despite association between excess FGF23 and kidney disease progression, the molecular

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mechanisms involved in direct effects of FGF23 on kidney function are unclear. Jansson et al. show that FGF23-mediated phosphaturia and increased tubular phosphate concentration might aggravate kidney damage and contribute to faster CKD progression. Indeed, while the reduction in kidney mass may contribute to a reduction in total phosphate excretion, the resulting accumulation of phosphate in the bloodstream coupled to increased FGF23 concentration, may lead to a disproportionate increase in phosphate filtration per nephron, increased tubular phosphate, tubular crystal deposition, and additional injury. Importantly, the fact that FGF23 excess may accelerate CKD progression stands as an additional rationale to support studies aimed at identifying key regulators of FGF23 production in clinical and preclinical studies. Recent examples of such studies have led to the discovery of non-classical regulators of FGF23, and provide insights into possible approaches to lower circulating FGF23 levels and improve cardio-renal outcomes in CKD. These are reviewed by Courbon et al. and Agoro et al. who emphasize the importance of iron metabolism in the regulation of FGF23. First, the inflammatory marker and iron carrier Lipocalin 2 (LCN2) (Courbon et al.), primarily established as a urinary marker of acute kidney injury, has recently been identified as a potent stimulator of FGF23 that is increased in the circulation in patients and mice with CKD. Courbon et al. showed that LCN2 is a direct regulator of FGF23 production in osteoblasts, and explain how reducing LCN2 levels in a mouse model of CKD has successfully lowered FGF23 levels, and prevented the development of cardiac hypertrophy. Whether the benefits on the heart were mediated only by the reduction in FGF23 remains to be determined, since LCN2 also has cardiotoxic effects. Second, reduced oxygenation and iron deficiency have also been shown to stimulate FGF23 production. While administration of erythropoietin (EPO) is effective at increasing erythropoiesis and mitigating anemia in CKD, its benefits on cardiovascular outcomes and mortality are strongly debated. Studies have shown that EPO directly induces FGF23 production, suggesting that EPO administration may result in further elevation of FGF23 in CKD. Agoro et al. discuss the promising effects of recently developed strategies to ameliorate anemia and iron deficiency in CKD, including an iron-based phosphate binder, ferric citrate, and inhibitors of Hif Prolyl hydroxylases, designed to mimic a state of repleted oxygenation via stabilization of Hif transcription factors. In animal models of CKD, these agents present the added benefits of reducing FGF23 levels and correcting anemia of CKD, opening new hopeful avenues for future clinical testing.

An additional approach to narrowing the knowledge gap has consisted in making careful observations and reporting the modifications of bone and mineral metabolism occurring in patients with CKD at various stages of progression. Duque et al. review the multiple parameters altering the phosphate balance and contributing to hyperphosphatemia in patients with CKD before and during dialysis, and their evolution post-kidney transplantation. They emphasize the level of complexity that comes with interpreting phosphate levels in patients with CKD due to varying contributions from intestinal absorption, kidney excretion, skeletal remodeling, and cellular metabolism. They further review the risks and benefits of currently employed strategies to maintain phosphate levels within near-normal range in patients with CKD. Bone loss and increased fracture risk are nearly universal among patients with CKD by the time they reach kidney transplantation and frequently persist after kidney replacement. Bone disease directly increases the risk of mortality in patients with

CKD. The limited diagnostic tools are often too invasive for this already vulnerable patient population, which has significantly impacted treatment success up to this day. Smout et al. review studies focusing on the identification of specific and reliable circulating markers of bone turnover that could be used in non-invasive and repeated diagnostic panels to predict bone loss and better address the therapeutic needs of each patient over time. Although not a single marker has yet qualified on its own for this potentially appealing new approach, future studies should reveal if compound panels of circulating bone turnover markers can be used in the evaluation and monitoring of bone health in patients with CKD.

New exciting developments lie with interventions to prevent secondary hyperparathyroidism (sHPT) using the calcimimetic etelcalcetide in patients with end stage kidney disease. Dörr et al. explain how in this group, etelcalcetide also prevented further development of LVH and led to reductions in FGF23 levels, as opposed to vitamin D treatment, which was associated with higher risk of cardiovascular events.[5] Prior studies performed in animal models and patients with CKD have converged to establish that FGF23 excess in CKD is associated with greater risks of cardiac hypertrophy and premature death. FGF23 exerts direct effects on the heart inducing LVH, and lowering FGF23 levels prevents the development of LVH and prolongs the lifespan in preclinical studies. This is the first interventional study in human that supports evidence suggesting that FGF23 should be directly targeted to prevent LVH in patients with CKD.

Finally, using similar approaches for over 40 years of active basic and clinical research, a new bridge was built for the rare genetic disorder of primary hyperoxaluria type 1 (PH1) that causes the overproduction of hepatic oxalate and an increased risk of calcium oxalate crystal formation in the kidney, resulting in CKD and kidney failure. New therapeutics, consisting in double stranded RNA interference, have been developed to reduce the production of oxalate by the liver, targeting enzymes involved in the conversion of glycolate to oxalate. Dejban et al. review the results of phase I and phase III clinical trials showing positive outcomes, and opening a path to a reduced need for combined liver and kidney transplant, and reduced mortality in patients with PH1.

We remain inspired by the work of thousands of investigators of the CKD-MBD community, bringing their skills and knowledge together to solve gargantuan puzzles, and to improve millions of lives around the globe, piece by piece. We thank our contributing authors for shedding light on these recent important advances.

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