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From Phosphaturia to Cardiovascular Protection: Is FGF-23 the Heart of the Matter?

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Mortality among patients on maintenance hemodialysis is excessive with an annualized mortality rate of 20% among U.S. patients. Moreover, cardiovascular disease is the leading cause of morbidity and mortality among this population. The phenotype of the patient on maintenance hemodialysis is extremely complex and indeed this patient population is well known to have a high prevalence of multiple traditional (e.g. hypertension and diabetes) and non-traditional cardiovascular (e.g., anemia, vascular calcification, etc) that contribute to excessive cardiovascular morbidity and mortality. Studies in animal models and humans have clearly demonstrated that derangements in hormonal regulators of mineral metabolism are associated with cardiovascular disease including vascular calcification and left ventricular hypertrophy, common complications of end-stage kidney disease. Dissecting out the leading target for intervention within the complex pathophysiology and hormonal milieu of the uremic environment in people on dialysis has been a vexing and difficult problem. Hence, over the past two decades large-scale randomized controlled trials aimed at dose of dialysis¹, dialysis membrane type², statins^{3, 4}, secondary hyperparathyroidism and vascular calcification^{5, 6}, and anemia^{7, 8} have failed to demonstrate improvement in clinical outcomes. Alas, worldwide no new therapies have been definitively shown to reduce morbidity and mortality in hemodialysis populations. Recently, the search for new targets has focused on the ever increasingly complex mineral metabolism milieu in uremic patients on hemodialysis.⁹

Fibroblast growth factor-23 is a hormone synthesized and secreted by osteocytes in response to several stimuli including PTH, vitamin D, serum calcium and increased dietary phosphate.⁹ FGF-23 functions principally as a phosphaturic hormone to maintain phosphorus homeostasis by binding to klotho-dependent receptors in the basolateral membrane of the proximal tubule of the kidney and inhibits phosphate reabsorption resulting in phosphaturia. In addition to the phosphaturic action FGF-23 has been shown to bind to receptors in other organs including the parathyroid gland and myocardium. Excess FGF-23

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in the heart is associated with the development of left ventricular hypertrophy in animal models of chronic kidney disease and is associated with increased risk for development of LVH among people with CKD¹⁰. Serum FGF-23 is an early marker of chronic kidney disease, its concentration increases before PTH or phosphorus as kidney disease evolves and it has been associated with progression of chronic kidney disease.^{11, 12} In addition, elevated serum FGF-23 level among hemodialysis patients is associated with increased all cause mortality and cardiovascular mortality independent of other known risk factors.^{10,13} Despite these provocative findings, it is not known whether reducing serum FGF-23 levels is associated with reduction in cardiovascular morbidity or mortality in chronic kidney disease.

Accordingly in this issue of *Circulation*, Moe et al hypothesized that cinacalcet would reduce FGF-23 level in plasma and the reduction would be associated with lower rates of nonfatal cardiovascular events.¹⁴ The authors conducted a secondary analysis of serum FGF-23 levels obtained from participants in the EVOLVE (Evaluation of Cinacalcet Hydrochloride Therapy to Lower Cardiovascular Events) trial. EVOLVE was a randomized double-blind placebo controlled trial evaluating the efficacy of cinacalcet, a calcium sensing receptor agonist, on all cause and cardiovascular mortality approximately 4000 patients undergoing maintenance hemodialysis. The present study included a subgroup of about 3000 patients in whom serum FGF-23 was measured at baseline and 20 weeks after randomization. The primary outcome was time to death or nonfatal cardiovascular events including myocardial infarction, hospitalization for unstable angina, heart failure or a peripheral vascular event. They found that after adjustment for other variables, higher baseline serum FGF-23 level was associated with higher risk for the primary endpoint, confirming previous association. Further, they demonstrated that among those randomized to cinacalcet a significantly higher proportion had ~30% reduction in serum FGF-23. Moreover, among those with this degree of reduction in FGF-23 there was a significantly lower likelihood of occurrence of the primary outcome, cardiovascular mortality and sudden cardiac death. In addition they found that those with blood levels of PTH, calcium and phosphorus within the recommended range for clinical practice guidelines exhibited the greatest reduction in FGF-23 level. This is an important finding and lends credence to the notion that FGF-23 may not only be a biomarker but also a potential pathogenetic factor for cardiovascular disease onset and progression. The strengths of this study included the large number of patients randomized, the largest trial of hemodialysis patients known, the randomized trial design and the repeated measures of serum FGF-23 in three-fourths of the study population and adjustment for various confounders (e.g., baseline serum FGF-23, vitamin D usage) and the independent adjudication of events. In addition, the finding that those with better serum PTH, calcium and phosphorus levels had greater reduction in serum FGF-23 suggests that factors other than cinacalcet could have contributed to the observed lower hazard ratios for the primary composite outcome. Interestingly among those randomized to placebo, a > 30% reduction in FGF-23 was not associated with a reduction in the primary composite endpoint.

This study also has many limitations, the most important of which is the lack of evidence for causality. It is important to note that this study was not designed to determine the effect of lowering FGF-23 on mortality and nonfatal cardiovascular events and this secondary

analysis does not provide crucial evidence to support use of cinacalcet for this purpose. And as the authors note, it is not possible to confirm whether the association was a direct or indirect effect, let alone a causal effect of FGF-23 on better outcome. The value of > 30% to define a meaningful reduction in FGF-23 level was based on studies evaluating the effect of cinacalcet and vitamin D receptor agonists on serum PTH. Cinacalcet is known to lower serum calcium and PTH both of which could play a role in lowering FGF-23 levels in patients undergoing maintenance hemodialysis, thus not surprising that cinacalcet administration lowered serum FGF-23 level.

While the association between reduction of FGF-23 and the composite outcome in EVOLVE is clear, it is of modest effect. Importantly, the authors do not present compelling evidence that there of “dose-dependent” effect of lowering of FGF-23, the observations among those with >50% reduction of FGF-23 notwithstanding. In fact there was no difference in the hazard ratio for sudden death among those with 30 vs 50% reduction in FGF-23 level. In observational studies there is an increasing risk of mortality with increasing FGF-23 level among patients on long-term hemodialysis.¹⁵ While the lack of any effect of lowering FGF-23 > 30% on the primary outcome in those on placebo could be attributed to small numbers (as the authors contend), it could also mean that other factors beyond FGF-23 are at play and uncovered despite adjustment for multiple risk factors.

What then is the role of FGF-23 in cardiovascular disease among people on dialysis? While serum FGF-23 level is strongly associated with mortality and has multiple effects on the cardiovascular system including increasing blood pressure, myocardial hypertrophy and vascular calcification, we do not know precisely how or why it might increase risk for heart failure, sudden death, stroke and cardiovascular death. The present study was not designed to and cannot shed light on potential mechanisms whereby FGF-23 could play a causal role. For instance the study does not provide any information on whether reported sudden deaths were from arrhythmia, myocardial infarction or other causes. In addition, the it is not possible to discern whether serum FGF-23 level correlated with any parameter of cardiac function since measurements of LV mass or function were not performed or not reported. Still, it is reasonable to hypothesize that chronically elevated levels of circulating FGF-23 could worsen cardiac function in a patient population with a high prevalence of volume overload and underlying heart disease (LVH, systolic heart failure). Clearly the present study is hypothesis generating. And there is much more to learn about the role of FGF-23, in both the onset and progression of cardiovascular disease in people with chronic kidney disease, especially for those on hemodialysis.

In summary, the present study has confirmed previous associations between elevated serum FGF-23 and increased risk for death in maintenance hemodialysis patients. And importantly this study reveals the provocative finding that chronic lowering of serum FGF-23 levels (by more than 30%) in patients administered cinacalcet is associated with improved clinical outcomes. Whether or not this association is a direct or indirect of cinacalcet is unknown and whether the reduction in FGF-23 levels, whatever the mechanism is responsible for the finding of improved clinical outcomes requires further studies in humans. These studies should examine whether interventions that specifically target FGF-23 can improve clinical outcomes in people on maintenance hemodialysis.

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