From Phosphaturia to Cardiovascular Protection
Is Fibroblast Growth Factor-23 the Heart of the Matter?

Robert D. Toto, MD

Mortality among patients on maintenance hemodialysis is excessive with an annualized mortality rate of 20% among US patients. Moreover, cardiovascular disease is the leading cause of morbidity and mortality in 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 (eg, hypertension and diabetes mellitus) and nontraditional cardiovascular (eg, anemia, vascular calcification) that contribute to excessive cardiovascular morbidity and mortality. Studies in animal models and in humans have clearly demonstrated that the 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 2 decades, large-scale randomized, controlled trials aimed at dose of dialysis, dialysis membrane type, statins, secondary hyperparathyroidism and vascular calcification, and anemia 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.

Article see p 27

Fibroblast growth factor-23 (FGF-23) is a hormone synthesized and secreted by osteocytes in response to several stimuli, including parathyroid hormone (PTH), vitamin D, serum calcium, and increased dietary phosphate. 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 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 left ventricular hypertrophy among people with chronic kidney disease. 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 the progression of chronic kidney disease. In addition, elevated serum FGF-23 levels among patients undergoing hemodialysis is associated with increased all-cause mortality and cardiovascular mortality independent of other known risk factors. Despite these provocative findings, it is not known whether reducing serum FGF-23 levels is associated with the reduction in cardiovascular morbidity or mortality in chronic kidney disease.

Accordingly, in this issue of Circulation, Moe et al hypothesize that cinacalcet would reduce the FGF-23 level in plasma and that the reduction would be associated with lower rates of nonfatal cardiovascular events. The authors conducted a secondary analysis of serum FGF-23 levels obtained from participants in the Evaluation of Cinacalcet Hydrochloride Therapy to Lower Cardiovascular Events (E-VOLVE) 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 in ≈4000 patients undergoing maintenance hemodialysis. The present study included a subgroup of ≈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 the adjustment for other variables, a higher baseline serum FGF-23 level was associated with higher risk for the primary end point, confirming the previous association. Furthermore, they demonstrated that, among those randomly assigned 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 randomly assigned (this is the largest trial
of patients undergoing hemodialysis known), the randomized trial design, the repeated measures of serum FGF-23 in three-fourths of the study population, the adjustment for various confounders (eg, 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 randomly assigned to placebo, a >30% reduction in FGF-23 was not associated with a reduction in the primary composite end point.

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 the 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, it is not surprising that cinacalcet administration lowered serum FGF-23 level.

Although the association between the reduction of FGF-23 and the composite outcome in EVOLVE is clear, it exerts a modest effect. Importantly, the authors do not present compelling evidence that there is a dose-dependent effect of the 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% versus 50% reduction in FGF-23 level. In observational studies, there is an increasing risk of mortality with increasing FGF-23 levels among patients on long-term hemodialysis. Although 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 the adjustment for multiple risk factors.

What then is the role of FGF-23 in cardiovascular disease among people on dialysis? Although 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 the 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 attributable to arrhythmia, myocardial infarction, or other causes. In addition, it is not possible to discern whether serum FGF-23 level correlated with any parameter of cardiac function, because measurements of left ventricular 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 (left ventricular hypertrophy, systolic heart failure). Clearly, the present study is hypothesis generating. 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 patients undergoing maintenance hemodialysis. And, importantly, this study reveals the provocative finding that the chronic lowering of serum FGF-23 levels (by >30%) in patients administered cinacalcet is associated with improved clinical outcomes. Whether or not this association is a direct or indirect effect of cinacalcet is unknown, and whether the reduction in FGF-23 levels, whatever the mechanism, is responsible for the finding of improved clinical outcomes require further studies in humans. These studies should examine whether interventions that specifically target FGF-23 can improve clinical outcomes in people on maintenance hemodialysis.

Sources of Funding
This work was supported by National Institutes of Health grant P30DK079328.

Disclosures
None.

References


Key Words: Editorials - fibroblast growth factors - outcome assessment (health care) - renal insufficiency, chronic
From Phosphaturia to Cardiovascular Protection: Is Fibroblast Growth Factor-23 the Heart of the Matter?
Robert D. Toto

*Circulation*. 2015;132:7-9; originally published online June 9, 2015; doi: 10.1161/CIRCULATIONAHA.115.017177

*Circulation* is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231

Copyright © 2015 American Heart Association, Inc. All rights reserved.

Print ISSN: 0009-7322. Online ISSN: 1524-4539

The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://circ.ahajournals.org/content/132/1/7

Permissions: Requests for permissions to reproduce figures, tables, or portions of articles originally published in *Circulation* can be obtained via RightsLink, a service of the Copyright Clearance Center, not the Editorial Office. Once the online version of the published article for which permission is being requested is located, click Request Permissions in the middle column of the Web page under Services. Further information about this process is available in the Permissions and Rights Question and Answer document.

Reprints: Information about reprints can be found online at:
http://www.lww.com/reprints

Subscriptions: Information about subscribing to *Circulation* is online at:
http://circ.ahajournals.org//subscriptions/