FGF23 Beyond Mineral Metabolism: A Bridge to Cardiovascular Disease

Tobias E. Larsson


One of the largest challenges in current clinical nephrology is to alleviate the massive increment in cardiovascular comorbidity in the chronic kidney disease (CKD) population. Over the past decade, a particular focus has been directed at optimizing treatment of disordered mineral metabolism, which, in innumerable scientific reports, is linked to cardiovascular disease and reduced survival. Defining the true culprits is, however, a complex matter, since all components of mineral metabolism (i.e., inorganic phosphate [Pi], calcium, parathyroid hormone [PTH], and vitamin D) influence each other through intricate physiologic feedback loops. In other words, intervention against one of these factors will inevitably invoke alterations in all of the others. That, in combination with a lack of randomized placebo-controlled trials, has sparked a never-ending debate on the optimal strategies for intervention against disordered mineral metabolism, forcing clinicians to rely upon the use of nonvalidated surrogate markers and treatment guidelines based on observational data.

In the aftermath of the initial excitement of selective vitamin D receptor activators, calcimimetics, and non-calcium-based Pi binders, which all remain to be proven effective in terms of reducing mortality in placebo controlled trials, a fifth element emerged as a key player of mineral metabolism: fibroblast growth factor-23 (FGF23). FGF23 has fundamentally revised our current models of mineral metabolism and has, even when accounting for the aforementioned pitfalls and shortcomings of epidemiologically based treatment regimens, a large potential to influence the practice pattern of CKD patients. FGF23 is a circulating peptide hormone secreted from bone cells (1,2), with three main physiologic actions: (1) reduce the reabsorption of filtered Pi in the kidney proximal tubules, (2) lower systemic 1,25 dihydroxyvitamin D levels through decreased activation and enhanced degradation of 25-hydroxyvitamin D, and (3) suppress PTH transcript level and protein secretion (3–11). Collectively, FGF23 is the prime phosphaturic hormone and indirectly reduces calcium level through its action on PTH and vitamin D. FGF23 is therefore a master regulator of the Calcium × Pi product, which is commonly monitored in CKD patients due to its predisposition to induce vascular calcification. Conversely, irrefutable clinical and experimental data favor that Pi, vitamin D, and PTH directly promote FGF23 production in bone, thus completing the FGF23 endocrine system (12–15).

In CKD, the decline in renal function is paralleled by a rise in circulating FGF23, and the levels are often dramatically elevated in end-stage renal disease, reaching up to 10,000-fold higher than in healthy individuals (16–18). The initial rise in FGF23 is conceptually attributed to an increased Pi load per nephron, although other yet unidentified factors may contribute. Numerous efforts have been undertaken to explore the predictive role of circulating FGF23 in terms of hard clinical endpoints such as cardiovascular events and mortality. High levels of FGF23 are independently associated with reduced survival rate and cardiovascular disease in a number of diverse cohorts (19–21), suggesting that FGF23 may serve as a biomarker in CKD. FGF23 possesses several characteristics that strengthen its potential clinical use. First, FGF23 is highly dysregulated in CKD and rises early during CKD development. As such, in vivo CKD models using neutralizing FGF23 antibodies and human studies of normal individuals and early CKD suggest that the rise in FGF23 precedes any other overt alteration in mineral metabolism (22,23,34). Second, there is a striking consistency in observational studies that supports an association between FGF23 and adverse clinical outcomes. Third, its predictive value is superior to any other component of mineral metabolism, even in relation to several classic cardiovascular risk factors (19,24,25). Fourth, the intraindividual variability is smaller, and its temporal stability greater, than for PTH and Pi, which would provide a significant advantage when establishing clinical guidelines based on FGF23 levels (26). Finally, FGF23 retains its predictive role across all strata of glomerular filtration rates, including non-CKD individuals, predialysis patients, patients receiving dialysis treatment, as well as renal transplant recipients.

Although FGF23 fulfills the criteria for a useful biomarker, it should not divert the attention from the perhaps most critical question: Why does FGF23 predict outcomes, that is, what is it a biomarker for? Several attempts have been made to decode FGF23 regulatory factors, such as in this issue of CJASN, where Gutierrez et al. examine the cross-sectional association between FGF23 and clinical parameters in a
The mean estimated GFR ranges from 81 to 91 ml/min per 1.73 m² between the lowest and highest FGF23 quartile, thus representing individuals with a largely normal age-adjusted renal function. An important contribution of this study is that the influence of dietary factors on circulating FGF23 was examined, which has not been reported in previous studies. The authors found a small but significant graded relation between dietary Pi intake and serum FGF23 (3.4 RU/ml higher FGF23 per 500 mg increase in Pi intake), suggesting that dietary Pi influences FGF23 level, even when renal function is normal. This was also previously found in small interventional studies in healthy volunteers (27–29) but has never been examined at the population level and has not been quantitatively assessed in various strata of Pi intake. Despite the obvious limitations of cross-sectional design and estimation of dietary Pi intake by self-reported semiquantitative questionnaires, these data are biologically plausible and in agreement with FGF23 action. It remains to be determined whether the subtle rise in FGF23 associated with higher dietary Pi intake is clinically relevant and to what extent FGF23 is a surrogate marker for overall Pi exposure. Assuming that FGF23 reflects cardiovascular risk, the data by Gutierrez et al. contradict the notion that high Pi exposure is harmless as long as serum Pi levels remain within the normal range. In analogy, impaired insulin sensitivity is strongly associated with cardiovascular disease, although blood glucose levels are normalized by enhanced insulin secretion. Given the mild impact of Pi intake on FGF23 level in this study, it is difficult to perceive that serum FGF23 solely is a biomarker of Pi retention, a concept that is generally endorsed by the nephrology community, but it is nonetheless difficult to demonstrate its true existence. Furthermore, the large variation in FGF23 observed in end-stage renal disease is unlikely to be attributed to fluctuations in Pi intake and/or differences in serum Pi level. Alternatively, FGF23 could be a marker of vitamin D deficiency, but this is also unlikely, given that the relation between FGF23 and outcome is quantitatively unchanged when corrected for vitamin D status and that FGF23 levels are increased followed by vitamin D administration. FGF23 has also been suggested as a marker of secondary hyperparathyroidism. This is interesting because parathyroidectomy in a rat CKD model lowers FGF23 and even prevents its early rise if performed before CKD induction (14). But the fact that hypoparathyroidism is paralleled by increased FGF23, likely due to hyperphosphatemia (12), excludes hyperparathyroidism as the sole regulator of FGF23.

In sum, FGF23 is unlikely to purely reflect a disordered mineral metabolism, and other mechanisms should be considered. Gutierrez et al. herein report that FGF23 associate with multiple classical cardiovascular risk factors such as smoking, hypertension, high body mass index, and dyslipidemia (low HDL cholesterol and high triglycerides). These data are confirmative of a previous study by Mirza et al., who reported that FGF23 was independently related to body mass index, obesity, dyslipidemia, and the metabolic syndrome in two large community-based cohorts of elderly Swedish individuals (30), and this was extended to encompass smoking and hypertension. The authors found substantially higher FGF23 in smokers (17.1 RU/ml higher FGF23 than in nonsmokers) and in subjects with hypertension (6.0 RU/ml higher FGF23 versus normotensive subjects). Although residual confounding and reverse causation cannot be excluded, these findings warrant further studies. The field of FGF23 and cardiovascular disease remains in its infancy, but recent studies have laid the groundwork for additional important work in this area. As such, vascular calcification can be prevented by the FGF23 co-receptor Klotho (31), which is also possibly expressed in human vascular tissue (32). As discussed by the authors, FGF23 may exert Klotho-independent effect on cardiomyocyte growth, which, indeed, was recently demonstrated in isolated cardiomyocytes and in vivo models with high systemic FGF23 levels (33). If such data can be validated in additional experimental settings, this would represent a major paradigm shift that transformed FGF23 from biomarker to mechanism of disease, at least in left ventricular hypertrophy, and raises the possibility of FGF23 being a primary target for intervention. Considering the herein reported link between FGF23, hypertension, and dyslipidemia, it will also be of interest to assess the impact of various antihypertensive and lipid-lowering agents on systemic FGF23.

Disclosures
Dr. Larsson served as a consultant and/or received honoraria from Genzyme, Abbott, Shire, Amgen, Swedish Orphan-Biowitzum, Astra-Zeneca, Novartis, and Astellas.

References

Published online ahead of print. Publication date available at www.cjasn.org.

See related article, “Fibroblast Growth Factor 23, Cardiovascular Disease Risk Factors, and Phosphorus Intake in the Health Professionals Follow-up Study,” on pages 2871–2878.